



European Partnership for Action Against Cancer (EPAAC)

**D5: Complementary and alternative medicine (CAM) in cancer care Development and opportunities of Integrative Oncology**

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# **Complementary and alternative medicine (CAM) in cancer care**

*Development and opportunities  
of Integrative Oncology*

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# Chapter 1

## The use of CAM in Integrative Oncology

### Introduction

Numerous studies that have been conducted in Europe demonstrate that one out of every three cancer patients resort to CAM (Complementary and Alternative Medicine), also defined as Complementary Medicine (CM), non conventional (NCM) or Complementary and Integrative Medicine (CIM). In the vast majority of cases these treatments are also associated with conventional therapy.

Most of these patients, who use complementary or alternative therapies, are young women with a high level of education. This is also true regarding other pathologies.

Often cancer patients use treatments and not “official” therapy as a form of self-medication despite scientific validity, quality and safety. The consequences of this phenomenon are multiple. There is a lack of communication with the oncologist regarding other therapies being used; there is the possibility of interactions with “official” drugs and a reduced compliance regarding the anti-cancer therapy.

There are numerous possible “complementary” treatments - 58 have been identified. The most frequently used are herbal infusions and products followed by homeopathic remedies, vitamins and minerals, spiritual therapy and relaxation techniques.

In contrast to the high number of patients who use these types of therapies, there are still few randomized and controlled trials, even though, there has been an increase in recent years.

### *Use of CAM among cancer patients*

A European research coordinated by Alex Molassiotis of the University of Manchester (2005) confirms that recourse to complementary and alternative therapies varies greatly from country to country (from 15% to 73%) and that the treatments most frequently used are homeopathy, herbal medicine and spiritual therapy. In the majority of cases, the patients followed the advice of friends, family, television or newspapers. Rarely did they consult with their doctor.

In 2008 a study was conducted in Italy using the same questionnaire as the authors of the British trial. One hundred and thirty-two patients undergoing chemotherapy in two hospitals were questioned (Johannessen H et al.). The use of NCM resulted to be 17% (herbal therapy 52%, homeopathy 30% and acupuncture 13%). This was in accordance with European data but not with the results of the Molassiotis study. The subjects in this Italian study were once again young women with a high cultural level.

A French study (Trager-Maury et al. 2007) reports that 34% of cancer patients utilize CAM (22% of whom use acupuncture) in order to reduce the negative effects of anti-cancer therapy.

The use of CAM among cancer patients in the USA has been estimated between 42% and 83% with specific use of acupuncture between 1,7% and 31% (Lu et al. 2008).

Another study was published in *Cancer* (Gannslar et al. 2008) and conducted in the USA on a group of 4,139 patients who had survived 10 types of tumours. The patients reported that they used acupuncture (1,2%) between the 10th and 24th month period after their diagnosis.

In Germany (Micke et al. 2009) carried out a study on the use of CAM in patients undergoing radiotherapy treatments. The results demonstrated that 59% of these patients used various types of CAM, particularly women with a variety of tumours (breast cancer, Hodgkin lymphoma, ovarian and uterine cancer, kidney cancer and rectal cancer).

Liu et al. (2011) analyzed 4 Chinese databases from which 716 reports were extracted regarding 1,198 cancer patients. The majority of these patients (66,44%) received treatments of combined Chinese medicine and conventional medicine: the use of herbal medicine was prevalent (98,50%) while the use of acupuncture was rare (1,8%).

According to a research conducted in 2011 by Saquib et al. in the USA, of 2,562 women between the ages of 28 and 74 who had survived breast cancer, only 50% used CAM while for other pathologies the percentage was 80%. Visualization, spiritual therapies and meditation were the most frequently used techniques. Regular use of CAM was significantly correlated to youth, high level of education, a greater intake of fruit and vegetables and less body weight.

McQuade et al. (2012) after having evaluated interviews conducted on samples of patients (245) and health care workers (72) in China, concluded that the use of TCM was very high (83%).

The majority of use (55,8%) referred to pharmacotherapy which was often used as an anti-tumor therapy (66,4%). Only 1,3% of the patients used acupuncture and 6,8% used Qi Gong or Tai Qi.

Contrary to what has been reported in the literature, in Norway it was discovered that in a group of 8,040 patients the proportion of CAM users with cancer or cardiac pathologies was not significantly different than patients with other pathologies (Kristoffersen et al. 2012).

A cross-sectional survey of medical oncology outpatients in an urban academic cancer center (Garland et al. 2013) has reported that among 316 participants, 193 (61.3%) used CAM following diagnosis. The relationship between specific CAM modalities and benefit finding was explored and the conclusion was that the patients who used CAM following a cancer diagnosis reported higher levels of benefit than those who did not.

#### *Use of CAM in paediatric patients*

Regarding the use of CAM in paediatric oncology, Laengler et al. conducted a study in Germany (2008) that documented the efficacy and risks related to “alternative” therapy in pediatric oncology. The study was carried out through a survey given to the parents of children who had had a first diagnosis of cancer. Of the sample 37% used CAM together with the standard therapy in 35% of the cases.

The most widely used therapies were homeopathy, food supplements and anthroposophic medicine - particularly mistletoe therapy. Certain factors induced these parents towards the use of these disciplines - previous positive experiences, the negative prognosis of the disease and a high socio-economic and educational level of the parents. The study revealed an improved stabilization of the disease, an improvement in immune status and a higher possibility of being cured. Information about CAM did not initiate from medical sources but 71% of the parents had spoken to their doctors about possible interactions with official medicine. The majority of parents reported to have perceived positive effects and 89% declared that they would recommend the use of CAM to other parents.

An observational study evaluated the use of CAM in children who were patients at the Istituto dei Tumori in Milan (Clerici et al. 2009). One hundred and forty-five parents received questionnaires. From 67% of the completed questionnaires it was revealed that 12,4% of the children utilized at least one form of CAM, homeopathy being the most commonly used. Eighty-three percent of the parents referred to the beneficial effects of using CAM as an addition to conventional therapy. The principal reason for using CAM was to reduce the iatrogenic effects of conventional therapy. In most cases the oncologists were not informed that their patients were using CAM.

Laengler et al. (2011) reported that in Germany, homeopathy was the form of CAM most often utilized. Heath et al. (2012) found that 30% of Australian children with cancer had used CAM during their final stage of life – particularly organic food and spiritual techniques. The majority of their parents (78%) referred that their child benefited from CAM treatments thus avoiding additional suffering.

In Germany a survey (Gottschling et al. 2013) conducted through a questionnaire on 405 children, both healthy and with chronic pathologies, revealed that 57% of the children used CAM (53% of the healthy children in comparison to 59% with chronic pathologies). The most prevalent therapies used were homeopathy (25%), herbal medicine (8%), anthroposophic medicine (7%) and acupuncture (5%). requested that, fill out a questionnaire.

A Dutch multicenter survey (Singendonk et al. 2013) investigated the prevalence and possible determinants of CAM use, and parental attitude towards communication and research on CAM therapies. The prevalence of CAM use in 1 year was assessed by a questionnaire filled out by parents of children visiting pediatric oncology outpatient clinics of 6 hospitals in the Netherlands. The questionnaire consisted of 26 questions on the child's clinical status, CAM use, and attitude towards communication and research on CAM therapies. One hundred and twenty-two of 288 respondents (42.4%) reported CAM use. The most frequently used categories were homeopathy (18.8%) and dietary supplements (11.5%, including botanicals). Female gender and parental CAM use were significant predictors for the use of CAM ( $p < 0.001$ ). More than 80% of the respondents identified a need for information about CAM from their pediatrician and 85.7% was positive towards research on CAM. Half of the parents were interested in participating in future CAM trials.

#### *Centres of Integrative Oncology*

To meet the needs of patients, many oncological centres have established departments for integrative and complementary medicine. In the United States there are such departments at the Dana-Farber Cancer Institute (DFCI) in Boston, at the Memorial Sloan-Kettering Cancer Center in New York and at the M.D.

Anderson Cancer Center in Houston. In these centres, various symptoms associated with cancer and the side effects of chemotherapy and radiotherapy are treated.

An example of this has been reported by Naing et al. (2011) at the Anderson Cancer Center in Houston where CAM is frequently used. Of the 309 patients interviewed, 52% referred to having used these therapeutic techniques (77% pharmacological therapies, 71% non-pharmacological therapies and 48% both types of therapy) and 43% of these patients had used these techniques for more than 5 years. The most frequently used treatments were vitamins (70%) followed by spiritual therapy (57%) and herbal medicine (26%). The use of CAM was not associated with socio-demographic factors but only with gender - women were more frequent users.

Considering the spread of the phenomenon, it is of utmost importance to develop health care that aims at integrating and not creating conflict between official medicine and non conventional medicine. It is crucial that the patient does not renounce valid cancer treatments in favour of complementary therapy as a first choice of cure. It is also essential to exclude any interactions between herbal medicine and antitumor drugs.

Therefore, it is fundamental that family practitioners, oncologists and health care workers are aware of the various problems caused by above-mentioned treatments in order to be able to advise their patients and to assist them in actualizing therapeutic programmes that integrate different approaches.

It is necessary to develop research in this field in order to examine, in depth, the benefits of CAM on the survival and well-being of oncological patients.

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## **Aims of EPAAC**

The Joint Action “European Partnership on Action against Cancer” (EPAAC) is an initiative started by the European Commission in September 2009 with the support of many partners and co-funded by the Programme “Health” of the European Union (EU).

This action – which collects the efforts of the European Commission, member States and corresponding Health Ministries, associations of patients, clinicians and researchers, industry and civil society – intends to face the cancer issue in an effective and harmonized way within the European Union. A high number of institutions, scientific societies of Europe participate in EPAAC, 36 associated partners and more than 90 collaborating members, which were divided in 10 Work Package (WP).

The Region of Tuscany participates in this project as an associated partner in the WP 7 “Healthcare” with the aim of identifying and promoting good practices in oncology.

The aim of Tuscany is to collect and review the evidence on the use of Complementary Medicine in oncology and propose criteria for a correct dissemination of the information for clinicians, patients and decision-makers; to map the European structures/centers which provide services of integrative oncology and put them in network activating synergies and a permanent co-ordination among the centers of integrative oncology.

The work of collecting and reviewing the trials and experiences published in literature is centered on Acupuncture and traditional Chinese medicine (TCM), Homeopathy, Herbal Medicine, Anthroposophic Medicine and Homotoxicology.

Among the criteria to analyze is the grading of the evidence and the strength of recommendation are also included.

## Chapter 2

### Materials and methods

#### Search strategy and MeSH terms

For this publication a search on complementary and alternative medicine (CAM) commonly used in human cancer treatment was conducted in MEDLINE (PubMed, Google Scholar and EBSCO) from January 2003 up to 30 June 2013.

Systematic reviews, meta-analyses and randomized clinical trials (RCTs) in the English language were selected using the following mesh terms: Cancer Symptoms (anxiety, cancer pain, cancer related fatigue, constipation, depression, diarrhea, edema and lymphedema, hot flashes, insomnia, leukopenia, mucositis, nausea and vomiting, neuropathy, xerostomia) AND type of CAM (Traditional Chinese Medicine/Acupuncture, Herbal medicine/Phytotherapy, Homeopathy, Homotoxicology, Anthroposophic Medicine) AND Cancer or Neoplasm or Oncology; a separate search was done for the quality of life.

Among the clinical trials were preferred, when possible, randomized double-blind trials versus placebo. Papers were chosen that specify the sample size, recruitment criteria and analysis methods, dosage and timing of natural compounds, tests and statistical power of the study.

For acupuncture, the paper had to include information about the acupuncture rationale, details of needling and treatment regimen, practitioner background and control or comparator interventions.

The research has also been extended to other papers (e.g. case reports) when the MeSH terms listed did not have any success. In this case we have reported the simple description of the results presented in literature.

In the case of homeopathy, homotoxicology and anthroposophic medicine some studies published before 2003 have also been included as they were significant for the report and a few articles not specific to cancer but referring to the efficacy of homeopathy in specific symptoms (for instance diarrhea) were also included.

## Grading System

The grading system chosen to assign the levels of efficacy and strength of the recommendations to evaluate research papers and trials on CAM published in international literature is that of the Society for Integrative Oncology (SIO) (Deng and al. 2009).

SIO recommendations are organized according to the clinical encounter and interventions and graded as 1A, 1B, 1C, 2A, 2B, or 2C based on the strength of evidence (see Table 1). Within each modality, recommendations supported by a strong level of evidence (grades A and B) are discussed first, followed by a review of selected topics in which only grade C recommendations can be made. Selectivity in grade C is often required because of the nascent research in this particular area; for some relevant therapies, there is not sufficient evidence to make meaningful recommendations.

The grading system is adapted from those of the American College of Chest Physicians.(Guyatt et al. 2006).

**Table 1.** Grading Recommendations

<i>Grade</i>	<i>Recommendations</i>	<i>Benefit vs Risk and Burdens</i>	<i>Strength of Supporting Evidence</i>	<i>Implications</i>
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	
1C	Strong recommendation, low- or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation may change when higher-quality evidence is available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	
2C	Weak recommendation, low- or very low-quality evidence	Uncertainty in estimates of benefits, risks, and burden; may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

RCTs = randomized controlled trials.

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## Chapter 3

### CAM in Integrative Oncology

#### Acupuncture and Traditional Chinese Medicine

##### *Definition and biological effects of TCM*

Traditional Chinese Medicine (TCM) is a type of treatment which was born in China more than 3,000 years ago and then spread throughout the Orient (above all to Korea and Japan). In the last century TCM has reached many Western countries such as the US, Great Britain, Canada, Australia, France, Germany, Italy etc.

The fundamental characteristic of this system of medicine is its holistic global vision of the organism which is considered to be composed of a single mind/body entity that is closely linked to the environment surrounding it. The knowledge and effectiveness of this branch of medicine has been transmitted for thousands of years and in 2010 TCM was listed by UNESCO as a world cultural heritage which should be defended and spread.

According to acupuncture and Traditional Chinese Medicine, illness is linked to an imbalance of energy of each organism. This energy is manifested in two opposite but complementary forms, Yin and Yang. Yin is defined as all the material aspects of the human body while Yang are the psychic and functional aspects.

The causes of illness can be of internal origin (emotions, psychic problems, incorrect diet, excessive work, stress, aging, lack of movement, hereditary factors) or of external origin (pathogenic bacteria, physical causes, climactic changes, chemical causes, work conditions, etc.). Prevention is fundamental to TCM. This is achieved by the choice of life style which permits a 'cautious management' of our energy.

The therapeutic treatment consists of re-balancing these disorders of energy through the uses of various techniques. All these techniques have the same theoretic base and the same mechanism of action and include acupuncture, moxibustion, cupping, Chinese tuina massage, diet, energetic exercises (qi gong and taijiquan), and Chinese herbal medicine, plum blossom ect. Acupuncture is the treatment which has been studied the most in the West. It is widely used in the academic field but, according to classical precepts, the different techniques are not interchangeable but should be chosen on the base of the pathology and the energetic characteristics of the organism. The various types of treatment are herewith outlined in greater detail.

Acupuncture consists of the insertion of needles in particular areas of the body, the depth of insertion varying according to the spot and the illness. These are called acupuncture points and are distributed throughout the surface of the body. There are particular areas where the entire organism is represented (e.g. ear, eye, scalp, hand, foot, face, abdomen etc.): treatment of these areas can be done with auricular acupuncture, craniopuncture, hand and foot acupuncture, face nose acupuncture, and abdominal acupuncture.

The needles can be stimulated by using various techniques (manually, electrostimulation, moxibustion etc.). Moxibustion is a therapeutic technique which is often associated with acupuncture. It utilizes cones or sticks of *Artemisia* to heat points or skin areas using different methods depending on the medical case. Traditional Chinese pharmacopoeia consists in the use of medicinal plants, animal derivatives or mineral derivatives which are often used together according to traditional 'recipes'.

The traditional Chinese diet has an important preventive role. It prescribes food based on the energetic typology and the pathology and complements the action of other therapeutic methods. Tuina massage is a therapeutic method that treats osteomuscular pathologies as well as pathologies of organs and systems. Finally, there are forms of medical gymnastics, qigong e taijiquan, which involve exercises to balance the breath with movement. The practice of these exercises has a preventive purpose and can improve wellbeing. Even tumours are considered a result of the imbalance of Yin and Yang dependent on superficial or defensive energy (Wei Qi) if the carcinogenic substances are inhaled or in contact with the skin; a discordance dependent on nutritive energy (Ying Qi) if the cause can be linked to emotions or incorrect diet; and finally a discordance dependent on deep layers (Yuan Qi, blood or body fluids) if the causes are genetic. These alterations cause a stagnation of energy which is transformed into heat or heat/humidity and then consumes energy, thus creating a vicious circle. The basic treatment for cancer patients uses different meridians according to the layers involved: distinct meridians (if wei qi is involved), luo meridians (when

ying qi is involved) and curious meridians (when yuan qi is involved). The objective is to regulate the energy and thus intervene on the substratum which supports the presence and the development of the neoplasia.

Therapy for cancer has been documented since the third century before Christ. It involves removal of the tumour (done with modern surgery), the use of herbal remedies (Chinese pharmacopoeia products and chemotherapy in the West) and the cauterization of the tumour mass (radiation therapy in modern medicine).

Furthermore, treatment with acupuncture or other TCM techniques can reduce the side effects of chemotherapy and radiation therapy, placate pain, improve the energetic equilibrium of the patient and reinforce the immune system. In China, besides Western therapy, traditional herbal medicine is principally used. In the West, the use of acupuncture is widespread and it does not have any negative interaction with the therapy of official medicine.

### **Biological effects**

According to literature, the biologic effects of acupuncture include:

- antalgic/analgesic effect, which is shown through an afferent path starting from an acupoint, passing through the medulla and the reticular substance and stopping at the hypothalamus, thalamus and pituitary gland. Descending inhibitory pathways (one serotonergic, the other noradrenergic) reach the spinal medulla and stop at interneurons having pre and post inhibitory synapses, which control the neuron that should transmit the pain message to the brain. The antalgic/analgesic effect is mediated by neurotransmitters such as endogenous opioids (endorphins, dinorphins and enkephalins), serotonin and noradrenalin. There also other mediators such as substance P and cholecystokinin with like-naloxone effects which inhibit the antalgic/analgesic action of acupuncture;
- immunomodulatory effect, which is shown through the increase of lymphocytes and neutrophil granulocytes, the activation of fagocytosis, humoral immunity and endothelial reticular system. By activating the cells of endothelial reticular system, especially at the spleen level, cellular clones are generated which are able to produce direct antibodies against any external protein molecule;
- neuroendocrine effect which activates the hypothalamus-pituitary-adrenal axis, modulates the secretion of sexual hormones, insulin, aldosterone, renin and angiotensin, gastrin, growth and thyroid hormones;
- trophic and vasomodulatory effect through cutaneous, muscle and microcirculation dilatation also in deeper districts such as the brain;
- effects on the psycho-emotional field and muscle tone, acts on anxiety, depression, insomnia (with a probable action on the monoaminergic system, serotonin, endogenous opioids, and endorphins);
- effect on the autonomic nervous system (sympathetic and parasympathetic) which regulates the neurovegetative activities of the cardiac system (frequency modulation, inotropism, conduction of heart impulse, heart electrophysiological balance); respiratory system (dilatation/contraction of bronchial tree), digestive system (gland secretion, gastrointestinal motility); vascular system.

These effects were pointed out in many studies in animals and humans, mostly Chinese; these studies have demonstrated that acupuncture can cause multiple biological responses and suggest that effect of acupuncture is primarily based on of the neuroendocrine system involving the central and peripheral nervous systems (Lu 2008, Lin 2012).

Needling may cause receptors to send neural impulses to the spinal cord or act on ascending pathways to the brain, and cause the release of neurotransmitters that subsequently modulate functions in the brain as well as in the periphery (Liu et al. 2004). Some studies include the stimulation of peripheral points in animal experimental settings (for instance on mice) and the following measure of biologic parameters such as the production of neurotransmitters directly measured in CNS through microdialysis. Using these techniques it was demonstrated that manual and electrical peripheral stimulation of acupoints in the animal *in vivo* is partially mediated through opiodergic and/or monoaminergic neurotransmission involving the brainstem, thalamus, hypothalamus as well as pituitary function. Kong et al. (2013) report that Wang (2008), Zhao (2008) and Han (2011) have published excellent comprehensive reviews of these studies and from a biochemical standpoint, it appears that acupuncture may alter the metabolism of substrates involved in both the ascending facilitory pathways (N-methyl-D- aspartate receptors, substance P, and interleukin-1) and the descending inhibitory pain pathways (endogenous opioids, serotonin and norepinephrine). The best known mechanism is via endogenous opiates and their receptors that play a role in the Central Nervous

System in acupuncture analgesia. The release of a morphine-like substrate in the central nervous system was hypothesized to be a possible mechanism (Lin and Chen 2009; Lee 2010). The release of different kinds of endogenous opiates, such as  $\beta$ -endorphin, enkephalin, endomorphin and dynorphin, has been reported to be frequency-dependent effects of EA. Several types of opioids may be released into the central nervous system during acupuncture treatment, thereby reducing pain. In addition to opioids, researchers have focused on the role of central monoaminergic systems, in particular serotonin: evidence suggests that serotonin levels increase in the spinal cord, and that its precursor (5-hydroxytryptophan) responds to enhanced analgesia at 2 Hz EA (Chang et al. 2004). It is increasingly clear that EA evokes serotonin release from regions of the upper brain stem and hypothalamus, in addition to the release of endogenous opiates (Lin and Chen 2008, Zhao 2008). Kim et al (2013) studied efficacy and mechanism of Electroacupuncture on neuropathic pain, analysing articles in research with animal models and particularly in the work performed in their laboratory. The results of this study demonstrate that  $\mu$  and  $\delta$  opioid receptors,  $\alpha$  2-adrenoreceptors, 5-HT<sub>1A</sub> and 5-HT<sub>3</sub> serotonergic receptors, M<sub>1</sub> muscarinic receptors, and GABA<sub>A</sub> and GABA<sub>B</sub> GABAergic receptors are involved in the mechanisms of EA-induced analgesia on neuropathic pain. The authors conclude that both the endogenous opioid system and the descending inhibitory system mediate the antiallodynic mechanism of EA, and that spinal opioidergic, adrenergic, serotonergic, and cholinergic and GABAergic systems are involved in the mechanisms.

Goldman et al. (2010) found that adenosine, a neuromodulator with anti-nociceptive properties, was released during acupuncture in mice and that its anti-nociceptive actions required adenosine A<sub>1</sub> receptor expression. Direct injection of an adenosine A<sub>1</sub> receptor agonist replicated the analgesic effect of acupuncture. Inhibition of enzymes involved in adenosine degradation potentiated the acupuncture-elicited increase in adenosine, as well as its anti-nociceptive effect. These observations indicate that adenosine mediates the effects of acupuncture and that interfering with adenosine metabolism may prolong the clinical benefit of acupuncture.

Stone and Johnstone (2010), in a publication about the mechanisms of action of acupuncture in the oncology setting, report that a biomedical database search for articles in the English-language literature revealed studies examining the effect of acupuncture on fibroblast cells (Langevin 2006), a decrease of inflammatory cytokines (Chae et al. 2007), an increase of T-lymphocytes (Lu et al. 2009) and increasing adenosine (Goldman 2010), neuropeptides, opioid peptides, peptide hormones, and stem cells (Moldenhauer et al. 2010). This limited review attempts to reveal some possible mechanisms of action for the effects of acupuncture for symptom relief in the oncology setting.

In addition to the analgesic effect of acupuncture, an increasing number of studies have demonstrated that acupuncture treatment can control autonomic nerve system functions such as blood pressure regulation, sphincter Oddi relaxation, and immune modulation (Kim et al. 2010). This review reports that mechanisms of electroacupuncture are a reinforcement of natural killer (NK) cell cytotoxicity in normal animals and a correction of the imbalance of Th1/Th2 cell response.

Kim et al. (2012) investigated neuronal responses in rodent models given acupuncture stimulation. In both mice and rats, acupuncture stimulation at Zusanli (ST36) generated an increased expression of axonal growth-associated protein (GAP-43) in the sensory neurons of the dorsal root ganglion (DRG). Electroacupuncture stimulation at ST36 in rats induced GAP-43 mRNA and protein expression in DRG neurons at the levels of lumbar 4 and 5. Stimulation on a non-acupuncture site as a sham control, induced GAP-43 expression as well, but the induction level was lower than it was with acupuncture. The authors further found that acupuncture stimulation up-regulated phospho- Erk1/2 signals in DRG neurons. Electroacupuncture stimulation induced c-Fos expression in the neurons of the dorsal motor nucleus of the vagus nerve (DMV), which was identified by retrograde tracing. These data suggest that acupuncture stimulation may generate physiological effects on the autonomic nervous system via the activation of a somatosensory pathway.

Lee et al. (2013) report that analgesic effects of acupuncture (in rats) are likely mediated in part by inhibiting inflammatory responses via inhibition of mitogen activated protein kinase (p38, ERK extracellular signal-regulated kinase, and JNK June –N-terminal kinase) in both activated microglia and astrocytes after Spinal cord injury (SCI). Furthermore, the authors suggest an application of acupuncture as an adjunct treatment for chronic neuropathic pain in SCI patients.

In addition to the classic neurotransmitters and anatomical pathways involved in central pain processing, other mechanisms also contribute to acupuncture analgesia, including the hypothalamus-pituitary-adrenal axis (regulating peripheral inflammatory response to pain), the autonomic nervous system (regulating local circulation) and glial cells (contributing to inflammation around spinal and cerebral neural pathways).

Acupuncture therapy is used not only to relieve pain but also to treat various medical conditions in traditional Chinese medicine. Some experiments have revealed a relationship between acupuncture and the autonomic nervous system (ANS). It is hypothesized that acupuncture can modulate these inflammatory conditions through an inflammatory reflex (Cabioglu 2008). The hypothalamus is the modulator for both hormonal and neuronal systems and therefore might play a key role in the mechanism of acupuncture.

The neuroendocrine effect of acupuncture was demonstrated in rats by activating the hypothalamic–pituitary–adrenal axis, the modulation of the secretion of sexual hormones, insulin, aldosterone, renin and angiotensin, gastrin, growth and pituitary hormones (Cheng 2012, Eshkevari 2013).

Huang et al. (2011) report that acupuncture has an effect on the hypothalamic–pituitary–ovarian axis mediated by neuropeptides at CNS and particularly by beta-endorphins, by the release of GnRH and by the pituitary secretion of gonadotropins. Wang et al. (2007), in a study on rats, showed that electroacupuncture increases the expression of GnRH in the medial preoptic area, in the arcuate nucleus and in the paraventricular nucleus of hypothalamus, in rats.

Finally Mo et al. (1993), in a study on 34 patients with ovulatory dysfunction, showed that acupuncture influences the plasmatic levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol and progesterone, stimulating the ovulation.

Acupuncture also has effects on the autonomic nervous system. Some studies on rats (Stener-Victorin et al. 2003, 2004) have demonstrated an increase in the afflux of blood in the ovary mediated by the activity of sympathetic nervous system after EA treatment on points located in the abdomen and posterior limbs. The same authors (2003) in another study on rats with polycystic ovary induced by steroids, point out that the EA effect on the sympathetic nervous activity at the ovary level causes a reduction in the ovary concentration of endothelin (a powerful vasoconstrictor) and of the nervous growth factor (involved in the pathophysiological process of steroid-induced polycystic ovaries).

Ding et al. (2013) report that numerous researches have shown that acupuncture can modulate the imbalance between the innate and acquired immune systems: it can regulate local immunomodulation of acupoints (Cabioglu 2008), the non specific immune function (Peng 2008) and has certain regulating effect on both cellular and humoral immunity (Liu 2010, Matsubara 2010).

Due to the recent progress in functional diagnostics, it was also possible to evaluate the effect of the acupoints by methods such as the EEG and functional imaging, for instance the Positron Emission Tomography (PET) and the functional magnetic resonance imaging (fMRI); from these studies it was possible to demonstrate that the stimulation of acupuncture points moderates a wide network of brain regions, including the primary somatosensory, secondary somatosensory and anterior cingulate, prefrontal, and insular cortices, amygdale, hippocampus, hypothalamus, and other areas, usually activated during nociceptive and painful processes, as it occurs in animal models.

A review of Huang et al (2012) included 149 studies for the descriptive and 34 eligible for meta-analyses applying fMRI to investigate brain responses to acupuncture stimulation. Results were heterogeneous but brain response to acupuncture stimuli demonstrated that acupuncture can modulate the activity within specific brain areas, consistent with not just somatosensory, but also affective and cognitive processing.

Ding et al. in a recent publication (2013) affirm that modern scientific research show that the body's inherent regulatory system is the neuro-endocrine-immune (NEI) network. Hence, they speculate that the regulatory effect of acupuncture may be produced through its regulation of NEI network. In this article authors reviewed the recent researches about acupuncture's effect on the NEI network, to find out the evidence of acupuncture adjusting NEI network and provide some evidences for revealing the mechanism of acupuncture.

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## ***Evidence Based Medicine and TCM***

Evidence-based medicine (EBM) is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research (Sackett et al. 1996).

This approach to health care promotes the collection, interpretation, and integration of valid, important and applicable patient-reported, clinician observed and research-derived evidence. The best available evidence, moderated by patient circumstances and preferences, is applied to improve the quality of clinical judgments (McKibbin et al. 1995).

EBM is therefore the integration of the best research evidence with clinical expertise and patient values and promotes the concept that one should apply the best evidence from medical research particularly that derived from randomized controlled trials (RCTs), to the treatment of patients. The aim is not to exclude, but to add to the methods associated with traditional clinical practice: clinical experience, clinical reasoning and pathophysiological inference.

EBM has some limitations, as would any system designed to resolve the complexities of medical practice. So far there has been a certain agreement in the scientific community on the so-called “evidence Pyramid” that ranks the reliability of evidence from low to high: at the bottom is classified preliminary research (animal models, in vitro etc.), then expert opinion, case series and case reports, case-control studies, cohort studies and at the top RCTs and meta-analyses and systematic reviews of RCTs.

Other authors have a different point of view. For instance, Wallach et al. (2006) state that “the hierarchical model is valid for limited questions of efficacy, but it is inadequate for the evaluation of complex interventions such as physiotherapy, surgery and complementary and alternative medicine (CAM)” and propose instead of an evidence hierarchy, a circular model. This would imply a multiplicity of methods, using different designs, counterbalancing their individual strengths and weaknesses to arrive at pragmatic but equally rigorous evidence which would provide significant assistance in clinical and health systems innovation. Such evidence would better inform national health care technology assessment agencies and promote evidence based health reform.

Over the last decade, the quantity of rigorously researched clinical practice guidelines has escalated and numerous evidence-based journals have emerged in many languages. In addition to the Cochrane Collaboration and Library, there are more than 30 dedicated websites.

### **Centre for Evidence Based Medicine**

#### **Level Type of evidence for Therapeutic Studies**

1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	“Outcomes” research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series (and poor quality cohort and case-control study)
5	Expert opinion without explicit critical appraisal or based on physiology bench research or “first principles”

Table 1. Levels of evidence.

The main problem in the planning of clinical studies in both acupuncture and traditional Chinese medicine is the choice of the control group.

In Western medicine the control group is usually composed of a group of patients who receive an inactive substance which is then compared to the drug which is being studied. The two substances are usually administered in pill form and therefore the patient in blind is unaware of which substance he/she received and the doctor may also not know to whom the actual drug was given (double blind). It is difficult to reach

the same objective with acupuncture and other branches of Western medicine that require an active intervention on the patient.

Vickers AJ. (2002) reports that for many years, there has been an active debate concerning the methodology that should be applied to the research on CAM. Considerable influence was exerted so that randomized and controlled double blinded studies could be conducted: the results have been many theoretical and practical efforts in order to identify a control group as a placebo which could be used in the trials of acupuncture. The author has evaluated 100 RCTs, chosen at random, and published in the Cochrane Collaboration Registry. These studies were conducted in Europe and North America and the majority of them (79%) included a control group with a placebo. The author states that there are probably more than 300 RCTs which include a placebo group. No standard methods exist to choose the placebo, therefore a large number of techniques were utilized; the same author selects the most important techniques that the various authors used, in an attempt to devise a true placebo (inactive treatment in unaware patients). Sham acupuncture has been defined as the insertion of needles in the skin but not according to the procedures of TCM. Sham acupuncture includes:

1. treating actual acupuncture points which are inappropriate for the condition being studied. For example in a study on asthma, a group of patients was treated on the active points for pulmonary disease and another group on the inactive points for this disease. The technique seems plausible for the patient but from a professional point of view, it is questionable, given the fact that different schools of TCM indicate different points as 'active' in different pathologies: therefore, the therapeutic indications of the various schools could choose diverse 'inappropriate' points;
2. treating non acupuncture points. This treatment seems credible for the patient but therapeutic effects are possible in the areas near those being treated. For example around L14, localizations not on the meridian have been reported. These have the same effect as the meridian. This is particularly true for the treatment of pain, given the fact that every type of acupuncture has an analgesic effect due to counter irritation and the possible release of endorphins;
3. the non insertion of needles. Some researchers have rubbed or touched the skin with a needle or a plastic tube. These methods can imitate the insertion of a needle. To maintain the 'blind' aspect the patients cannot see the points being used or the patients have to be blindfolded. This can create problems of patient compliance;
4. minimal acupuncture. This consists in inserting the needle superficially in points distant from the classical acupuncture points and the trigger points. This technique gives only minimal stimuli but since a needle is inserted, it is credible.

A placebo needle is considered the Streitberger and Kleinhenz placebo needle. It is a retractable needle with a round point and a plastic handle which holds the needle. When the needle is pushed, it returns into its case and the skin is not penetrated. This type of placebo has a minimum physiological activity, particularly if it is inserted distant from points. But it has many disadvantages. The first problem is that this needle has to be also used in patients who are treated with true acupuncture; therefore it is time consuming and can interfere with the actual treatment.

"Sham acupressure" has been utilized in studies which use acupressure. The acupressure method adopts elastic strips under which are rapeseed, micro needles that press on the points used to treat nausea. The "sham acupressure" deactivates the elastic strips by removing the means of stimulation. This method has obvious limitations.

Finally, treatment with sham electroacupuncture utilizes a device for TENS without electrical current. Patients are told that they are going to receive a subliminal level of stimulation. This method is considered plausible as a placebo because it is clearly distinguishable from acupuncture.

The author concludes that the placebo group has been considered pertinent to RCTs in acupuncture. The rationale for using a placebo in a particular type of trial is not explained but the choice should be motivated. The decision to use a placebo group should be linked to ethical, practical and methodological reasons and applicable to RCT studies in general regardless of the type of study.

According to some authors, it is likely that the procedures of control chosen because they were "inactive" actually activate nervous afferences. Therefore neither a "minimal superficial sham acupuncture" nor "placebo needles" can be considered a true placebo because they are not inactive. This would call into question the design of numerous acupuncture studies and meta-analyses. It is difficult to use a placebo

control group that is actually such, since in those used up to now, the non specific effects of the treatment have to be considered.

Kaptchuk TJ et al. (2006) conducted a study involving 270 people with chronic pain in the arm. In the first phase, 135 randomized patients received sham acupuncture and the other 135 a pill placebo for 2 weeks. During this period there were no significant differences between the 2 groups. In the second phase the same patients, again randomly, were divided into 4 groups: one group was treated with sham acupuncture, another was given true acupuncture, and a third group was administered a pill composed of an actual analgesic and a fourth group received a placebo pill.

The group treated with acupuncture received an additional 4 weeks of treatment so that an improvement could be seen. The group treated with the analgesic in pill form continued treatment for 6 weeks in order for an effective dose to be absorbed.

In the second phase of the study, the patients treated with sham acupuncture reported a reduction in pain and the severity of their symptoms. This was more significant than those who had been treated with the placebo pill. The results of the study demonstrate that the effects of the placebo vary according to the placebo which is used. These results also suggest that the presence of a doctor as in the sham acupuncture can elicit a greater placebo effect than a placebo pill.

The authors add that there are many conditions in which the ritual is irrelevant when compared to the use of medication. Such is the case in the treatment of bacteriological infections but in some cases the ritual can be a critical component. This study is the first step in examining the placebo effect, not as a general phenomenon, but how it varies in specific clinical settings.

According to Lund I. and Lundeberg T. (2006), during the last 10 years, many studies have compared manual acupuncture, electroacupuncture and placebo acupuncture for the treatment of pain. The control procedures which were often used included minimum or superficial acupuncture, the puncturing of non acupuncture areas and placebo needles.

Some studies report that acupuncture has an effect on various components of perceived pain; for example, it alleviates the discriminatory aspect (intensity) and diminishes the affective (unpleasantness) of the pain. Physiologically, the afferent stimulation of acupuncture activates ergoreceptors that carry information to the spinal cord and the sensory cortex.

Therefore, it can be said that acupuncture activates descendent pathways which inhibit the pain and deactivates the limbic structures. These mechanisms are linked respectively to the sensorial and affective component of the pain. It was recently demonstrated that a “soft touch” of the skin stimulates the non myelinated mechanoreceptors (C). The activity in these afferent C fibers suggests the induction of a “limbic touch” such as the hormonal and emotional response observed after caresses.

It is plausible that procedures of control used in many studies which were chosen because they are “inactive”, actually activate C tactiles and consequently diminish the ‘unpleasantness’ and re-establish a feeling of self-esteem and well-being of the patient. Therefore, neither “minimal, superficial, sham acupuncture” nor “placebo needles” can be considered as a placebo, because they are not inactive (inert). If the control used is not inert, it can be assumed that the results would have been superior if they had been compared to other placebos.

Lund et al. (2009) studied acupuncture–placebo which was used as a control in various scientific works to evaluate and distinguish between the specific and non-specific effects of the treatment. During the “true” acupuncture, the needles were inserted into a point until the sensation of qi was obtained (the arrival of energy).

On the contrary, during placebo acupuncture, the needles were inserted into inactive zones or in correspondence to points but in a superficial manner (minimal acupuncture). Nevertheless, even this insertion caused an electrical activity in the cutaneous afferent nerves which cause a “limbic response” in the brain. Clinical studies have demonstrated that both true acupuncture and placebo acupuncture cause a reduction in migraine pain, with equal (or almost equal) effectiveness. In patients with lumbar pain or osteoarthritis true acupuncture is more effective than a placebo. The differences are probably attributable to the different etiology of the pain. Similarly, it is very probable that healthy and unhealthy individuals exhibit different responses. In this work the authors discuss the poor validity of minimal acupuncture as a control in studies regarding acupuncture.

A recent Cochrane review reported on placebo systems for all clinical conditions in 202 papers (16,566 patients) (Hrobjartsson et al. 2010). It showed that “physical” systems (which included sham-acupuncture) were associated with more intense effects in comparison to the control group without treatment (SMD -0.31 from -0.41 to -0.22) and to pharmacological placebos (SMD -0.10 from - 0.20 to -0.01), ( $p = 0.002$ ).

Linde et al. (2010) decided to again analyze the data of this review in order to establish the role of sham acupuncture in comparison to other 'physical' systems.

The data was entered into the software RevMan 5 and a meta-analysis was done. Of the 61 studies analyzed reporting continuous outcome measurements, 19 compared sham acupuncture to a control group without treatment and 42 compared the other physical placebos (acupressure, laser acupuncture, electrical transcutaneous stimulation); 2 groups were not treated.

The difference between sham acupuncture and non treatment was  $-0.41$  (95% confidence interval  $-0.56, -0.24$ ) and the difference between the other physical placebos and non treatment was  $-0.26$  (95% CI  $-0.37, -0.15$ ) ( $p$  value = 0.007). In 2 studies, sham acupuncture was executed on areas which were distant from acupuncture points, in 2 studies on true acupuncture points and in another 2 studies on points which were not specified. Furthermore, 16 publications reported penetration of the skin with needles and in 3 studies there was no penetration of the needles. The heterogeneity between the various studies was at a high level in relation to the patients, the interventions and the measured outcomes. This factor indicates the necessity of interpreting the results with caution. However, the analysis demonstrates that on the average sham acupuncture is associated with greater positive effects in comparison to other physical placebo systems and is thus more effective.

Numerous RCTs conducted in 2011 and 2012 did not demonstrate any difference between the effectiveness of true acupuncture in comparison to sham or placebo acupuncture. The studies looked at the hormonal improvement and the frequency of ovulation in the polycystic ovary syndrome (Pastore et al. 2011, 84 patients); the frequency of hot flashes in menopause (Kim et al. 2011, 54 women); the improvement of vasomotor symptoms (Painovich et al. 2012, 33 women); the prevention of migraines (Li et al. 2012, 480 patients); osteoarticular pain (White et al. 2012, 221 patients); and carpal tunnel syndrome with improvement after treatment but with no significant difference compared to the placebo acupuncture group (Yao et al. 2012, 41 subjects).

Furlan et al. (2012) published a review and a meta-analysis on the efficacy of the treatment with complementary medicine and in particular acupuncture for pain in the neck (24 works) and for back pain (33 works). Furlan's work demonstrated that acupuncture was significantly more effective immediately and on short term and reduced the disability in comparison to non treatment but not in comparison to sham acupuncture. Other recent reviews found significant differences regarding the efficacy of acupuncture as opposed to usual care but not compared to sham acupuncture regarding fibromyalgia symptoms (Deare et al. Cochrane 2013) and backache symptoms in 2,678 patients (Xu et al. 2013).

The choice of a control group among the patients treated with sham or placebo acupuncture in a RCT cannot be considered an inactive control.

Another problem relevant to the research on the effectiveness of acupuncture pertains to the choice of therapeutic protocol. It is noted that there is no concordance between the diagnosis in Western medicine and that of Chinese Medicine. For example, according to the classification of G. Maciocia (2009) different clinical situations correspond to the nosology of migraine and therefore there are different protocols in relation to etiology (body build, psyche, work, sexual activity, nutrition, traumas, pregnancies, external pathogenic factors), to the meridian involved and to the relation between qi and blood. To understand the efficacy of acupuncture, it is necessary to divide the patients according to their various syndromes and this greatly increases the number of groups studied in order to obtain significant results. Since acupuncture is a holistic and global form of medicine, specific points for each patient should be added to the specific points of each syndrome.

Finally, the absence of a consensus on the method of diagnosis and the choice of points to be treated makes it difficult to compare research even when it is of high quality.

An example is the study of Alraek et al. (2011) which reported the consensus of 10 expert acupuncturists (Delphi Consensus) on diagnosis (identification of menopausal syndromes) and the therapy (the acupuncture points to be used) for the treatment of hot flashes. He then evaluated the clinical practice of acupuncturists who had been conveniently informed on the results of the consensus.

The consensus reached reviewed a list of 6 syndromes described by G. Maciocia (deficiency of Kidney yin and empty heat, deficiency of Kidney yang and empty cold; deficiency of Kidney yin and yang, deficiency of Kidney and Liver yin with increase of Liver yang, unbalance Kidney-Heart, accumulation of phlegm and stagnation of qi with the addition of Liver qi stagnation or Stomach heat). Since the menopausal syndrome is not described in the antique texts of Chinese Medicine, an approach to the symptoms was devised for acupuncturists in the 1960's. The same was done for other pathologies, one of which being anxiety.

In addition, the acupuncturists were free to diagnose any other syndrome without restrictions. They were requested to note the primary and secondary diagnosis for each treatment session. In this study 134 women in menopause were treated in 10 sessions and received written advice concerning lifestyle. The control group of 133 women only received indications in reference to lifestyle and no treatment with acupuncture.

After the initial diagnosis, each woman was to be treated with points selected according to the syndrome that was diagnosed. The acupuncturists were free to add individual points to treat other symptoms related to menopause, that is, symptoms included in WHO (Women's Health Questionnaire), such as depression, anxiety and insomnia. They were not going to treat symptoms that were not correlated to menopause; the needles could be manipulated.

During each session the acupuncturist had to note: the points used; the direction of the needle; the technique of insertion; if the Qi was felt; the reason for eventual changes in points in reference to the previous session; if other techniques were used (moxibustion, cupping, electroacupuncture) herbs; if treatment, such as specific exercises, tai chi, yoga, relaxation exercises, self massage were prescribed; if nutrition advice was given (few milk products, no wine or alcohol, little wheat, reduction of coffee, hot food and cooked food); if non nutrition advice was given (more physical exercise, reduction or no longer smoking, more rest, protection from cold and dampness etc.). The doctors also had to note the reaction to the treatment and any negative reactions.

The primary outcome was to reduce the frequency and intensity of the hot flashes in a 24 hour period and the secondary outcome was to improve the quality of life.

In this study, the first 5 syndromes, objects of consensus, were diagnosed as the most frequent. The points used were SP6, HT6, KI7, KI6, CV4, LU7, LI4, LR3, ST36, KI3. The average number of points stimulated per treatment were 6. One hundred and four different acupuncture points were used once or more than once. In the group of patients treated with acupuncture, 67 (50%) had a reduction in the number of hot flashes in 24 hours superior to 50%. There was a reduction in the intensity of these hot flashes ( $p < 0.001$ ) and a significant change in the quality of life (reduction of vasomotor symptoms, sleep disturbances and somatic symptoms). The patients who had a positive response to the treatment were equally divided into 5 groups according to syndromes (Borud et al. 2009). The authors conclude that the results were correspondent regarding the syndromes and mostly contradictory or not correspondent regarding the points used (the points used for two groups coincided only 28%).

An integral part of the study is the attempt at trying to explain the reasons for the inconsistencies observed: these differences depend on the dissimilarities of the approaches of the various schools and it was not understood whether this fact was or wasn't relevant to the clinical results.

In reference to the points treated for single diseases, it is necessary to develop a consensus to establish which points should be treated in each therapeutic treatment. This would permit a common therapeutic base in the various studies.

It is also essential to determine which therapeutic techniques are recommended for different pathologies: for example, in the current treatment of fatigue, it is preferable to heat points on the meridians rather than to use acupuncture.

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### *Adverse reactions and interactions*

There is not much research on the adverse effects of TCM, although in recent years the increasing use of acupuncture as a treatment option is supported by a large number of research on safety (MacPherson 2012). Not all the works published in the literature report the adverse effects: Capili et al. (2010) in a review of 10 RCTs (2005-2008) relating to back pain acupuncture report that in only 6 of these adverse effects were mentioned or discussed and in 4 of them it is not stated how the adverse effects were collected.

The risks of treatment of acupuncture and TCM are currently classified in accordance with the guidelines of the European Commission utilized for adverse effects of medicinal products (2005): they are defined very common (more than 1 in 10 people treated); frequent (between 1 and 10 out of 100 treated patients); infrequent (1 to 10 out of 1000 people treated); rare (between 1 and 10 in every 10,000 people treated) very rare (less than 1 in 10,000 treated patients). More studies on the adverse effects are related to acupuncture .

A review of papers published in the last 20 years (Ernst E et al. 2001) shows that the rate of serious adverse effects is very low (0.02 % - 0.1%) and is mainly linked to the insertion of the needles by professionals who are not graduates of medicine and have a low professionalism. A similar conclusion was reached by the National Institute of Health (USA) during the Consensus Conference on Acupuncture in 1999.

Only 2 cases of pneumothorax in 250,000 treatments are described. Regarding minor adverse effects, the most common ones are pain during the insertion of the needle (1 - 45 %), fatigue (2 - 41 %) and bleeding and/or hematoma and bruising (0.03 - 38%); in 86% of patients there was a feeling of relaxation. Mc Pherson et al. (2001) also carried out a study on the type and frequency of adverse effects consulting 1,848 professionals by mail, all were members of the British Acupuncture Council. The 574 who responded (referring to 34,407 treatments) did not report any serious adverse effect that is defined with recourse to hospitalization, permanent disability or death, but reported 43 significant minor adverse effects (1.3 per 1000 treatments) consisting of severe nausea and fainting (12), aggravation of symptoms (7), pain and bruising (5), emotional reactions (4). There were adverse reactions in the areas of insertion of needles such as mild hematoma (1.7 %), pain (1.2%) and bleeding (0.4 %).

White (2004) on the basis of existing international literature, examined 715 cases of significant adverse effects and concluded that the risk of serious adverse effects in acupuncture is very low, lower than that of other treatments and can be estimated as a percentage of 0.05 per 10,000 treatments and 0.55 per 10,000 patients.

Most of the 715 adverse events were constituted by trauma (pneumothorax) and infections (60% hepatitis B). Subsequently these events were further reduced by the use of disposable needles and better aseptic techniques. MacPherson et al. in the UK (2004) based on 6,348 completed questionnaires from patients treated with acupuncture, reported that 682 patients (10.7%) had experienced at least one adverse effect in 3 months (the most common symptoms were fatigue, pain during needle insertion and headache) which prevented them from repeating the acupuncture treatment.

The study of Melchart et al. (2004) in Germany included 9,429 medical acupuncturists of whom 7,050 reported adverse effects of 97,733 patients and approximately 760,000 sessions. They observed soft adverse effects in 7.1% of patients with pain during the needle insertion (3.28%) and hematoma. These two are the most frequent events. Witt et al. (2009) published an interesting prospective observational study in Germany on 229,230 patients who underwent an average of 10 acupuncture treatments by 13,579 medical acupuncturists. After the treatment, the patients documented adverse effects associated with acupuncture and if they needed a treatment for the adverse effect, they completed an additional standardized questionnaire. The study reports that 19,726 subjects (8.6%) showed adverse effects, of which 4963 (2.2%) had requested therapy. The most common were bleeding or hematoma (6.1%), pain (1.7%) and autonomic symptoms such as nausea and dizziness (0.7%). Two patients had pneumothorax and one showed a nerve injury which healed in 3 months. Adverse effects that indicate negligence and bad practice (broken or forgotten needles, pneumothorax, burns after moxibustion) accounted for 0.1% of all adverse effects. Furthermore, no side effect is related to the diagnostic phase, which is based solely on history, on the examination of the wrists and the tongue and physical examination. The authors' conclusions were that acupuncture performed by physicians is a relatively safe treatment and that informed consent might be useful to both patients and physicians.

Park et al. in 2010 described 3,071 treatments carried out in Korea by 13 Eastern acupuncturists on 2,226 patients. There were 99 adverse events (3.2 on 100 treatments), none of which was serious. The most common adverse events were bleeding (32%) hematomas (28%), and pain during the insertion of the needle

(13%). Acupuncture is therefore considered by the authors safe, when performed by operators with sufficient experience. Zhang et al. (2010) in a review of 115 articles (98 case reports and 17 case series) in Chinese reported 479 cases of adverse events, 14 people died. Adverse events were divided into traumatic, and other infections. The most frequent were the traumatic ones (296) classified into 7 subgroups among which 201 were pneumothorax (4 deaths), followed by 35 cases of subarachnoid hemorrhage (including 3 deaths), 150 faintings and 11 infections. (9 bacterial and 2 viral).

The most serious adverse events were represented by cardiovascular lesions, subarachnoid hemorrhage, pneumothorax and bleeding in the brain. The adverse events seen in China are also reported in other countries as a result of improper technique. The authors state that acupuncture can be considered safe when performed by well-trained professionals with experience and following the instructions of the guidelines. However, efforts should be carried out to find effective ways to monitor adverse effects and minimize the risk related to acupuncture. Zhao et al. (2011) conducted a study to evaluate the safety of acupuncture in China in 3 RCTs performed on 1,968 patients treated with acupuncture (use of disposable needles) by physicians with at least 8 years of training. 74 of these patients (3.76%) presented at least one adverse event, but so serious; subcutaneous hematoma (25.68%) and hemorrhage (37.84%) at the points of insertion of needles were the most common adverse effects.

It was found that older patients had a higher risk of adverse events and also males had slightly higher risk than females. The conclusions of the authors confirm that acupuncture is safe considering that the reduction of adverse events is achieved by improved healthcare environments and the preparation of acupuncturists. Regarding electroacupuncture (EA), in 2011 Cummings reported a case with adverse effects caused by the electric current. This effect is considered preventable with appropriate equipment that uses charge balanced waveforms.

Witt et al. (2011) reported adverse effects of acupuncture correlated with their economic impact in a study of 73,406 patients with back or neck pain. The costs were reported by insurance companies and were related to health care costs and indirect costs such as loss of work days. The results were that at least one adverse event had occurred in 5,440 patients (7.4%): the most frequent were bleeding, hematoma (546, 0.74%) and pain (429, 0.58%). 1422 patients (1.9%) needed treatment for adverse effects: self treatment was predominant (1.2%), followed by treatment with medication and/or a doctor (0.6%) and treatment in the hospital (0.03%). Adverse effects were present during (34.5%) and after treatment (66%).

Adverse effects persisted with a median of 3 days and were associated with higher costs (difference after 3 months: € 125 [38, 211],  $p = 0.005$  and after 12 months: € 285 [4, 566],  $p = 0.047$ ) if a medical treatment was required. The cost was 9-11% higher in the group with adverse effects than those without adverse effects caused by the expenses for medical and higher indirect costs.

Wheway et al. (2012) argue that safety in acupuncture has become a major public health problem in the UK and they have therefore looked for accidents from 2009 to 2011 in the database of the National Reporting and Learning System (NRLS). 428 adverse events were identified, the majority (95%) evaluated as mild or no damage. The others were: needles remaining in place (31%), dizziness (30%), loss of consciousness (19%), falls (4%), hematoma (2%), pneumothorax (1%).

Xe et al. (2012) published a review of 167 Chinese articles (the years 1956-2010) with 1,038 cases, 35 of whom died. The most frequent adverse events were syncope (468 cases), pneumothorax (307) and subarachnoid hemorrhage (64). The authors believe that the majority of these can be avoided with standardized clinical practices.

Xu et al. (2013) reviewed 117 researches (308 cases) on the adverse effects of acupuncture published in English in 25 countries between 2000 and 2011 (103 researches and 294 cases), moxibustion (4 cases and researches) and cupping (10 cases and researches). Regarding acupuncture, the highest number of cases (239) was made up of infections reported in 17 states (162 in Korea, 33 in Canada, 8 in Australia, 7 in Hong Kong, 6 in the U.S., Japan and Taiwan 5, 4 in UK) of which 193 (80%) were associated with mycobacterium, 19 to staphylococcus. In a previous review the authors had found that the major cause was created by infection of hepatitis. Of the 38 cases of diseases of organs and tissues identified, 13 were pneumothorax, 9 lesions in the central nervous system and peripheral nerves 4, 5 affected the heart. The conclusions are that although serious adverse events are rare, the acupuncture practice is not without risk and that guidelines are needed as the Clean Needle Technique (CNT) to reduce adverse events of acupuncture.

Stenger et al. (2013) reported that in their Department of Cardiothoracic Surgery in Denmark 2 cases of pneumothorax in patients treated with acupuncture occurred in 3 months. The authors want to bring attention to this complication that may be linked to acupuncturists who have not been trained well.

Sinh et al. (2013) reported adverse events recorded in Korea from 1999 to 2010 by the Food and Drug Administration, Consumer Agency and the Association of Traditional Korean Medicine: 1104 of these were related to acupuncture or moxibustion. The most frequent causes of adverse events 2006-2009 were infections (38.4 to 47.7%), pneumothorax (13.5 to 16.9%) and nerve damage (from 9 to 10.8%), while moxibustion burns accounted for 58 to 96.2%.

Among children, an interesting work by Jindal et al. (2008) reported adverse effects in 22 randomized controlled clinical trials: the most frequently reported were sedation (32%), pain caused by needles (26%) and neuropathy or disorders of the nervous system (16%). In 9 trials of 782 subjects aged 2 to 18 years, the incidence of adverse effects was estimated to be 1.55 per 100 treatments of acupuncture or sham acupuncture (the redness in the area of the needle was the most frequent), while that of serious adverse effects were 5.36 in 10,000 treatments (1 case).

In Canada, Adam et al. (2011) in a review of 37 works on acupuncture treatments in pediatric patients, reported 279 adverse events of which 25 were severe (12 cases of thumb deformity, 5 infections, and 1 case each of cardiac rupture, pneumothorax, compromise of a nerve, subarachnoid hemorrhage, intestinal obstruction, hemoptysis, reversible coma, and overnight hospitalization), 1 moderate (infection) and 253 mild (pain, bruising, bleeding, worsening of symptoms) with an incidence of 168 patients of 1,422 (11.8% [95% confidence interval: 10.1 to 13.5]). The authors conclude that the adverse effects associated with acupuncture needles practiced in pediatric patients are in most cases mild and usually caused by poor training of the operator and that, similarly to what is observed in adult patients, acupuncture is a safe practice when performed by adequately trained operators.

Gentry et al. (2012) did a retrospective study of 10 children (aged from 9 days to 9 months) who received acupuncture for stirring and feeding problems during hospitalization between 2008 and 2010 in Seattle (USA) and they do not report any observed complication.

Raith et al. (2013) carried out a review on safety and efficacy of acupuncture (on the point LI4) in preterm and term infants and included only 4 of the 26 studies (3 on infantile colic, 1 reduction of pain) with a total of 140 children. The conclusions were that acupuncture may be a safe option of non-pharmacological treatment to reduce pain and treat infantile colic in preterm and term infants, but it should only be performed by acupuncturists with adequate training and experience.

In patients with tumors, necessary specific safeguards applying to acupuncture therapy have always been considered necessary.

The guidelines S.I.O. (Deng 2009) in Recommendation 13 state: "Acupuncture should only be performed by trained operators and used with caution in patients with a tendency to bleed (grade of recommendation 1C); it is stated that it is prudent to avoid acupuncture in place of the tumor or of metastases in limbs with lymphedema, in areas with considerable anatomical changes from surgery and in patients with severe thrombocytopenia, neutropenia, or coagulopathy. Cancer patients require certified professionals who have experience in treating patients with malignant tumors".

The most recent literature data have shown positive results of treatment with acupuncture without adverse effects in patients with lymphedema, neutropenia and thrombocytopenia.

Ladas et al. (2010) reported no adverse event in the retrospective analysis of data from 32 children and adolescents with cancer (mean age 15.7 years) who underwent 237 sessions of acupuncture in which the 20, 8 and 19% were carried out in patients with severe, moderate and mild thrombocytopenia respectively, without the effects of bleeding. The excellent result apparently depended on a specific type of needle part of a skilled acupuncturist in a cancer center with an established program of acupuncture.

Lu et al. (2010) state that patients with cancer may have a higher risk of developing adverse effects caused by their impaired immune function (chemo-and radio-related) and increased susceptibility to infections and bleeding.

According to the guidelines acupuncture should not be used in the following situations presented by the patient: a neutrophil count less than 500/microL, platelets less than 35,000/microL, altered mental status, significant cardiac arrhythmias, unstable medical conditions (to be decided case by case).

Regarding treatment with other TMC techniques, the use of plum blossom reports that the most frequent adverse events are related to pain and bleeding, skin lesions, infections, easy bruising (bibliography on the subject was not found).

Following tuina massage, fatigue, damage from mishandling, infections and worsening of symptoms have been described. There are no specific articles on the subject in the literature.

Regarding the use of cupping, Cao et al. (2010) in a review of 6 papers, reported that in a research with acupuncture treatment together with cupping there were no adverse events. Kim et al. (2012) referred 3 minor adverse events (skin laceration, local and generalized pain) of 40 in users of video display treated for neck pain.

In 2012 Klempner in the US reported a case of cupping treatment in patients with advanced non-small lung cancer cells treated with bevacizumab without the appearance of any adverse event or bleeding skin.

Xu et al. conducted a review (2013) which reported 10 cases of adverse events (10 researched in 4 countries): they were keloid scars, burns (2) and bubbles (2), but also serious events such as acquired haemophilia A, haemorrhagic stroke after 14 hours from the cupping on the back and neck, anemia, and reversible cardiac hypertrophy in 2 subjects who had undergone cupping, and bleeding.

Moxibustion can cause burns: 28 cases have been reported (4/1000) by McPherson (2001), 14 cases by Witt (2009). These adverse effects indicate negligence or fault of the operator.

Lee et al. (2010) conducted a review including in a meta-analysis only 4 papers (of 515 found in the literature) on moxibustion used to treat cancer for a total of 112 patients. None of these publications evaluated adverse events. Xu et al. (2013) conducted a review that reported 4 cases of adverse events (4 works in Canada, USA, and Korea): they were bruising, burns, spinal epidural abscess and basal cell carcinoma; the last 2 adverse events were related to moxibustion self-administered.

## Conclusions

In adults, according to the international literature, adverse events consist in transitional fainting, pain, bruising, dizziness, addiction to acupuncture, skin infections or allergies to metal needles and burns (in the case of moxibustion). Some rare cases of pneumothorax, hepatitis, spinal injuries, bacterial endocarditis are also described. These adverse effects can all be avoided with the application of usual aseptic techniques or by choosing a different depth of the needles according to the areas of the body treated.

The majority of authors conclude, on the basis of the literature, that acupuncture is safe when performed by well trained professionals. Serious adverse events have been reported in the literature but seem to be really rare. Precautions should be taken including follow-up and prevention of infections to reduce the rates of serious adverse events.

The publication of the National Cancer Institute (NCI) on adverse effects of acupuncture updated to 08/06/2013 states that the serious adverse effects of acupuncture are rare. The reported adverse events and infections appear to be related to violations of the procedure for sterility, negligence of the operator or both causes. Minor adverse effects (pain, hematoma, tiredness etc.) can be minimized by appropriate treatment of the patient, including local pressure and massage in the place of insertion of the needle after the treatment.

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## ***Methodology of the discipline in oncology***

The fundamental characteristic of traditional Chinese medicine (TCM) is the holistic global vision of the organism which is considered to be composed of a single mind/body entity closely linked to the environment surrounding it.

In cancer care, as well, it is believed that the pathologies are caused by a disturbance in the balance of Yin and Yang which then affects both Zang and Fu. This energetic disturbance can be caused by external factors, internal factors (changes in emotions and feelings, incorrect diet or genetic causes), factors that are partly internal and partly external (external causes can influence psychological disorders).

These changes lead to a block of Qi which is then transformed into heat or heat/dampness. The therapeutic treatment of the tumour induces an energetic imbalance; surgery causes a Qi deficiency, while chemotherapy and radiotherapy cause an increase in heat.

In all cases, there are adverse side effects of the therapy. The majority of the literature considers the efficacy of TCM in treating these adverse side effects. It must be remembered that in treating cancer diseases, according to the principles of TCM, the origin of the disease must always be dealt with. Thus, a treatment must be provided that is related to the cause and location of the disease, and to the patient's energetic typology.

As TCM considers prevention and the choice of lifestyle as techniques of self-cure, particular importance is given to the correct diet, sleep habits, movement and anything that can increase the self-defence ability of the body.

## ***Glossary***

**Acupuncture points:** energetic points called "acupoints" are located along the meridians. When these points are stimulated (with needles, moxibustion or massage) they produce a local effect or an effect in another area of the body. The points do not have an anatomic entity but are the location of the least resistance and greater electrical conductance. There are also points which are not on the meridians, also called "extra points and local points" which are particularly painful to pressure (called "Ashi points").

**Meridians:** are energetic channels which are distributed throughout the body and have multiple functions such as linking man to the outside world, insuring unity and coordination between internal and external regions, higher and lower regions and the organs and the viscera. They also have a protective function.

**Nomenclature of the meridians referred to in the text:** the meridians have different denominations depending on the various schools of TCM. In general the international classification (IC) is used, the Chinese pinyin (phonetic transcription of the ideogram), or the French definition. These definitions and their corresponding names are listed below.

LV	Liver	Tsou jue yin	F	foie
GB	Gall bladder	Tsou shao yang	VB	vesicule biliaire
HT	Heart	shou shao yin	C	coeur
SI	Small intestine	shou Tae yang	IG	intestin grêle
PC	Pericardium	shou jue yin	MC	maitre coeur
SJ	San jiao	shou shao yang	TR	triple réchauffeur
SP	Spleen	Tsou Tae yin	RT	rate
ST	Stomach	Tsou Yang ming	E	estomac
LU	Lung	shou Tae yin	P	poumon
LI	Large intestine	shou Yang ming	GI	gros intestin
KI	Kidney	Tsou Chao yin	RN	rein
BL	Bladder	Tsou tae yang	V	vessie
CV	Conception vessel	Ren Mai	VC	vaisseau conception
GV	Governing vessel	Du Mai	VG	vaisseau gouverneur

## **Herbal Medicine**

### ***Definition and biological effects of herbal medicine***

For centuries traditional medical systems (TMS) were the primary medical system in the countries of origin, and now despite the present dominance of the Western scientific medical model, citizens and health caregivers are starting to rely and trust TMS, substituting conventional scientifically proved therapies with unconventional ones.

Generally cultural rootedness enduring and wide-spread use of TMS may indicate safety, but not the efficacy of the treatments especially in herbal medicines where tradition is almost completely based on remedies containing active principles at very low and ultra low concentrations, or relying on magical-energetic properties of sun, moon, etc.

Herbal medicine has become a popular form of healthcare. Even though several differences exist between herbal and conventional pharmacological treatments, herbal medicine needs to be tested for efficacy using conventional trial methodology and several specific herbal extracts have been demonstrated to be efficacious for specific conditions. Nevertheless, the public is often misled to believe that all natural treatments are inherently safe. Herbal medicines do carry risks, so research in this area must be intensified.

The main question that has not been often answered satisfactorily deals with the triad absorption/metabolism/efficacy of herbs and their extracts and is actually an important unsolved problem in judging their many alleged health effects (Firenzuoli F. 2004).

Mind–body medicine can be considered as a complementary or an alternative mode to traditional Western medicine, and a variety of other modes of interventions that are presently used in a CAM paradigm may act in large part via the mind–body connection (Chiapparelli F. 2006). Trusting in the traditional principles of a medicine that is deeply rooted in a culture can represent a type of mind-body connection having a real pharmacological activity through a placebo like effect. So a successful treatment is often the consequence of both types of treatments acting synergistically. Nevertheless, efficacy assessment of traditional medicines cannot be different from that of conventional medicine.

Long-term use of medicinal herbs enables a process of selection but limited and only partial, of short and medium-term safe remedies, that do not match with modern issues relative to the interferences with synthetic drugs. Treatment selection is often limited because of the multiple meaning of efficacy in relation to pathology and diseases in different cultures.

The transfer of a medical concept to a new country may be misleading and lead to deep modifications of its medical-therapeutic and cultural essence, especially if a remedy is part of a TMS, and modifications follow adaptation to local conditions and cultural habits.

Botanical products used in cancer care can be raw herbs (whole or cut plants or isolated plant parts); herbal materials (processed herbs, juices, resins, or oils); or herbal preparations (purified or extracted components mixed with other materials). The finished products may contain multiple ingredients and may take the form of powder, liquid, pills, or topical preparations. Most herbs have a long history of use for specific diseases in traditional medicine and are mostly marketed based only on their real or claimed traditional uses. Some existing herbs are investigated for new uses, and there are studies on botanicals for novel indications that are not used commonly as food or drugs.

### ***Evidence Based Medicine and herbal medicine***

Several factors are important in determining the outcome of any traditional treatment, both in experimental and clinical settings including *forma mentis*, beliefs, knowledge and practical abilities of the provider, as well as the positive or negative prejudices of the patient with respect to the provider of the therapy, cultural differences in the acceptability of the treatment and adherence to it, the patient–doctor encounter, and differences in access to other treatments (Cardini F. 2006).

In the age of globalization and of the so-called ‘plate world’, assessing the ‘transferability’ of treatments in herbal medicines is not a relevant goal for clinical research, while efficacy and safety should be based on the normal patterns of mainstream clinical medicine. The CONSORT statement for trials of herbal medicines (Gagnier JJ. 2006) can be a very important paradigm to follow; and in fact, it elaborated 9 of the 22 CONSORT checklist items to enhance their relevance to trials of herbal interventions, including minor recommendations for eight items. Besides, Nahin and Straus from the National Center of Complementary and Alternative Medicine (NCCAM) proposed a pragmatic schema for allocation of resources in the USA.

The authors recommend five criteria: quantity and quality of available preliminary data to help determine the most appropriate type of research; extent of use by the public; public health importance of the disease being treated; feasibility of conducting the research; cost of the research (Firenzuoli F. 2007).

Many cancer patients are using herbal medicines during all phases of cancer treatment, and few topics are more controversial in integrative oncology. Despite increasing use by cancer patients, most conventional oncologists and other specialists recommend complete avoidance of all supplements throughout all phases of cancer care. This stance by conventional health caregivers is a major limit to disclose the use of herbal supplements in patients and can largely increase patients' risk. Scientific literature in this area does not support the interdiction and clamor of some clinicians. Evidence of harm remains largely theoretic, contrary to evidence of benefit warrant, active recommendation, and medical competence. The main problem remains the lack of any knowledge both by patients (too optimist) and health caregivers, often physicians (too pessimist).

Efforts to subject botanicals to rigorous scientific research began in the last decade, and many problems are associated with botanicals research: getting the correct study agents, finding real experts of herbal medicines, selecting appropriate study methods and clinical trial designs and navigating through regulatory obstacles. Evidence-based medicine researches remain the base to validate traditional uses and to facilitate new drug development and concerted efforts of governmental agencies and industry, and are essential to ensure continuance of high-quality herbal research on clinical efficacy and toxicology especially in cancer care.

It is very important to keep in mind the differences between explanatory and pragmatic studies, and the concepts of efficacy and effectiveness; efficacy is the benefit a treatment produces under ideal conditions, often using carefully defined subjects, while effectiveness defines the benefit the treatment produces in routine clinical practice. Explanatory trials evaluate the efficacy of a treatment under controlled conditions that optimize isolation of the treatment effect through design features, such as a control or placebo, randomization, standardized protocols, homogeneous samples, blindness; these type of studies often represent the treatment of a particular patient, that is not the usual patient that enter a medical office. Pragmatic studies do not provide conclusive information on the specificity of the treatment effect but they have some interesting characteristics (Firenzuoli F. 2007).

Pragmatic trials (PT) are designed to determine how effective a treatment actually is in everyday practice; while explanatory trials are designed to determine whether a treatment has any efficacy, usually compared with placebo under ideal conditions. PT answers questions about the overall effectiveness of an intervention, and cannot study the contributions of its different components. The participant in these studies have to be representative of the wider population because results need to be generalized; wide criteria of inclusion are needed, so that patients having more medical diseases or taking different medications are included.

It would be more satisfactory and sensible to choose conditions where conventional treatment is often unsatisfactory like irritable bowel syndrome or panic crises. In PT it is not usually mandatory to use a placebo, while it is needed with both arms of the trial on normal practice, since the aim is to produce an evidence to facilitate a real practical choice. The treatment protocol is more complex because patients with wider criteria are included; therefore a larger sample of patients is necessary and may need a handbook that defines parameters for treatment. The main advantage of PT is that they can deliver evidence of effectiveness directly in clinical practice. Nevertheless, they have important methodological limits: most of all the lack of placebo and blindness, increased costs, the need for several therapists, more complexity and lack of clarification about the mechanism of action; but PT should be seen not as an alternative to explanatory studies, but as a mandatory complement that defines and improves evidence primarily coming from explanatory trials, the only ones that can reliably confirm efficacy (Firenzuoli F. 2007).

### ***Adverse reactions and interactions***

The efficacy of drug therapy depends on many factors related to a drug's pharmacokinetic and pharmacodynamic properties, which can be modified by differences in genetic polymorphisms, age, gender, circadian rhythms, intestinal bacteria, pathophysiological conditions, pharmaceutical dosage form and xenobiotics (Colalto C 2010).

Most important is co-administration of traditional drugs and herbal medicinal products, because of unexpected interactions. The high risk inherent to drug interactions is well known, even although various studies have indicated that 14–31% of prescription drug users combine herbal products with traditional medicines, even in Israel 45% use concomitantly herb and synthetic drugs. The growth in sales of herbal medicinal products over recent years has consequently led many researchers to turn their focus to the

pharmacological mechanisms underlying herb–drug interactions (Colalto C 2010).

One aspect of safety is the risk of adverse effects due to pharmacological interactions between herbal medicinal products and conventional therapies is often underestimated for two main reasons: consumers generally consider herbal medicinal products safe and holistic because of their natural origin, and they are often taken without consulting a physician and just reading indications on the product label, because they are self-care products, and because health caregivers often have scarce knowledge of herbal products.

In the United States, more than 100,000 deaths per year may be caused by drug interactions, but these are not easily recognizable because of factors associated with individual variability, history of use, differences in clinical conditions, etc.; so in the case of herbal medicinal products, recognizing interactions may be very complicated because of the still higher number of variables involved. Many products are available on the market, and plant extracts contain many different types of chemical compound with various pharmacological properties. Furthermore, the composition of an extract may vary depending on its geographic origin, the stage of growth of the plant at harvest, post-harvest treatments, standardization criteria, and stability. In some cases, herbal medicinal products may also be subject to contamination and errors in identification and concentrations. For this reason, some investigations of interactions include an independent analysis of the major phytochemicals, these not rarely revealing values different from those on the label.

In today's drug development process of synthetic drugs, the assessment of drug-drug interactions comprises a systematic combination of *in vitro* and *in vivo* investigations aiming at identifying possible interactions with *in vitro* screens which are then followed up by dedicated *in vivo* studies. Thereby, the role of *in vitro* investigations and perhaps nonclinical pharmacokinetics interaction studies is only to inform the clinical drug-drug interaction program, not to serve as substitutes for clinical drug-drug interaction studies. Nonclinical studies in animals are generally discouraged due to the marked species differences, which renders extrapolation of such results to humans difficult.

Extrapolation of *in vitro* data to the *in vivo* situation by physiologically-based pharmacokinetic modelling, which is being used to guide *in vivo* drug-drug interaction trials and drug labelling, is difficult to apply to herbal drugs because it requires I) the identification of the herbal component(s) acting as a perpetrator of the herb-drug interaction, II) content uniformity of these components within and across marketed products, III) well designed *in vitro* studies characterizing the drug-drug interactions potential, and IV) most importantly, knowledge about the systemic bioavailability and human pharmacokinetics of this (these) component(s). Information on the pharmacokinetics characteristics of herbal components, however, is often lacking with only a few exceptions. Therefore, it is not surprising that the extrapolation from *in vitro* herb-drug interaction data, in most cases, did not correctly predict the outcome of the corresponding *in vivo* study.

It is, however, estimated that CAM-anticancer drug interactions are responsible for substantially more unexpected toxicities of chemotherapeutic drugs and possible under treatment seen in cancer patients. Induction of drug-metabolizing enzymes and ATP-binding cassette drug transporters can be one of the mechanisms behind CAM-anticancer drug interactions. Induction will often lead to therapeutic failure because of lower plasma levels of the anticancer drugs, and will easily go unrecognized in cancer treatment, where therapeutic failure is common. Recently identified nuclear receptors, such as the pregnane X receptor, the constitutive androstane receptor, and the vitamin D-binding receptor, play an important role in the induction of metabolizing enzymes and drug transporters.

The table 1 provides a summary table on the known interactions *in vitro* and *in vivo* of medicinal plants. It shows the drugs that have been seen or could potentially interact with medicinal plants investigated. In addition, to facilitate understanding and where present, it is reported the opinion of the EMA or other experts about the uses and/or interactions as well as the “reversed grading” proposed by the Tuscan Network for Integrated Medicine, so called because the main level of evidence corresponds to the main level of negative recommendation and structured as follows:

<b>Reversed Grading</b>	<b>Evidence</b>	<b>Recommendation</b>
IA	Laboratory evidence <i>in vitro</i> and <i>in vivo</i> and clinical reports of pharmacological interference with proven risk of effectiveness reduction of anticancer therapy	ABSTAIN from prescription during oncological therapy
IIA	Only in vitro and in vivo laboratory evidence without any signalling of clinic interference, and no research carried out to study the clinical interactions in oncology	Evaluate whether ABSTAIN or NOT from prescription on the basis of a risk/benefit assessment of therapy. Stop the administration in presence of reduced effectiveness or ineffectiveness of anti-cancer therapy and/or adverse effects
IIB	Only in vitro and in vivo laboratory evidence, without any signalling of clinic interference in spite of the research carried out	PRESCRIPTION and monitoring. Stop the administration in presence of reduced effectiveness or ineffectiveness of anti-cancer therapy and/or adverse effects
IIIB	Only in vitro laboratory evidence (NOT in vivo), without any signalling of clinic interference in spite of the research carried out	PRESCRIPTION and monitoring. Stop the administration in presence of reduced effectiveness or ineffectiveness of anti-cancer therapy and/or adverse effects
IVB	No evidence of negative interference rather, positive evidence of oncological-therapy potentiation	PRESCRIPTION and monitoring. Report to the reference oncologist for any reformulation in the dose of anticancer treatment and/or adverse effects
VB	No evidence of negative interference and positive evidence of oncological-therapy potentiation	PRESCRIPTION. Report to the reference oncologist

**Reversed Grading.** I-V grade of evidence correlated to risk. A (Abstain), B (Prescription).

As indicated in “Reversed Grading”, the proposal is to associate A and B respectively to the recommendation “ABSTAIN” and “PRESCRIPTION”; in the case of IA the abstention must be referred to the whole period of administration of anti-cancer therapy.

Herb	Evidences <i>in vitro</i>		Evidence <i>in vivo</i>	Evidences on Human			Possible interactions	Advices	EMA and other sources	Reversed Grading by TNIM (Tuscan Network for Integrated Medicine)
	transporter	metabolism	On animals	transporter	cythochrome	Reported Clinical effect on chemotherapies				
<i>Allium sativum</i> (Common name: Garlic)	P-gp↓	CYP3A4↓	Glutathione S-transferase ↑  Quinone reductase ↑		CYP3E1,2E1 ↓		<b>Possible:</b> bisantrene, dacarbazine, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib, busulfan, doxorubicin, carboplatin, cisplatin, cyclophosphamide, thiotepa, actinomycin D, daunorubicin, docetaxel, etoposide, irinotecan, mitoxantrone, paclitaxel, teniposide, topotecan, mitomycin C, epirubicin			IIA
<i>Aloe</i> spp		CYP3A4, 2D6↓					<b>Possible:</b> tamoxifen, doxorubicin, vinblastine, teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan,		No documented negative interactions with anticancer therapy	IIB

							tipifarnib, gefitinib, imatinib			
<i>Boswellia serrata</i>		CYP 1A2/2C8/2C9 /2C19/2D6, 3A4↓					<b>Possible:</b> dacarbazine, cyclophosphamide, ifosfamide, paclitaxel, Teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib, tamoxifen, doxorubicin, vinblastine	Possible improved bioavailability by more pathways Enhanced risk of toxicity	No interferences with anticancer therapy pointed out by EMA, but “quality safety and efficacy will be necessary before a market authorization will be released”	IIIB
<i>Camellia sinensis</i> (Common name: green tea)	P-gp↓ OATP-B↓	CYP1A1,1A2 ↓↑	CYP3A4 ↓↓		CYP3A4↓	Folic acid ↓↓	<b>Possible:</b> dacarbazine, teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, folic acid tipifarnib, gefitinib, imatinib, actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, teniposide, topotecan, vinblastine, vincristine, tamoxifen, mitomycin C, tipifarnib, epirubicin, bisantrene	Possible improved bioavailability by more pathways	No interferences with anticancer therapy pointed out by EMA	IIB
<i>Capsicum spp</i> (Common	P-gp ↓				CYP3A4 ↓↓		<b>Possible:</b> teniposide, etoposide, epipodophyllotoxin, cyclophosphamide,		No pharmacovigilance action is recommended at this	IIB

name: hot pepper)							ifosfamide, vindesine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib, Actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, topotecan, vinblastine, vincristine, tamoxifen, mitomycin C, tipifarnib, epirubicin, bisantrene		time in relation to herbal medicinal products containing Capsicum/capsicin	
<i>Citrus paradisi</i> (Common name, grapefruit)	P-gp ↓	CYP3A4 ↓↓		OATP1A2 ↓	CYP3A4 ↓↓	etoposide↓↓	<b>Possible:</b> teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib, actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, topotecan, mitomycin C, tipifarnib, epirubicin, bisantrene	Possible improved bioavailability by more pathways Enhanced risk of toxicity	No data available in EMA website, but a review on drug interactions by:  Bailey DG, Dresser G, Arnold JMA. Grapefruit and medication interactions: forbidden fruit or avoidable consequences? <i>CMAJ</i> 2012	IA

<i>Curcuma longa</i>		CYP3A4 ↓↓, Sulfotransferase ↓, UGT ↓	P-gp ↓↓, CYP3A4 ↓↓, UGT ↓↓			gemcitabin ↑	<b>Possible:</b> Teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tipifarnib, gefitinib, imatinib, irinotecan, epirubicin, topotecan, etoposide, flavopiridol, tipifarnib, actinomycin D, daunorubicin, doxorubicin, mitoxantrone, paclitaxel, teniposide, tamoxifen, mitomycin C, tipifarnib, epirubicin, bisantrene		In EMA website a Phase I trial with 25 patients with various high risk of cancerous conditions and no toxic reactions were observed (Dose up to 8 gr. daily)  FDA classifies turmeric as a substance generally recognized as safe	IVB
<i>Echinacea spp</i>	OATP-B ↓				1A2 ↓, 2C9 ↓	etoposide ↑	<b>Possible:</b> Dacarbazine, etoposide, Cyclophosphamide, ifosfamide	Improved bioavailability of etoposide	Safeness of <i>Echinacea</i> in short term therapy but no data available in long term. “... no appears to be a risk to consumers”	IVB
<i>Ginkgo biloba</i>	P-gp ↓, OATP-B ↓	CYP2C9 ↓↓	CYP1A2 ↑	P-gp ↓↓	CYP2C19 ↑↑; CYP3A4 ↑		<b>Possible:</b> Dacarbazine, cyclophosphamide, ifosfamide, teniposide, etoposide, epipodophyllotoxin, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib, actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel,	Mixed interference		IIA

							topotecan, vinblastine, vincristine, tamoxifen, mitomycin C, epirubicin, bisantrene			
<i>Glycyrrhiza glabra</i>	P-gp ↓	2B6,2C9,3A4 ↓					<b>Possible:</b> Actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, teniposide, topotecan, vinblastine, vincristine, tamoxifen, mitomycin C, tipifarnib, epirubicin, bisantrene	Possible improved bioavailability by more pathways	In the EMA website: “Clinical studies show that short-term use (not more than 4 weeks) is safe. However, chronic use can cause hypokalaemia, hypertension (corresponding dose: 80-100 mg of glycyrryzic acid), and, more rarely, cardiac rhythm disorders”. Concomitant use with diuretics, cardiac glycosides, corticosteroids, stimulant laxatives or other medications which may aggravate electrolyte imbalance is not recommended	IIA

<i>Glycine max</i>		2C9,3A4 ↑			CYP1A2↓2A6↑		<b>Possible:</b> Cyclophosphamide, ifosfamide, tegafurteniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib, dacarbazine	Possible improved bioavailability by more pathways  Mixed interference		IIB
<i>Hypericum perforatum</i>	P-gp ↑			P-gp ↑↑	CYP3A4 ↑↑, 2E1 ↑↑,	Irinotecan↓ ↓; imatinib↓↓, docetaxel ↓↓	<b>Possible:</b> Dacarbazine, teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib, Actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, topotecan, tamoxifen, mitomycin C, tipifarnib, epirubicin, bisantrene	Mixed interference; reduced bioavailability of many drugs	From EMA monograph: "In the case of a daily intake of hyperforin less than 1 mg and of a duration of use not longer than 2 weeks, no clinically relevant interactions are to be expected (...) Patients taking other medicines on prescription should consult a doctor or pharmacist before taking Hypericum"	IA

<i>Rhodiola rosea</i>	P-gp↓	3A4↓					<b>Possible:</b> Teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib, Actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, teniposide, topotecan, vinblastine, vincristine, tamoxifen, mitomycin C, tipifarnib, epirubicin, bisantrene		From Assessment report on <i>Rhodiola rosea</i> L (EMA 2012): “Neither clinical data nor case reports on interactions are published. Zubeldia et al.(2010) propose <i>Rhodiola rosea</i> as a viable alternative treatment for the symptoms of short-term hypothyroidism in patients with differentiated thyroid cancer who require hormone withdrawal”	IIIB
<i>Panax spp</i>		3A4,2C9,2C19, 2D6 ↓↑				imatinib↓ (*)	<b>Possible:</b> Cyclophosphamide, ifosfamide, doxorubicin, vinblastine, Teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib	Mixed interference, reduced bioavailability of imatinib	From Assessment report on <i>Panax ginseng</i> (EMA2013): “Studies in healthy human volunteers showed no clinically relevant impact on CYP3A, CYP1A2, and CYP2D6. Case reports on interactions could not be verified in clinical trials. Therefore, the benefit/risk balance is considered positive”	IIB

<i>Piper nigrum</i>		AHH,UDP↓↓		P-gp↓	CYP3A4↓	rifampicin ↑	<b>Possible:</b> actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, teniposide, topotecan, vinblastine, vincristine, tamoxifen, mitomycin C, tipifarnib, epirubicin, bisantrene, teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinorelbine, paclitaxel, docetaxel, tamoxifen, tipifarnib, gefitinib, imatinib	Possible improved bioavailability by more pathways	No published data of interactions with anti-cancer treatment in EMA website and PubMed	IIA
<i>Serenoa repens</i>		3A4 ↓, 2D6 ↓, 2C9 ↓					Cyclophosphamide, ifosfamide, tamoxifen, doxorubicin, vinblastine, teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib	Possible improved bioavailability by more pathways	EMA data available only in veterinary medicine	IIIB

<i>Silybum marianum</i>	P-gp ↓				CYP2C9↓	Irinotecan (*)	<b>Possible</b> :Cyclophosphamide, ifosfamide, actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, teniposide, topotecan, vinblastine, vincristine, tamoxifen, mitomycin C, tipifarnib, epirubicin, bisantrene	Interference on irinotecan metabolism	No published data of interactions in EMA website	IIB
<i>Valeriana officinalis</i>	P-gp ↓	CYP3A4 ↓					<b>Possible:</b> Teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib, imatinib, actinomycin D, daunorubicin, docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, teniposide, topotecan, vinblastine, vincristine, tamoxifen, mitomycin C, tipifarnib, epirubicin, bisantrene		From Community Herbal Monograph on <i>Valeriana officinalis</i> L (2009): “Only limited data on pharmacological interactions with other medicinal products are available.  Clinically relevant interaction with drugs metabolised by the CYP 2D6, CYP 3A4/5, CYP 1A2 or CYP 2E1 pathway has not been observed.  Combination with synthetic sedatives requires medical diagnosis and supervision	VB

Tab. 1. Summary table of interactions *in vitro* and *in vivo* known about medicinal plants. (\*) The interaction was reported only for this drug.

### Chinese Herbal Medicine

Traditional Chinese Medicine (TCM) formulas with fixed combinations rely on "sovereign, minister, assistant and guide" and fuzzy mathematical quantitative law, leading to greater challenges for the identification of active ingredients. Transformation and metabolic studies involving the Phase I drug-metabolizing enzyme cytochrome P450 might potentially solve some of these challenges. The pharmacological effects cannot be attributed to one active ingredient in TCMs, but integrated effects resulting from the combined actions of multiple ingredients.

Often it is only after medium and long-term administration that most ingredients exert their actions, which can result in prolonged exposure to herbs in patients. Unlike synthetic drugs, experimental determination of the absorption and disposition properties is not commonly carried out for TCMs. Moreover, the use of TCM as injections is an innovation aimed to improve efficiency in extensive clinical use in Mainland China. Therefore, in recent years, cases of adverse drug reactions mainly concerning allergic reactions involving TCMs such as ShenMai injection and Qing Kai Ling injection have been reported, which have attracted attention with regard to the legal responsibilities for TCM approval. The lack of information on the ADME characteristics, especially the metabolic stability and interaction potential between CYPs and herbs, increases ADR occurrence due to TCM.

The safe use of Chinese herbs depends on following the dicta prescribed by the ancient canon. There are caveats about the use of specific herbs in Chinese medicine practice. For example, the "18 incompatible herbs" and the "19 antagonistic herbs," when used in combination, will produce toxic reactions, harmful side effects, or a diminished therapeutic effect. The ancient wisdom about herb-herb interaction provides an alert that inappropriate combinations of herbs will bring out negative results; it also suggests that mixing herbs with chemotherapy drugs could also generate negative effects. Therefore, the negative effects from using herbal medicines could come from quality issues of herbal medicine or incompatible combinations of herbal medicine with other herbs or with new chemotherapeutic agents. Because cancer patients are already in a state of weakened health, safety issues about the use of herbal medicine in clinical practice need close attention.

### Herb adverse reactions in cancer patients

In literature, very few ADRs due to herbs respect to chemotherapy are reported; the suspect is that are probably underreported, although we think that ADRs are substantially less severe than synthetic drugs.

Herb	Concomitant treatment	Neoplastic diagnosis	ADR
<i>Aristolochia fangchi</i>	Low calorie diet	none	Urothelial cancer
<i>Aronia melanocarpa</i>	trabectedin	metastatic sarcoma	Rhabdomyolysis
<i>Aristolochia longa</i>	chemotherapy	metastatic cancer	Fatal renal failure
<i>Echinacea</i>	etoposide	non small cell lung cancer	Profound thrombocytopenia
<i>Panax ginseng</i>	imatinib	leukemia	Hepatotoxicity
<i>Sophora subprostrata</i>			Necrotizing encephalopathy
<i>Catharantus roseus</i>	None, used as alternative treatment	hepatoma	Severe pancytopenia
<i>Selaginella doederleinii</i>	None, used as alternative treatment	cholangiocarcinoma	Severe pancytopenia

### Conclusions

The advantages and disadvantages of adding herbal drugs to established useful chemotherapies in psychologically frail patients looking for natural detoxifying, relaxing, anxiolytic, adaptogenic substances should be carefully weighed.

It is therefore necessary that oncologists are correctly informed as to the potential benefits of herbs as well as their possible interactions and interferences with anti-cancer therapies in order to avoid the risk of eliminating or on the contrary of excessively enhancing the therapeutic effect of anti-cancer therapies. Therefore, a multidisciplinary team approach aimed at integrating medicinal plants or their active components with the appropriate cancer therapy should be encouraged.

This approach would permit the monitoring of the patient for any possible drug interaction and/or adverse effects. It would improve the quality of life as a consequence of medicinal plants integration in the treatment of cancer-related symptoms reducing also, when possible, the toxicity of synthetic drugs and their impact on the patient.

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### *Methodology of the discipline in oncology*

There is a pressing need to connect the evidence-based use of medicinal plants and their derivatives to emerging strategies of medicine and conceptual models of healing, which aim to be culturally sensitive in nature and take into account the cultural and historical backgrounds of patients.

A key turning point in this challenge has come from the interdisciplinary science of medical ethnobiology, which addresses traditional/folk uses of plants and other remedies, in both rural and urban environments.

Botanicals share the same metabolic pathway and transport proteins, (including cytochrome P450 enzymes - CYP, glucuronosyl transferases - UGTs, P-glycoprotein - Pgp, breast cancer resistance protein and multi-drug resistance proteins) with over-the-counter and prescription drugs. Thus, there is an increase in the likelihood of drug-botanical interactions like inhibition and/or induction of both the metabolism and pharmacokinetics of anticancer agents. Today, there are increasing reports on the interaction of herbal medicines with anticancer agents, and unfortunately only limited data exist on the safety and efficacy of many botanicals because of the paucity of scientific researches.

### *Glossary*

**Adaptogen:** the term “adaptogen” describes substances considered to help symptoms like tiredness and irritability by bulding up “resistance to stress”.

**Drug:** part of the plant (fresh or dried) that contains the greatest amount of substances with pharmacological properties.

**Dry extract:** the dry extract is a concentrate of active ingredients which are, generally, obtained by drying and concentrating the fluid extracts obtained from plants.

**Essential Oil:** an essential oil is a concentrated hydrophobic liquid containing volatile aroma compounds from plants.

**Herbal medicines:** the herbal medicines are substances derived from plants, leaves, root and flowers used for medicinal purposes in the prevention or management of a human condition.

**Mother tincture:** it is an extract of a plant prepared with standardized amount of alcohol and water.

**Phytotherapy/Herbal medicine:** the study of the medicinal use of plants.

**Standardized extract:** botanical preparation in which one or several active components are present in the final product at pre-determined concentration(s).

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## Homeopathy

### *Definition and biological effects of homeopathy*

The fundamental idea of homeopathy is the Similarity (or Similia) Principle: *Similia similibus curentur* (Let like be cured by like), stated by the German physician Samuel Hahnemann (1755–1843) in 1796. This implies that substances capable of causing disorder in healthy subjects are used as medicines to treat similar patterns of disorder experienced by ill people. Hippocrates too, wrote of curing 'like with like' more than 2,000 years ago but it was formally systematized by Hahnemann who viewed health as a dynamic process tending to maintain a state of optimum equilibrium. Homeopathic medicines are aimed at directing and stimulating the body's self-regulatory mechanisms.

A second principle in homeopathy is the individualization of treatment for the patient. The characteristics of the chosen medicine should be as similar as possible to the characteristics of the illness in the patient. This closest match is called the 'simillimum'. Similarity may be at the 'whole person' level, taking into account the symptoms and signs of the disease, the patient's physical build, personality, temperament and genetic predispositions. This high level of individualization is not always required: 'similarity' may be at a more specific, local level, especially in the treatment of acute conditions.

A third principle is the use of the minimum dose. The doses used in homeopathy range from those that are similar in concentration to some conventional medicines to very high dilutions containing no material trace of the starting substance – the latter are referred to as 'ultra-molecular' dilutions. Vigorous shaking of the solution together with impact or 'elastic collision' (known as succussion) during the manufacturing process is a key element in the production of homeopathic medicines.

### *Worldwide Diffusion Data*

Homeopathy is a very common medical discipline used worldwide. In India, for instance, homeopathic education and practice are regulated through an Act of Parliament, "The Homoeopathy Central Council Act, 1973", and the Central Council of Homoeopathy has been constituted by Government of India under the provisions of Homoeopathy Central Council Act, 1973 (Ayush annual report final 1973). With its 659 manufacturing units, India is the biggest market for homeopathy and has the largest number of homeopaths in the world. Different State Governments have opened 228 hospitals with 11,099 beds and 5,770 homeopathic dispensaries. It has been estimated that there are more than 150,000 qualified homeopathic doctors, and at least 300-400 million patients (Das E. 2009). Also Brazil has developed a policy of full integration of homeopathy into the system of international sanitary politics, in consonance with the principles of comprehensiveness, equity, universality that underlie its sanitary reform and Unified Health System, and some municipalities have begun offering homeopathy as a treatment option (Justo Gomes C.M. 2007). Homeopathy has proved to be one of the most frequent complementary therapies also for children residing in Western countries. According to E.C.H. (European Committee for Homeopathy), when looking at the European Union as a whole, approximately 40,000 physicians, mainly in the outpatients clinics and among GPs, have taken a training course in homeopathy. About 6 to 8 times more general practitioners (GPs) prescribe homeopathic medicines on a regular basis without specific training, and even more do so occasionally, i.e. 40% of all French GPs and as many as 75% of all German GPs (E.C.H. 2012).

In Italy the last multipurpose survey on the diffusion of non-conventional medicine by the Italian National Statistics Institute (Istat, 2007) was conducted on a wider sample of families than in the previous survey of year 2000 (60,000 compared to 25,000). The data confirmed that 13.6% of Italians (7,900,000) had used at least one form of non-conventional therapy in the last 3 years. The most widespread form of non-conventional medicine is homeopathy, used by 7.0% of the population. The variables associated with more frequent use of non-conventional medicine are: female gender; adulthood, in particular the 35-44 year age range; high level of education; residence in Northern Italy. Children and adolescents up to the age of 14 were 9.6% of users of non-conventional medicine and the most widely used form of therapy was homeopathy (7.9%).

### *Biological effects: hypothesis on the mechanism of action*

The issue concerning the state of research on the mechanism of the action of homeopathic remedies in high dilution (HD) was recently discussed at the XXVI Meeting of GIRI (International Research Group on Very-low-dose and High Dilution Effects), held in Florence (Italy), on September 20-22, 2012. Following is the synthesis of the major contributions proposed by P. Bellavite, and L. Betti (2012).

“The study of HD is a new interdisciplinary field almost inextricably linked to the two-century old problem on the nature of homeopathic medicines. Notwithstanding its widespread practice and the high levels of patient satisfaction, homeopathy gives rise to intense skepticism, because its medicines are subjected to a process of serial dilution that results in extremely low (often non-measurable) levels of active principles. Skepticism is only one short step away from ridicule, which would be justified were homeopathic medicines be nothing besides high dilutions. However, the preparation of HD also involves agitation, which introduces mechanical energy and strong turbulence into the system. This step might impart a nano-heterogenous structure to water by means of phenomena such as coherence, epitaxy, temperature-pressure alterations, and formation of nanobubbles containing gaseous inclusions of oxygen, nitrogen, carbon dioxide, silica, and possibly also the source materials of medicines. The existence and nature of clathrate-like hydrate nanostructures formed during the dilution/agitation process might be explained by cluster science, according to which the chemical reactivity of different geometrical structures of clusters of a same chemical species may differ”.

HD are not like ordinary drugs and recent evidence suggests they should be considered as colloidal solutions of nanoparticles of the source material, the solvent and possibly also the containers (e.g. silica). This view agrees with observations performed with low-temperature thermoluminescence spectroscopy by Rey, and results obtained with UV spectroscopy, biocrystallization and the droplet evaporation method presented at the XXVI GIRI meeting. These methods are considered to be promising tools for the investigation of subtle changes in the structure of water and the effects of homeopathic preparations, particularly in plants and biological fluids. New applications of DNA microarray technology to the investigation of homeopathic drugs will also be discussed.

Vittorio Elia's group in Naples gathered an impressive amount of experimental evidence on “anomalous states of water”. These authors studied the electrical conductivity, heat of mixing with acid or basic solutions, and pH of water, and found that all three were able to detect changes in the structure of water in space-time. This phenomenon might be accounted for by a common working hypothesis, i.e., formation of dissipative structures. Water is a complex liquid capable of self-organization induced by mechanical and/or electromagnetic perturbations even when small. The increase of environmental entropy due to dissipation, and decrease due to the formation of local orders still amount to the overall increase in entropy, whereby formation of local structures in water occurs spontaneously. In the liquid phase, such structures are able to remain in a far-from-equilibrium state through dissipation of radiant energy drawn from the environment, whereas in the solid phase they are able to retain their properties indefinitely without dissipation. When sufficient water becomes available, these nanostructures are able to exploit radiating energy from the environment and thus revert to the far-from-equilibrium state. The existence of these aqueous nanostructures in the solid phase represents a novel and totally unexpected phenomenon that is met in clinical practice whenever homeopathic globules are dissolved in the patient's mouth: the aggregates are restored to the liquid phase and thus recover their ability to dissipate environmental energy to maintain their far-from-equilibrium state. Under such conditions, they might exert their therapeutic action as dissipative structures.

The biological mechanisms underlying the regulatory processes affected by HD have yet to be elucidated. Various lines of investigation suggest that HD might affect some subtle and early levels of signal transduction and/or genetic expression. Changes in the structure of water induced by HD might influence a crucial layer of water surrounding the cells, and thus also signal detection and transduction. Further studies are needed to confirm whether this hypothesis applies to the effects of HD observed in humans and plants.

“One thing is certain: HD pharmacology challenges the dose-response dogma. Rather than an exception, non-linearity between dose and response is the rule in biological systems. The occurrence of dual effects (both stimulatory and inhibitory) caused by a same agent in different doses or at different times was described in various experimental systems, and is often referred to as “hormoligosis”, or “hormesis”.

So-called “paradoxical pharmacology” is a related phenomenon belonging with the *in vivo* effects of drugs, whereby the acute and chronic actions of drugs often exhibit opposite effects. This is particularly true for receptor-mediated events. The susceptibility of a complex system is greatly enhanced close to a transitional phase or critical point, and under such conditions, when random energy (“noise”) is added, even minute perturbations push the system over the energy barrier. This phenomenon, called stochastic resonance, may represent the physical explanation of the effect of agitation in the preparation of HD. This same mechanism may also operate *in vivo*, where the stochastic resonance provided by noise from biochemical reactions may amplify the effect of the small but highly specific information supplied by the drug inside the living organism. Interestingly, the results obtained by Jäger's group comparing the response to homeopathic preparations of duckweed and yeast agree with the hypothesis that more complex organisms show stronger

reactions to homeopathic medicines compared to less complex organisms. Others, including the authors have intuitively predicted that the “potency” increase induced by serial dilution might have a physical basis grounded on the theory of self-similarity and fractal structures formation in serial dilutions (seen as mathematical iteration processes”).

Further development of basic research is highly desirable and several reports presented at the GIRI meeting suggest that cell- and plant-based bioassays may be suitable tools for this purpose. Botanical bioassays seem particularly suitable for this because they allow for large numbers of experimental replications. One major challenge basic research must meet is the development of test systems able to yield consistent results. The hindrance represented by subjective evaluation is avoided by means of the systematic use of:

- spectroscopic quantitative methods
- multiple intra-series and inter-series replications
- coded test samples
- highly pure compounds and parallel comparisons with control pure-water dilutions
- mechanical shaking methods with standardized duration and frequency.

A variety of protocols and different experimental conditions in terms of types of dilution/shaking procedures and solvent used should be explored. Research on extremely sensitive systems and very high dilutions of substances suggests that trace elements, container materials, storage duration and shaking methods may influence the results. Therefore, suitable water controls prepared in an identical manner and subjected to a same storage time must be used. As a function of these considerations and the controversial nature of the investigated subject, independent replications are crucial in establishing stable models that could be used by different investigators worldwide.

For two centuries, homeopathy and science were considered to be opposing and conflicting fields. Now things are changing, as scientific evidence begins to support many homeopathic tenets and the homeopathic world increasingly stimulates science to investigate previously under-evaluated and little understood subtle phenomena.

### ***Evidence Based Medicine and homeopathy***

Homeopathic treatment is an effective method of healing in both acute and chronic conditions, as claimed by millions of patients and thousands of homeopathic doctors. It may even offer long lasting to permanent cure, treating the disease at its roots, for most ailments. The body of clinical evidence for the effectiveness of homeopathy continues to accumulate. Several research studies have shown overall that three quarters of the chronically ill patients reported that they felt ‘moderately better’ or ‘much better’. A number of rigorous clinical trials have shown homeopathy superior to placebo; others have shown it has effects similar to conventional treatments.

Homeopathy is effective for a variety of complaints occurring in children, including behavioral problems. Other medical conditions successfully treated are: skin diseases such as acne, boils, eczema, psoriasis, warts; musculoskeletal pain, arthritis, osteoarthritis, sciatica, bursitis and fibromyalgia; allergies, frequent infections; tension headache and migraine; heartburn, gastritis, constipation, intestinal conditions, irritable bowel syndrome, inflammatory bowel disease; frequent colds, sinusitis, tonsillitis, cough, asthma and respiratory infections; emotional conditions such as depression, anxiety, insomnia; menstrual disorders, premenstrual syndrome, infertility, hot flashes; morning sickness, labour induction, labour pain, lactation problems, breast inflammation (mastitis); coronary dysfunctions, liver disorders, Ménière's disease. There are many other conditions besides those listed above in which homeopathy is found to be effective. It can be a possible alternative to antibiotics in infectious diseases, producing no toxic side effects and bringing about rapid recovery. Viral infections are also very well treated with homeopathy.

Rigorous research projects of the highest scientific standards have been conducted and published in leading international medical journals over the last few decades. In many controlled clinical trials homeopathic treatment has proven its effectiveness.

### *Randomised controlled trials in homeopathy*

A total of 163 randomised controlled trials (RCTs) in homeopathy have been published in good quality scientific journals. Positive effects have been reported in 41% of the total, 7% have a balance of negative evidence, while 52% have not been conclusively positive or negative. That research has investigated over 77 different medical conditions. In 36 of those conditions, there has been replicated research (i.e. there have been 2 or more trials); for each of the other 39 conditions, there are singleton RCTs. Differing study designs and the small size of many trials means that there are few conditions where there has been an opportunity to achieve consistent results.

There are at least 35 medical conditions in which positive conclusions for homeopathy may be derived from systematic reviews and/or randomised controlled trials: Brain injury (Chapman EH 1999); Bronchitis (Diefenbach M 1999); Childhood diarrhea (Jacobs J, 2003; 1993; 1994; 2000; 2006); Chronic fatigue syndrome (Weatherley-Jones E 2004); Common cold (Maiwald VL 1988); Depression (Adler UC 2009); Extended sports recovery time (Egocheaga Rodriguez J 2000); Fibromyalgia (Bell IR 2004; Fisher P 1989; Perry R 2010; Relton C 2009); Immune function (Kuzeff RM 1998); Influenza (Vickers A 2006; Attena F 1995; Brydak LB 1999; Ferley JP 1989; Papp R 1998); Insomnia (Bell IR 2010; Brooks AJ 2010; Carlini EA 1987; Naudé DF 2010); Low back pain (Gmünder R 2002; Stam C 2001); Otitis media (Jacobs J 2001; Taylor JA 2011); Perennial allergic rhinitis (Taylor MA 2000); Plantar fasciitis (Clark J 2000); Post-operative ileus (Barnes J 1997); Post-operative edema (Totonchi A 2007); Post-operative wound healing (Karow J-H 2008); Postpartum bleeding (Oberbaum M 2005); Postpartum lactation (Berrebi A 2001); Premenstrual syndrome (Yakir M 2001); Psoriasis (Bernstein S 2006; Wiesenauer M 1996); Radiodermatitis (Balzarini A 2000); Renal failure (Saruggia M 1992); Rheumatic diseases (Jonas WB 2000); Seasonal allergic rhinitis (Wiesenauer M 1996; Taylor MA 2006; Ernst E 2011; Aabel S 2000; Aabel S 2000; Aabel S 2001; Kim LS 2005; Reilly DT 1986; Weiser M 1999; Wiesenauer M 1985; Wiesenauer M 1990; Wiesenauer M 1995); Seborrhoeic dermatitis (Smith SA 2002); Sepsis (Frass M 2005); Sinusitis (Friese K; 2007; Zabolotnyi DI 2007; Wiesenauer M 1989); Snoring (Lipman D 1999); Stomatitis (Oberbaum M 2001); Tracheal secretions (Frass M 2005); Upper respiratory tract infections, including otitis media (Bellavite P 2006; Bornhöft G 2006); Uraemic pruritus (Cavalcanti AM 2003); Varicose veins (Ernst E 1990); Vertigo (Schneider B 2005; Issing W 2005; Weiser M 1998).

### *Reviews and meta-analyses*

A health technology assessment report on the effectiveness, the cost-effectiveness and the appropriateness of homeopathy was compiled on behalf of the Swiss Federal Office for Public Health. The article was published by authors who took part in the Program for Evaluation of Complementary Medicine (PEK). Results showed a positive overall result in favour of homeopathy in 29 studies on upper respiratory tract infections and allergic reactions. Results also showed many high-quality investigations of pre-clinical basic research proved homeopathic high-potencies inducing regulative and specific changes in cells or living organisms. Twenty of 22 systematic reviews detected at least a trend in favour of homeopathy. The authors of this article concluded that the effectiveness of homeopathy can be supported by clinical evidence and treatment is safe (Bornhöft et al. 2006).

In the same program, in August 2005, Shang et al. published an article where the conclusion was that the effect of homeopathy is placebo (Bornhoeft et al. 2006). In a review of homeopathy research the authors found 3 independent systematic reviews of placebo-controlled trials on homeopathy that reported effects that seem to be more than placebo and one review that found its effects consistent with placebo (Jonas W. 2003). A systematic review and meta-analysis showed highly significant results for surveys adding up to a total of 2 617 patients ( $P=0.000036$ ). Results were not that significant for high quality surveys ( $P=0.08$ ). The author concludes that further high quality studies are needed to confirm results (Cucherat M. et al. 2000). A systematic review of results from 93 substantive RCTs was carried out by Robert Mathie (2003). It concludes that of the 35 different medical conditions covered by these trials the weight of evidence favours a positive treatment effect in 8: childhood diarrhea, fibrositosis, hay fever, influenza, pain (miscellaneous), side-effects of chemotherapy or radiotherapy, sprains and upper-respiratory tract infections (Mathie R. et al. 2003). A meta-analysis of 3 trials on homeopathic immunotherapy. The result shows a significant effect in favour of homeopathic treatment (Reilly D et al. 1994). A review of placebo-controlled clinical trials using homeopathic medicines to treat people with AIDS or who are HIV-positive found 5 controlled clinical trials. Results showed statistically significant results in subjects with stage III AIDS, and specific physical, immunologic, neurologic, metabolic, and quality-of-life benefits, including improvements in lymphocyte counts and functions and reductions in HIV viral loads in patients receiving homeopathic treatment (Ullman

D. et al. 2003). Also a meta-analysis of 105 articles on laboratory research has been published. The result shows a positive effect, 50% more frequently than negative effect among trials of the highest methodological quality (Linde K. et al.1994).

The most important meta-analysis completed at the end of the 90's was done by Klaus Linde (1997), who took into consideration 89 trials of homeopathic treatment versus placebo. The result was significantly in favour of homeopathy (OR 2,45 (95% CI 2,05-2,93). This meta-analysis included 186 placebo-controlled studies of homeopathy published until mid-1996, of which data for analysis could be extracted from 89. The overall odds ratio was 2.45 (95% confidence intervals 2.05-2.93) in favour of homeopathy, which means that the chances that homeopathy would benefit the patient were 2.45 times greater than placebo. When considering just those trials of high quality published in MEDLINE listed journals and with predefined primary outcome measures, the pooled odds ratio was 1.97 and significant. Even after correction for publication bias the results remained significant. The main conclusion was that the results "were not compatible with the hypothesis that the effects of homeopathy are completely due to placebo". If the result of new trials were to show no difference between homeopathy and placebo, we would have to add 923 trials with no effect with 118 patients in each in order to balance the two (Linde K. et al. 1997). A HMRG report of an overview of clinical research in homeopathy identified 184 controlled clinical trials. They selected the highest quality randomized control trials, which included a total of 2,617 patients for a meta-analysis. This meta-analysis resulted in a p-value of 0.000036 (which means that results are highly significant) indicating that homeopathy is more effective than placebo. The researchers concluded that the "hypothesis that homeopathy has no effect can be rejected with certainty" (Homeopathic Medicine Research Group, 1996). Of the 105 trials with interpretable results, 81 trials indicated positive results. Most studies showed results in favour of homeopathy even among those randomized controlled trials that received high-quality ratings for randomization, blinding, sample size, and other methodological criteria. They came to the following conclusion: "The amount of positive evidence even among the best studies came as a surprise to us. Based on this evidence we would readily accept that homeopathy can be efficacious, if only the mechanism of action were more plausible. The evidence presented in this review would probably be sufficient for establishing homeopathy as a regular treatment for certain indications" (Kleijnen J 1991).

#### *The meta-analysis published in The Lancet*

A negative meta-analysis was published by Shang A et al. from *The Lancet* (2005), which would prove the equivalence between homeopathy and placebo. The authors of the study started from the declared belief that the specific effects of homeopathy are "implausible" and that the positive results so far reported in clinical trials are the result of "bias" (methodological errors or misinterpretation of data) in the trial or in the publication. They collected 110 homeopathic trials and in order to make a comparison with conventional medicine, randomly selected from the literature as many allopathic clinical trials on the same diseases (mainly respiratory infections, allergies and asthma, obstetrics-gynecology, surgery and anesthesiology, gastroenterology, rheumatic diseases, neurology). All of the studies examined were randomized and placebo-controlled. The results were essentially the following:

- In both groups (publications of homeopathy and conventional medicine) the vast majority of clinical trials reported positive effects of the drug compared to placebo.
- An analysis of the methodological quality and then ranking of these studies was performed using qualitative parameters as methods of randomisation, the procedures for masking (doctors, patients and outcome assessors) and the type of analysis data. Only 21 homeopathic trials (19%) and even fewer trials (9, 8%) of conventional medicine were judged to be of high quality. However, considering the set of all studies, the differences in quality between homeopathy and conventional medicine were not significant.
- In both groups, smaller trials and those of lower quality effects reported greater benefits than the trials of higher quality. Selecting between studies of higher quality and those with the largest number of patients, the odds ratio of homeopathy (8 studies) was 0.88 (95 % CI 0.65 -1 · 19), while the odds ratio of conventional medicine (6 studies) was 0.58 (0.39 -0 · 85). From this the authors derived that homeopathy is no different from placebo.

In essence, the analysis of the results, excluding 102 researches of 110, was completed in order to arrive at an interpretation that seems to be a confirmation of the belief of the ineffectiveness of homeopathy.

The work of Shang et al. was criticized for various reasons which are summarized in these papers (Fisher 2005, Walach 2005, Bellavite 2006, Keine 2006, Ludtke 2008, Rutten 2008). In fact, the results of the survey are basically a confirmation of previous meta-analysis of homeopathic trials, which had always highlighted

the prevalence of positive therapeutic effects. The most controversial operation of the Swiss authors, in terms of data usage collected, was to extract, according to a further quantitative criterion (i.e., studies with larger number of cases among those in the group with high quality) 8 homeopathic trials and 6 allopathic trials. Comparing only those very few studies the authors came to the conclusion of the ineffectiveness of homeopathy. The strength of this conclusion is therefore very doubtful, because the text was not declared in such studies, nor what topics or what type of homeopathy (unicist, complex or pluralist homeopathy).

The weakness of the study published in *The Lancet* consists in the omission from the statistical evaluation of a large part of the literature on the basis of a unilateral application of quality criteria and an arbitrary choice of how many jobs have been considered. Even to merge only very few studies, very different from each other and apply the calculations typical of meta-analysis (usually performed on homogeneous trials at least as a pathology and drug used) is a procedure that is not accepted by epidemiologists (Ludtke R. 2008).

A paper has recently been published that compared the magnitude of the “placebo” effect reported in clinical trials of homeopathy with those reported in conventional medicine. The result shows that these effects are the same, which means that the methodology used in the homeopathic treatment does not induce a greater effect of “suggestion” than the conventional field (Nuhn, Ludtke et al. 2010).

### *Main observational studies*

In an observational study of 6,544 consecutive patients during a 6-year period, and over 23,000 consultations, results showed that 70.7% reported positive health changes, with 50.7 % recording their improvement as better (+2) or much better (+3). Of the 1,270 children that were treated 80.5 % had some improvement, and 65.8 % were better (+2) or much better (+3) (Spence DS, 2005). In a prospective, multi-centre cohort study with 103 primary care practices treating 3,981 patients, disease severity decreased significantly ( $p < 0.001$ ) over a 2 year period. Major improvements were observed for quality of life for adults and young children. 1,130 (28 %) of the patients were children and 97 % of all diagnoses were chronic with an average duration of 8.8 years. The most frequent diagnoses were allergic rhinitis in men, headache in women, and atopic dermatitis in children (Witt CM, 2005). Seven out of ten patients visiting Norwegian homeopaths reported a meaningful improvement in their main complaint 6 months after the initial consultation (Steinsbekk, A.2005). One year after their first visit to a homeopathic clinic, 609 patients were asked to rate their general health compared with a year ago. 73.5 % reported a marked or moderate improvement in their health status (Attena F. 2000). A study of 829 patients treated with homeopathy, where conventional treatment had been unsatisfactory or contraindicated. 61 % had a substantial improvement with homeopathy (Sevar, R. 2000). A survey of more than 900 patients treated homeopathically showed substantial improvement in quality of life over the first 6 months after treatment and this effect remained more or less stable over the following years (Güthlin C, 2004). British prospective survey of homeopathic treatment of 223 patients has shown 90% improvement or more: 32%. 60% improvement or more: 65% 50% improvement or more: 72% (Report on NHS practice-based homeopathy project, 1996). British prospective survey of homeopathic treatment of 160 patients: very positive effect 73%, some effect 27%, no effect 0% (1994). British prospective survey of homeopathic treatment of 37 patients suffering from psychological complaints: very satisfied 81%, satisfied 16%, not satisfied at all 3%. (Homeopathy within the NHS, 1998). Retrospective survey of homeopathic treatment (Danmarks Farmaceutiske HÅ\_jskole, 1995): 73% of patients stated they improved after homeopathic treatment (Andersen HE, 1999). The effect of homeopathy, acupuncture and osteopathy: 89% of patients stated they experienced positive effect from the treatment. Particularly clear effect on reduction of pain, increased vitality, ability to function socially and with regards to limitations at work and in daily activities influenced by physical problems. Homeopathy was particularly effective for patients suffering from arthritis, hay fever, asthma and skin complaints (Richardson J. 1996).

### *Adverse reactions and interactions*

Homeopathy is generally safe; homeopathic medicines are non-toxic and harmless and do not have or have very few adverse side effects. Patients unable to use conventional prescription drugs due to side effects can often safely use these medicines. Homeopathic medicines are natural, prepared from minute amounts of herbs, minerals and animal products. Their quality and safety are assured by the national medicine agencies based on European Union legislation and European Pharmacopoeia requirements. They are suitable for pregnant women, infants and children without worrying about the dosage.

A review of data from 1970 to 1995 highlighted a higher incidence of adverse drug events in homeopathic medicines compared to placebo in placebo controlled trials, although these were generally minor and

transient. The authors conclude that homeopathic medicines prescribed in high dilutions by doctors with experience in homeopathy, are generally safe and reaffirm the necessity for accurate clinical research (Dantas F. 2000). One of the potential harms relating to non-conventional treatment relates to the patients' wish to discontinue conventional therapy inappropriately (Schmidt K 2002).

To assess the possible harm arising from the use of homeopathic medicine a prospective study was conducted about adverse drug events related to these medicines, between June 1<sup>st</sup>, 2003 and June 30<sup>th</sup> 2004. In 2004 follow-up visits were consecutively carried out at the Homeopathic Clinic of Lucca (Endrizzi C. 2005). They refer to effects following the administration of a homeopathic medicine, prescribed according to the classical homeopathic method and reports collected by a homeopathic doctor (not the prescribing doctor) on the nature and intensity of the effect, dose and frequency of administration, time relationship between drug use and adverse events, challenge, dechallenge, possible concomitant factors, causality (improbable, unlikely, possible, probable, certain). Out of 335 homeopathic consecutive follow-up visits, 9 adverse reactions were reported (2.68%), including one case of allergy to lactose, excipient of the granules.

In conclusion, homeopathic pills do not hamper digestion, or lower the body's resistance. Neither do they cause any allergies nor any damage, even if taken over a long period. There is no toxicity, no addiction, no dependency, and no withdrawal. Millions of people use them to help themselves, their families and their pets without any dangerous physical repercussions.

### *Methodology of the discipline in oncology*

Generally, the homeopathic intervention in cancer cases is divided into two basic approaches: the treatment of cancer patients in a general sense, "constitutional", usually offered after conventional treatment, e.g. after surgical removal of the tumor or after any cycles of chemotherapy, with the aim to improve the overall quality of life of cancer patients and consequently to affect the survival and reduction in the frequency of recurrence/metastasis.

There is then a second type of intervention, specifically limited to the symptoms resulting from the adverse effects of chemo-radio-hormone therapy and intercurrent symptoms, such as, for instance, the case of acute diseases that can arise during the cancer disease. This type of treatment is only used as a support to conventional therapy to reduce its adverse effects.

The approaches in daily clinical practice can be mixed with each other, used in succession, in other words they may be applied in a number of ways that take into consideration the phase of the disease and the patient's clinical condition.

### *Clinical findings*

The role and efficacy of homeopathic medicines for the treatment of malignant tumors is largely unknown and unproven so far. Homeopathic therapy is mainly used for supportive cancer care and some have suggested an integration of this therapy with conventional methods (Kassab S, 2009). However, along with a search for conventional solutions, researchers are actively trying to identify treatment options offered by various systems of complementary and alternative medicine, including homeopathy.

Güthlin C et al. (2010) compared the characteristics of two cancer patient cohorts: one was treated in a homeopathic cancer care clinic and the other in a conventional oncology care (CC) outpatient clinic. Six-hundred and forty-seven patients were included in this cross-sectional cohort study and had to fill in questionnaires: health-related quality of life (QoL) (Functional Assessment of Cancer Therapy-General Scale), depression and anxiety (Hospital Anxiety and Depression Scale), fatigue (Multidimensional Fatigue Inventory) and expectancies toward treatment. Clinical data were extracted from medical records. This study presents the comparison of both cohorts. The most pronounced differences indicate longer disease histories and different diagnostic and clinical pretreatment variables. Despite the clinical differences, QoL as well as anxiety, depression and fatigue was similar in both the groups.

### *General approach to the cancer patient: the Indian Banerji Protocol*

It may be useful to point out that a review has been recently conducted on this kind of treatment, analyzing the existing studies to evaluate the effect of homeopathic therapy in reducing the adverse effects of cancer therapies (Banerji 2008).

It reports the data on 14 Indian patients treated apparently effectively with homeopathic remedies as part of a unique National Cancer Institute (NCI) program and drew the conclusion that homeopathy might have effects on cancer care.

In 1999, the NCI-BCS programme (Best Case Serial) evaluated the cancer treatment protocol developed at the P. Banerji Homeopathic Research Foundation (PBHRF) in Kolkata, India. The "Banerji Protocol" constitutes a new method of using ultradiluted natural substances classically used in homeopathic medicines through prescribing specific remedies for specific diseases. As documented by this clinic, a group of 21,888 patients with malignant tumors were monitored at PBHRF between 1990 and 2005. This group of patients used the Banerji Protocol without being subjected to any additional method of conventional care.

Of these, 941 patients had breast cancer. The clinic's physicians reported that in 19% of the cases, the malignant tumors completely regressed and in another 21% of cases, the tumors were static or improved after treatment. For patients with static tumors, the follow-up continued for at least 2 years, and for some, follow-up has continued for 10 years.

Moreover, 10 cases from the PBHRF were presented to the NCI for review by the BCS program. Four cases of lung and esophageal cancer were found to have confirmed pathological diagnoses of cancer and adequate pre- and post-treatment medical imaging studies indicating tumor response. The patients treated with the Banerji Protocol approach received only the remedies prescribed at the PBHRF clinic and did not receive any additional conventional treatment such as surgery, radiation, or chemotherapy.

The remedies prescribed have been classically used as homeopathic medicines. After rigorous evaluation of the findings, the NCI concluded that there was sufficient evidence of possible efficacy to warrant further research.

### *The Spinedi system*

The department of Homeopathy in the Clinica Santa Croce, Orselina in Switzerland was started in 1997 by Dr. Dario Spinedi, and has treated about 6-7,000 patients with various types of cancers. After 15 years of activities they consider that classical homeopathy is valuable as complementary medicine in the treatment of cancer.

The homeopathic approach to the cancer patient starts with a detailed analysis of the complete history in order to decide a treatment plan. After this first phase, a remedy for the acute mental and physical sufferings has to be found— effects of the shock of the diagnosis, operation, chemotherapy, radiation etc. Moreover a specific organotropic remedy if necessary and a constitutional remedy for long term treatment must be defined. The aim of this plan is to apply the correct therapy in curable cases and give an efficient and smooth palliative care in advanced and incurable cases.

The patients are hospitalized in the clinic for 2-3 weeks. The acute problems are treated first by giving the homeopathic remedy in Quinquagintamillesimal (Q) potency with daily visits and observation. Every day the subjective and objective symptoms of the patients are observed and evaluated, the dose adjusted and the remedy changed if necessary. After treating the acute symptoms, the patient is treated either by the organotropic or the constitutional remedy depending on the case. After recovery, the treatment continues at home with regular feedback and follow up of the case.

Preliminary results of this approach were published by Matthias Rostock and Johannes Naumann (2011). They conducted a prospective observational study with cancer patients in two differently treated cohorts: one cohort with patients under complementary homeopathic treatment (HG; n=259), and one cohort with conventionally treated cancer patients (CG; n=380). For a direct comparison, matched pairs with patients of the same tumour entity and comparable prognosis were to be formed. The main outcome parameter was the change in quality of life (FACT-G, FACIT-Sp) after 3 months, the secondary outcome parameters: change in quality of life (FACT-G, FACIT-Sp) after 1 year, as well as impairment by fatigue (MFI) and by anxiety and depression (HADS). These are the results: HG: FACT-G, or FACIT-Sp, respectively improved statistically significantly in the first 3 months, from 75.6 (SD 14.6) to 81.1 (SD 16.9), or from 32.1 (SD 8.2) to 34.9 (SD 8.32), respectively. After 12 months, a further increase to 84.1 (SD 15.5) or 35.2 (SD 8.6) was found. Fatigue (MFI) decreased; anxiety and depression (HADS) did not change. CG: FACT-G remained constant in the first 3 months: 75.3 (SD 17.3) at t<sub>0</sub>, and 76.6 (SD 16.6) at t<sub>1</sub>. After 12 months, there was a slight increase to 78.9 (SD 18.1). FACIT-Sp scores improved significantly from t<sub>0</sub> (31.0 - SD 8.9) to t<sub>1</sub> (32.1 - SD 8.9) and

declined again after 1 year (31.6 - SD 9.4). For fatigue, anxiety, and depression, no relevant changes were found. 120 patients of HG and 206 patients of CG met the criteria for matched-pairs selection. Due to large differences between the 2 patient populations, however, only 11 matched pairs could be formed. This is not sufficient for a comparative study.

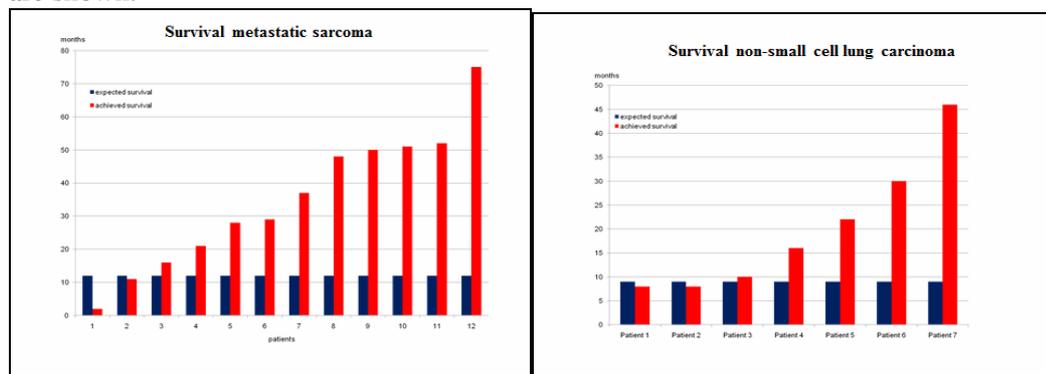
In conclusion the authors affirm: “We have shown that under homeopathic care sizeable benefits were achieved for patient’s quality of life and spiritual well-being. The improvement was clinically relevant and statistically significant. It could also be seen in symptoms of physical and mental fatigue. Thus our data suggest that classical homeopathic care could complement conventional cancer care to the benefit of patients”.

The Spinedi method has been used also by M. Frass at the University Clinic in Wien (Austria). The results of this approach were published in a research and are summarized here (M. Frass, 2009). In total 90 patients with breast (35), colorectal (10), renal (7), cerebral (7), and pancreatic (6) cancer; sarcoma (5); bronchial (4) cancer; lymphoma (4); pharyngeal (3) cancer; and others (9) underwent an elaborate medical history including questions on social and private circumstances. Symptoms given by the patients were correlated with the signs of homeopathic evaluation of remedies as recorded in Repertories (Zandvoort, Complete Repertory; MacRepertory®). Patients were requested to complete visual analogue scales as well as a specially developed form evaluating subjective existential orientation and, finally, EORTC QLQ-C30 form version 3.0.

With respect to the latter, the mean QoL improved by 0.31 points (4.33±1.54 before vs. 4.64±1.59 after additive homeopathic therapy; p=0.008, Student's-t-test for paired data) between first and last registered consultation which lay apart by a mean of 24 weeks. This result corresponded to an improvement of 11.6% in a seven part-series. Similar results were found for the specially developed form: the visual analogue scale showed a difference of 0.71 (5.60±2.06 before vs. 6.31±2.3 at the third consultation, p=0.043; corresponding to an improvement of 16.1% in a 10 part-series), and a difference of 0.59 (5.56±2.15 vs. 6.15±2.31, p=0.007; 13.3% improvement in a 10 part-series) between first and last consultation. Following the fourth consultation, analysis in 45 participants revealed that 80% (n=36) felt an improvement of the general condition, while 20% (n=9) experienced no effect. In total 24.4% (n=11) sensed the improvement mainly physically; 51.1% (n=23) physically as well as psychologically; 2.2% (n=1) only psychologically; the remaining one patient did not comment. Improvement was ascribed to a combination of homeopathy and conventional therapy by 23/36 (63.9%) of the improved patients; 10 (27.8%) ascribed improvement to homeopathic treatment only, 1 patient (2.8%) to oncologic therapy only, 1 to the season, 1 patient remained without comment. All patients were interested in continuing the homeopathic treatment.

In another study Frass (2009) published a comparison between the survival of patients treated with homeopathy and those treated with conventional therapy. The tumors selected were: metastatic sarcoma, non-small cells lung carcinoma and glioblastoma.

Below the survival data of patients treated with homeopathy compared with the average survival for cancer are shown.



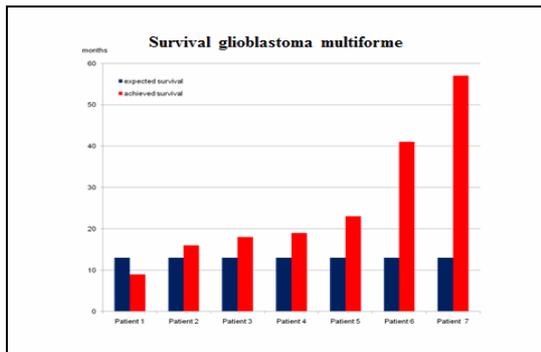


Table 1: Survival data of patients treated with homeopathy compared with the average survival for cancer.

### *Laboratory findings of the antitumor activity of homeopathic remedies*

Several studies *in vitro* have investigated the antitumor activity of homeopathic remedies.

A study reported the antitumor effect of 5 homeopathic remedies used for the treatment of prostate cancer. There was a 23% reduction in tumor incidence, and for animals with tumors, there was a 38% reduction in tumor volume in homeopathy-treated animals versus controls (Jonas W.B. 2006). However, in another study there were no direct cellular anticancer effects demonstrated in these researchers' *in vitro* and *in vivo* studies (Thangapazham R.L. 2006).

In other studies conducted in India, the laboratory of Khuda-Bukhsh reported a significant anti-tumor effect of homeopathically prepared *Chelidonium* and *Lycopodium* (Banerji A. et al., 2010; Pathak, S. et al., 2006). A third study examined *in vivo* effects on mice treated with homeopathically prepared *Sabal serrulata* and clearly demonstrated a biologic response to homeopathic treatment as manifested by cell proliferation and tumor growth. Two other homeopathic medicines tested did not show similar anti-tumor effects (MacLaughlin B.W., 2006). Another study done in India reported that homeopathic drugs retarded liver tumor growth in mice and reduced the incidence of chemically-induced sarcomas also increasing the life span of mice harboring these tumors (Kumar K.B. 2007).

A study done by P. Banerji Homeopathic Research Foundation in collaboration with American researchers at the M.D. Anderson Cancer Center, University of Texas demonstrated plausible biological mechanisms for the antitumor effects of the homeopathic medicines tested.

In one report there is a description of 15 patients diagnosed with documented intracranial tumors who were treated exclusively with the homeopathic remedies *Ruta graveolens* 6 CH and *Calcarea phosphorica* 3 DH without additional chemotherapy or radiation. Of these 15 patients, 6 of the 7 who had glioma showed a complete regression of the tumors. In this study the authors also reported that these medicines stimulated induction of survival-signaling pathways in normal lymphocytes and induction of death-signaling pathways in brain cancer cells. Cancer cell death was initiated by telomere erosion and completed through mitotic catastrophe events (Pathak S. 2003).

In another interesting study conducted at the University of Texas MD Anderson Cancer Center, 4 ultradiluted remedies (*Carcinosinum*, *Phytolacca*, *Conium*, and *Thuja*) exerted preferential cytotoxic effects against 2 breast cancer cell lines, causing cell cycle delay/arrest and apoptosis without affecting the normal mammary epithelial cells. These effects were accompanied by altered expression of the cell cycle regulatory proteins, including down regulation of phosphorylated Rb and upregulation of the CDK inhibitor p27, which were likely responsible for the cell cycle delay/arrest as well as induction of the apoptotic cascade that manifested in the activation of caspase 7 and cleavage of PARP in the treated cells. Interestingly, the cytotoxic effect of 2 of the remedies investigated in this study, *Carcinosinum* and *Phytolacca*, appeared similar to the activity of paclitaxel, the most commonly used chemotherapeutic drug for breast cancer (Frenkel et al., 2010).

### **Homeopathic drugs specifically used as anti-cancer**

#### *Carcinosinum*

The remedy *Carcinosinum* was often used successfully in traditional homeopathy in the treatment of cancer. *Carcinosinum* is made by first preparing a specimen of the cancerous tissue, usually taken from the breast, and subsequently sterilizing and dissolving it in disinfected water. This blend is then diluted as well as succussed repeatedly. While it is uncertain who was the first to use cancer nosodes, we know that the Scottish homeopath J. Compton Burnett (1840-1901) was the first to write about their use.

The homeopath J. Clarke recorded many cases where he used the cancer nosode to treat cancer, *Carcinosinum* being the most predominant.

Ramakrishnan has been using cancer nosodes in cancer treatment for the last 30 years and he is leading the world in the homoeopathic treatment of cancer, treating at least 2,000 cancer patients a year. One of the nosodes he uses is *Carcinosinum*.

Many homoeopaths use *Carcinosinum* to remove the predisposition to cancer. The American homeopath James Tyler Kent ((1849–1916) said on cancer, “Patients have been kept comfortable...and the sufferings usually accompanying this condition were avoided” . So it was noted that *Carcinosinum* has relieved cancer pains. *Carcinosinum* doesn’t cure cancer, but according to Kent, it palliates the cancer for years taking away the sharp, burning and tearing pains.

Foubister studied 200 pregnant women who had cancer and, later, their children. The children had a tendency to birthmarks. He claimed that *Carcinosinum* was useful for deep pigmentations. Foubister also made an observation that people who lived under severe fear for long periods of time often needed this remedy.

### *Embryos of Zebrafish*

The use of embryonic differentiation factors in tumor growth was initiated by Biava et al. in 1988. Cells with tumor homogenates, embryo and gravid uterus were administered in several mice together with cells of Lewis tumor. The result was a block of the primary tumor and the formation of lung metastases. The authors found that all the differentiation processes occur during organogenesis and these are able to oppose those that cause cancer. There are regulators that prevent the indefinite multiplication of the cell, typical of malignant growth. Thus, the first hypothesis was born: can you use the regulatory activity of the growth and differentiation of embryonic to control the development of cancer?

The stem cells are a population of embryonic cells which differ in the adult under the effect of growth factors (e.g. interleukin 3), but is also important in the micro environment for the differentiation of various cell lines. Therefore, if a progenitor cell is stopped in its development and differentiation and has produced a leukemia because the growth factors are missed, a possible solution is to give the factors which are in the embryo during the differentiation process; the same happens to cancer cells: give them the items they need to the differentiation process. Oviparous embryos were used at different stages of differentiation in an attempt to regulate the growth. Various homogenates of Zebrafish embryos were prepared, taken at different times of differentiation process, starting from embryos more undifferentiated to get to the most differentiated, in an attempt to regulate the development of cancerous cells differentiation.

Various works have been carried out *in vitro*, in animals but also *in vivo*. In a study conducted by Biava (Biava PM et al. 2002), the therapy was the administration of sublingual extracts gliceroalcolic in D4 dilution (9-12 per day) of Embryo Zebrafish.

The cases studied were only the most serious ones, where often oncologists had stopped the traditional therapy, or patients with severe metastasis, but yet undergoing chemo or radiotherapy. Patients in the early stages were excluded from the study. In 3 years, 200 patients with various tumors (glioblastoma, hepatocellular carcinoma, ovarian cancer, lung cancer, cancer of the colon) were treated. The following are the results: 80% of the cases showed an improvement of the performance in the assessment of ECOG (Eastern Cooperative Oncology Group); the survival curve showed a stabilization of the disease in a certain number of cases; 8% of the cases showed a regression of the tumor mass.

The clinical trial is an open study, no conclusions can be drawn except for the non-toxicity of the therapy. The study (Livrighi T et al 2005) was performed on 179 patients with liver cancer no longer responding to other therapies, some were subjected to SCDS (extracts of embryonic Zebrafish), others to palliative care. The randomized trial was stopped after 6 months due to the marked improvement in patients undergoing SCDSF. Therefore, 154 patients were included in the study now open. Three patients were excluded because the therapy was discontinued.

Number of Patients	%	Results
151		
4	2,6%	Complete regression of the cancer
26	17,2%	Regression of the cancer
24	16%	Stabilization of the cancer
97	64,2%	Progression of the disease
<b>Observation period: from 3 to 21 months</b>		

Results of the RCTs on Embryo Zebrafish treatment. (Biava personal communication).

### *Canova therapy*

Canova is a homeopathic product produced in Brazil composed of homeopathic dilutions of *Aconitum napellus*, *Arsenicum album* (*arsenic trioxide*), *Bryonia alba*, *Lachesis muta* and *Thuja occidentalis* according to the Hahnemannian homeopathic method. Its role in cancer, bone marrow and haematopoiesis as well as macrophage and monocyte activation is reviewed by the Brazilian research group but the results have not been published in peer reviewed journals. Canova seems to stabilize platelet morphology in HIV/AIDS. The data suggest that the future of immunomodulators and homeopathic products which appear to have an effect on the immune response requires a better understanding of the relative need for immune activation versus immune modulation.

### *Vidatox treatment*

Cuban researchers have reported that the venom of the scorpion *Rophalorus Junceus* (commonly known as blue scorpion), endemic to Cuba, has “an analgesic, anti-inflammatory and antitumor effect”, according to Pavel Pizart and Isbel Gonzalez, responsible for the research in Labiofam, which prepares Escozul®, also known as Vidatox®.

The potential benefits according to the clinical experience are:

1. Referral of tumor activity for over 5 years.
2. Amelioration of the quality of life (improved sleep quality, better appetite).
3. Help to placate the unwanted effects of radio-chemo and other anti-cancer therapies.
4. Increased survival.
5. Help to relieve pain.
6. Amelioration of the patient's immune response.

It has been reported that these benefits have occurred in approximately 85% of individuals undergoing treatment depending on the stage and general deterioration of the patient, but there is no available clinical evidence till today.

The sheer number of compounds and their diverse pharmacologic properties among different scorpion species leave their mechanisms poorly understood. Most scorpion venoms are known to contain peptide toxins that mainly act on ion channels.

The treatment with the toxin of scorpion *Rophalorus Junceus* includes at least 50 components, and among them:

- Enzymes (phospholipase, hyaluronidase)
- Antimicrobials similar to other scorpion venoms
- Venom peptides: RjAa12f, a component similar to insect toxins in other scorpion venoms; Na<sup>+</sup> and K<sup>+</sup> ion channel components.

### **Glossary**

**Grades of drug symptoms:** the grades of the drug symptoms are designated in the Repertory by the use of different sized type. Kent used 3 grades, Boenninghausen had 4, but this fourth grade is included in those of the third under Kent's classification. Distinction in the drug symptoms by placing one in the first grade by using capitals and heavy faced type; under the second grade by using italics and under the third grade by using small letters. Under the first grade are included all those symptoms which were brought out in every prover and that have since been verified. Under the second grade those symptoms which were brought out in the majority of provers and have since been verified, and under the third grade those symptoms which only a few of the provers developed, those symptoms which are clinical and which have since been verified.

**Homeopathic dilutions or potencies:** three logarithmic potency scales are regularly used in homeopathy. Hahnemann created the "centesimal" or "C scale", diluting a substance by a factor of 100 at each stage. The centesimal scale was favored by Hahnemann for most of his life. A 2C dilution requires a substance to be diluted to one part in 100, and then some of that diluted solution diluted by a further factor of 100. This works out to one part of the original substance in 10,000 parts of the solution. A 6C dilution repeats this process 6times, ending up with the original substance diluted by a factor of  $100^{-6}=10^{-12}$  (one part in one trillion or 1/1,000,000,000,000). Higher dilutions follow the same pattern. In homeopathy, a solution that is more dilute is described as having a higher potency, and more dilute substances are considered by homeopaths to be stronger and deeper-acting remedies. The end product is often so diluted as to be

indistinguishable from the dilutant (pure water, sugar or alcohol). There is also a decimal potency scale (notated as "X" or "D") in which the remedy is diluted by a factor of 10 at each stage. Hahnemann advocated 30C dilutions for most purposes (that is, dilution by a factor of 10<sup>60</sup>). In Hahnemann's time, it was reasonable to assume the remedies could be diluted indefinitely, as the concept of the atom or molecule as the smallest possible unit of a chemical substance was just beginning to be recognized. The greatest dilution reasonably likely to contain even one molecule of the original substance is 12C.

**Homeopathic Materia Medica:** this is an encyclopedia of materials which may be used to prepare homeopathic medicines. It lists the materials along with details of the provings which establish the symptoms and conditions for which they are claimed to be suitable. It thus constitutes a homeopathic prescribing reference guide and is often used along with the Repertory. Although there are various homeopathic Materia Medicas written by different authors and covering different specialties, the term *Homeopathic Materia Medica* is often used to reference the total sum of homeopathic preparations and prescribing options. Hahnemann developed the first Homeopathic Materia Medica by a system of homeopathic provings, where a substance was ingested by the "prover" and the symptoms that the "prover" developed were recorded in great detail. Materia Medica may also include accidental poisoning and some information from clinical treatment. Drug proving is the basic source of Materia Medica through which are known the symptomatology of the drugs that have found a place in Materia Medica and the symptomatology, physical and mental presentation of new drugs. The other sources of Homeopathic Materia Medica are as follows:

1. Noting of signs and symptoms which occur because of drug overdose of medicines.
2. Noting of signs and symptoms which occur in poisoning in a person.
3. Noting of signs and symptoms which occur after administering the medicines in sick people and following the appearance of side effects.

The books written by the pioneers of Homeopathy have been the base for the further works on the subject.

**Proving:** a homeopathic drug proving or 'homeopathic pathogenetic trial (HPT)' is a form of investigative clinical trial used to establish the potential therapeutic action of a new homeopathic medicine. A pre-defined number of repeated doses of the homeopathic remedy are given to healthy volunteers until symptoms are experienced. These are collated by observers and distinctive symptoms common to multiple participants (which are most likely to be related to the medicine) are identified. According to the central homeopathic principle that 'like cures like', the remedy may have the potential to treat these specific characteristic symptoms. To avoid influencing the results, depending on the precise trial design used, participants and/or those collating and analysing the results may be unaware of what substance is being tested and/or whether they are receiving placebo, until the trial has been completed.

**Repertory:** the Repertory is a book that lists all of the symptoms for the homeopathic single remedies. It is like an index for the Materia Medica. Here's a little more detail: every single remedy has a set of symptoms associated with it. Rather than read the entire Materia Medica every time you want to find a remedy, it is easier to look up the specific symptoms first. The Repertory lists the guiding symptoms and corresponding single remedies. The Repertory is like an index to the Materia Medica.

A sample listing in the Repertory is as follows:

Throat

Pain

Sore

Right: Ars., bell., calc-p., carb-ac., ham., ind., lac-c., lith., Lyc., lyss., mag-c., merc., merc-i-f., nat-p., nicc., phyt., ptel., sars., tarent., ter., xan.

The "code" to the listing of remedies is as follows: Bold = 1, Italic = 2, Normal Type = 3. When looking up symptoms, each remedy should be listed in terms of importance. Bold symptoms are stronger than italicised symptoms and italicized symptoms are stronger than normal typed symptoms. Unless you are very sure of the symptoms, stick with the strongest symptoms in bold or italics.

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## **Homotoxicology**

### ***Definition and biological effects of homotoxicology***

Within the growing interest on biotherapies, homotoxicology is a cutting-edge treatment and it was born as a link between classical homeopathy and biomedicine.

Homotoxicology was born in Germany in the '30s and '40s, thanks to the work of Dr. Hans Heinrich Reckeweg, a clinical expert and passionate homeopath. He lived when biochemistry and immunology rose to the role of the protagonists of contemporary medicine, and it is precisely inside these two disciplines that Reckeweg forces himself to interpret the fundamentals of homeopathy.

Today, it is clear the great contribution made by Reckeweg towards medical science: he was able to integrate, in a single vision, the principles of Hahnemann and the new trends of modern medicine.

Some modern researchers have defined homotoxicology as "homeopathy of the year 2000," others viewed it as a meeting point between the genius of Hahnemann empiricism, the charming Eastern medical philosophy and Western science focused on experimentation.

Homotoxicology has its roots in classical homeopathy but it is linked to pathophysiology and it is used during the diagnosis while the substances used as therapy are prepared according to the standards of the Homeopathic Pharmacopoeia.

Inside the pharmacology there is one of the most brilliant aspects of Reckeweg: in addition to classical homeopathic remedies, he introduces a series of "new", pharmacological principles as a result of the interpretation of biochemical and immunological aspect of the diseases; new nosodes appear ranging beyond the diathesis nosodes introduced by Hahnemann, there are the intermediates catalysts of Krebs cycle, the organotherapies and the class of compounds prepared. The compounds are an association of remedies whose principle can be summed up in three words: synergy, complementarity, completeness in accordance with the Burgi principle.

### ***The principles of homotoxicology***

The antihomotoxic homeopathy or homotoxicology is etymologically the study of toxic factors for humans and identifies the "homotoxines" as the causes attributed to all diseases.

In fact any organism is continuously stressed by an enormous amount of exogenous toxins (bacteria, viruses, toxins, food, factors of environmental pollution, etc.) and endogenous (intermediate products of the various metabolisms, catabolites final, etc.).

According to the theory of Von Bertalanffy, for which the organism is a flow system in dynamic equilibrium, if the homotoxin is not particularly "virulent" and if the excretory systems are efficient, it passes through the body-flow system without determining any interference in its homeostasis, which will therefore remain in the condition of equilibrium, i.e. of health.

If, however, either because the toxin is particularly "aggressive" or because excretory systems are not enough, there is an alteration of the equilibrium, that the body, in its natural tendency towards the maintenance or restoration of its "restricted homeostasis" (Laborit), will try to compensate by triggering additional self defense mechanisms: the diseases.

For Hahnemann "the noxa is nothing, the terrain is everything", and in later years after Pasteur there is a focus on the war on "microbe". For Reckeweg, however, the disease is to be interpreted as the consequence that flows from "interaction between pathogenic agent, environmental factors and especially responsiveness". To quote the father of homotoxicology: "diseases are the expression of the body's fight against toxins, in order to neutralize and expel them, or are the expression of the struggle that the body makes to compensate for the damage caused by irreversible toxins".

Depending on the extent of the attack and the integrity of the autologous defense system that Reckeweg called the "Great Defense System"; the body manifests different clinical pictures that can be easily classified into six stages.

In his Table of Homotoxicosis or the application chart that categorizes various diseases, Reckeweg represents the various degrees of reactivity by which the body attempts to maintain or restore its homeostasis, his balance, his state of health.

Each stage represents the expression of the different reactive capability (inflammatory) of the organism, the expression of many types of equilibrium flow achieved by the body to maintain its homeostasis restricted.

There are two different humoral phases, two stages of fundamental substance and two cell phases.

### *The Humoral Phases*

They represent pathological situations in which the prognosis is favorable, as expressions of a good reactivity:

- a) Phase of excretion: toxins do not even come in contact with the epithelial cells of the mucous membranes, but are absorbed and expelled with the physiological secretions.
- b) Phase-reaction or inflammation: due to the process of inflammation, the body neutralizes toxins before, and ejects but the toxins enter in the flow system.

### *The basic steps of the fundamental substance*

It is good to specify that the cellular intoxication follows a bi-directional flow, in the sense that it may be the result of the impregnation of homotoxines that exceed the level of "containment" of the interstitial space, as well as the result of the difficulty of the cell to eliminate the catabolites intracellular because of the mesenchymal "pollution".

- c) Phase-storage: storage followed by deactivation of the toxins in connective and fat tissue and in the vascular system.
- d) Phase-impregnation: from this phase toxins are no longer localized at the level of the mesenchyme but they are channeled at the organic level to a "locus minoris resistentiae" expression of a pre-disposition constitutional or iatrogenic. Incorporated at this level, in the parenchyma nobility, began to dismantle the cell attacking first its enzymatic mechanisms.

### *The cell phase*

It represents pathological situations in which the prognosis is not more favorable, as expressions of the low reactivity of a typical alteration lesion:

- e) Phase of degeneration: the continuing accumulation of toxins impregnation determines, after partial enzymatic block, the damage of intracellular organs, and consequent degeneration of tissues.
- f) Phase-dedifferentiation: chronic inflammatory stimulation of the cell can determine its differentiation into abnormal cells that, even for the simultaneous weakening of the body's defenses-subversion, will take over the entire body.

Great importance is given by Reckeweg to the inflammation phase-reaction; one can say that homotoxicology begins with a critical review of the inflammatory phenomenon: its physiological trigger is in fact the mechanism by which the body has the task of restoring or maintaining its state of health.

We must consider that highly active drugs such as antibiotics, salicylates, steroids, sulfonamides, etc. used in the exudative phase of inflammation determine the change from the acidotic phase that is physiological during inflammation into the alkalotic phase.

The result is the cessation of inflammation: unburned material, bacterial endotoxin, catabolites, and drug molecules synthesis, connective remain in the frame preventing the physiological subsequent restoration.

Modern physiology has taught us that the phase of alkalosis is characterized by the neo-synthesis of protein molecules, if on the ground there are still foreign molecules, it is possible that this untimely neo-synthesis leads to the formation of protein in which amino acids are combined with foreign molecules and residual block inflammation. This creates the formation of abnormal polypeptides in part self and part non-self.

### *The homotoxicological pharmacology*

After these premises, it is clear what is the rationale of the homotoxicological treatment: not to suppress, but detoxify the body and to repair the damage caused by toxins.

The protagonists of this ambitious plan are therapeutic homotoxicological drugs, i.e. dilution of chemicals to trigger the reversal effect which, occurring in enzymatic reactions on which act as inducers, can activate "defensive systems" yet in reserve.

The mechanism can be interpreted in the light of the laws of enzyme kinetics (Michaelis-Menten), and is supported experimentally by the work of Conney and Burns (proof of methylcholanthrene - by Conney AH *Enzyme Regul.*, Vol I, Oxford: Pergamon Press, 1963), Hauss et al. (proof of cortisone - by Hauss, Junge-Husling, Gerlach: *Reactions mesenchymal not soecifiche*, Ed Thieme, 1968) and Wallenfels and Weil (phosphathasis alkaline and galactosyl-glycerol-from Wallenfels and Weil, *Molekularbiologie*, Umschau-Verlag, 1967).

Immunologically, the mechanism of action of the homotoxicological remedy is interpretable in the sense of an increase of the cell-mediated response, but not only. It is now known that the antibody response is

addressed to the specific antigen that has been triggered, but it can also go to any target that has something "similar" (even if only a part of the molecule).

In the complex network of the immune system, the antibody can thus enlarge the purpose of attacking and neutralizing antigens not only identical, but also resembling the original one.

The substance, as diluted (i.e. homeopathic) is immediately neutralized and all the new defensive system can contact against the toxin causal.

### ***Evidence Based Medicine and homotoxicology***

The aim of the review made by Ernst and Schmidt (2004) is to summarise and critically evaluate the evidence from rigorous clinical trials with homotoxicology.

Seven electronic databases were searched for all studies of homotoxicological medicines for any human condition. To be included, trials had to be randomised and placebo-controlled. Data from such studies were validated and extracted according to pre-defined criteria. Their methodological quality was formally assessed using the Jadad score. Key data of all included trials were tabulated and summarised in narrative form.

The searches identified 23 articles related to homotoxicology; the majority of these RCTs were not included in previously published reviews of homoeopathy.

Zell et al. (1989) randomised patients with sprains of one ankle joint into receiving either topical treatment with Traumeel cream® \* or a placebo. All patients also received a compression bandage and electrotherapy. The primary outcome measure was determined on the basis of data from a pilot study as "patients experiencing successful therapy within 8-10 days". The objective measure for this was the mobility of the injured joint. The results show a significant difference favouring verum over placebo. Secondary outcome measures (e.g. pain) corroborate this finding.

Thiel and Borho (1994) conducted a RCT in which 73 patients with knee haemarthros were randomised to receive an injection of either Traumeel or Nall into the affected joint. The therapy was repeated three times during 8 days. The primary endpoint was predefined as an increase of joint mobility to 10 and a decrease of the knee circumference to no more than 0.5 cm above that of the healthy knee. Of the patients in the verum group and the placebo group, 64.9% and 36.1%, respectively, reached this aim. Secondary outcome measures (e.g. number of bloody joint punctures) corroborate this difference. However, the authors do not provide a statistical analysis (or data sufficient to calculate it), and it is thus not possible to tell whether the differences are significant or only reflect a numerical trend. The study is burdened with further serious limitations.

Heilmann (1994) conducted an RCT of twice weekly prophylactic intravenous injections of Engystol N\*\* versus NaCl in healthy army recruits. The primary outcome measure was the frequency of flu or common cold during the ensuing 2 months. Eleven such endpoints were noted in the experimental group and ten in the placebo group, a difference which is obviously neither statistically significant nor clinically relevant.

Böhmer and Ambrus (1992) randomised 102 patients with minor sports injuries into three groups. One group self-administered Traumeel cream, another one Traumeel S cream\* and the control group placebo cream over the injured area. Skin temperature and swelling were the primary outcome measures. The former showed no inter-group difference while the latter did: swelling decreased by 1.9 cm (Traumeel) and 2.2 cm (Traumeel S) and 1.4 cm (placebo) on days 3–5 and by 4.4 cm, 4.7 cm and 3.5 cm respectively on days 13–15. These results were statistically significant, but it seems debatable whether they are clinically relevant.

Weiser and Clasen (1994) published a three-armed RCT of 155 patients with chronic sinusitis. They were randomised to receive either Euphorbium compositum\*\*\* or a similar spray or placebo nasal spray for 5 months. Only results of one verum group (n =53) and the placebo group (n =51) were reported. Therapeutic success was evaluated by a custom-made score, which improved significantly more in the verum than in the control group. Secondary endpoints corroborated this finding. Even though this study has several strengths, it is also burdened with several flaws. Several poignant indicators raise suspicion of bias: the first author is a member of the manufacturer's staff, the stated aim of the study was the "scientific proof of Euphorbium" (while, in science, the aim should be to test rather than to prove), the authors describe their study as of "high standard of methods".

Matusiewicz et al. (1997) separated 61 patients suffering from chronic asthma into 38 who received subcutaneous injections of Asthma H \*\*\*\* and 23 who received placebo for 9 months. The authors used at least 14 different outcome measures that were measured at a frequency not reported. The results section implies that all outcomes improved with verum and many deteriorated with placebo. No statistical details are provided and the study is burdened with too many serious flaws to be interpretable.

Oberbaum et al. (2001) reported a RCT of 30 cancer patients with chemotherapy-induced stomatitis. They

were given either Traumeel S as a mouth rinse or a placebo, which was not described. Patients were thus treated to prevent stomatitis from occurring. This could be achieved in 33% of verum and 7% of placebo patients.

Other outcome variables corroborated this result. Even though small, this study was well designed. The lack of information regarding the placebo treatment is unfortunate as it opens the possibility that the placebo mouth rinse increased the likelihood of stomatitis and the verum was essentially inactive.

\* Gel: 100 g contains: medicinal ingredients: Calendula officinalis Ø 0.45 g; Hamamelis virginiana Ø 0.45 g; Echinacea Ø 0.15 g; Echinacea purpurea Ø 0.15 g; Chamomilla Ø 0.15 g; Bellis perennis Ø 0.1 g; Millefolium Ø 0.09 g; Aconitum napellus D1 0.05 g; Belladonna D1 0.05 g; Arnica montana D3 1.5 g; Symphytum officinale D4 0.1 g; Hypericum perforatum D6 0.09 g; Mercurius solubilis Hahnemanni D6 0.04 g; Hepar sulfuris calcareum D6 0.025 g. Non-medicinal ingredients: carbomer 940, sodium hydroxide solution 18% m/m, purified water, ethanol. Ø: mother tincture.

\*\* 1.1ml ampoule of Engystol N contains: *Vincetoxicum hirundinaria* D6, *Vincetoxicum hirundinaria* D10, *Vincetoxicum hirundinaria* D30 6.6µl each, Sulfur D4, Sulfur D10 3.3µl each.

\*\*\* Nasal spray: 100 ml contains: medicinal ingredients: Luffa operculata D2; Pulsatilla D2; Euphorbium D4; Mercurius bijodatus D8; Mucosa nasali suis D8; Argentum nitricum D10; Hepar sulfuris calcareum D10; Sinusitisinum D13 1 g each. Non-medicinal ingredients: benzalkonium chloride, monobasic sodium phosphate (dihydrate), dibasic sodium phosphate (dihydrate), sodium chloride, purified water.

\*\*\*\* Asthma H. Blatta orientalis D5; Cetraria islandica D5; Ammi visnaga D4; Cactus D3; Yerba santa D4; Ipecacuanha D6; Drosera D4; Natrium sulfuricum D6; Spongia officinalis D5; Datura stramonium D6; Grindelia robusta D3; Chamomilla recutita D5; Gelsemium semperv. D6; Echinacea angustifolia D4. Non-medicinal ingredients: sodium chloride, purified water.

Table of Homotoxicosis (abridged form)

<b>Recovery</b> ←		<b>Biological Division</b>		<b>→ Lingering Illness</b>		
<b>Humoral Phases / Diseases of Disposition</b>		<b>Cellular Phases / Constitutional Diseases</b>				
<b>Tissue</b>	<b>Excretion phases</b>	<b>Reaction phases</b>	<b>Deposition phases</b>	<b>Impregnation phases</b>	<b>Degeneration phases</b>	<b>Neoplasm phases</b>
<b>1. Ectodermal</b> a) Epidermal	Perspiration, cerumen, sebum, etc.	Furuncles, erythema, dermatitis, eczema, pyoderma, etc.	Atheroma, warts, keratosis, clavi, etc.	"Tattooing", pigmentation, etc.	Dermatitis, lupus vulgaris, leprosy, etc.	Ulcus rodens, basalioma, etc.
	Saliva, coryza, etc.	Stomatitis, rhinitis, aphthous stomatitis, etc.	Nasal polypus, cysts, etc.	Leukoplakia, etc.	Ozaena, atrophic rhinitis, etc.	Cancer of the nasal and oral mucosa
	Neurohormonal secretion of cells, etc.	Poliomyelitis in the pyrexial stage, herpes zoster, etc.	Benign neuromas, neuralgia, etc.	Migraine, tics, etc., virus infections (poliomyelitis)	Paresis, multiple sclerosis, optic atrophy, syringomyelia, etc.	Neuroma, gliosarcoma, etc.
	Neurohormonal secretion of cells, etc.	Neuralgia, herpes zoster, etc.	Benign neuromas, neuralgia, etc.	Asthma, ulcer ventr. et duodeni, etc.	Neurofibromatosis, etc.	Gliosarcoma, etc.
<b>2. Entodermal</b> a) Mucodermal	Gastrointestinal secretions, CO <sub>2</sub> , stercobilin, etc., toxins with faeces	Pharyngitis, laryngitis, enteritis, colitis, etc.	Polypi of the mucous membranes, constipation, megacolon, etc.	Asthma, hoarseness, ulcus ventr. et duodeni, carcinoid syndr., etc.	Tuberculosis of the lung and of the intestine, etc.	Cancer of the larynx, stomach, rectum, etc.
	Bile, Pancreatic juice, thyroid hormones, etc.	Parotitis, pneumonia, hepatitis, cholangitis, etc.	Silicosis, goitre, cholelithiasis, etc.	Toxic damage to the liver, pneumonopathy, virus infections, etc.	Cirrhosis of the liver, hyperthyroidism, myxoedema, etc.	Cancer of the liver, gall bladder, pancreas, thyroid gland, lungs
<b>3. Mesenchymal</b> a) Interstitiodermal	Mesenchymal interstitial substance, hyaluronic acid, etc.	Abscesses, phlegmons, carbuncles, etc.	Adiposis, gouty tophi, oedema, etc.	Forestages of elephantiasis, etc., influenza virus infections	Sclerodema, cachexia, velamen vulvae, etc.	Sarcoma of various locations, etc.
	Haemopoiesis, etc.	Osteomyelitis, etc.	Osteophytosis, etc.	Osteomalacia, etc.	Spondylitis, etc.	Osteosarcoma, etc.
b) Osteodermal	Menses, blood and antibody formation	Endocarditis, typhus, sepsis, embolism, etc.	Varicose veins, thrombosis, sclerosis, etc.	Angina pectoris, myocarditis, etc.	Myocardial infarct, panmyelophthisis, pernicious anaemia, etc.	Myeloid leukaemia, angiosarcomas, etc.
	Lymph, etc., antibody formation	Angina tonsillar, appendicitis, etc.	Swelling of the lymph glands, etc.	Lymphatism, etc.	Lymphogranulomatosis, etc.	Lymphatic leukaemia, lymphosarcomas, etc.
e) Cavodermal	Fluid, synovia	Polyarthritis, etc.	Dropsy, etc.	Hydrocephalus, etc.	Coxarthrits, etc.	Chondrosarcoma, etc.
	Urine with catabolites	Cystitis, pyelitis, nephritis, etc.	Hypertrophy of the prostate glands, nephrolithiasis, etc.	Albuminuria, hydronephrosis, etc.	Nephrosis, contracted kidney, etc.	Renal carcinomas, hypernephroma, etc.
b) Serodermal	Secretions of the serous membranes	Pleuritis, pericarditis, peritonitis, etc.	Pleural effusions, ascites, etc.	Forestages of tumours, etc.	Tbc. of the serous membranes, etc.	Cancer of the serous membranes, etc.
	Menses, semen, prostatic fluid, ovulation, etc.	Adnexitis, metritis, ovaritis, salpingitis, prostatitis, etc.	Myomas, hypertrophy of the prostate gland, hydrocele, cysts, ovarian cysts, etc.	Forestages of tumours, (adnexa, uterus, testicles, etc.)	Impotentia virilis, sterility, etc.	Cancer of the uterus, ovaries, testes, etc.
d) Musculodermal	Lactic acid, lactacidogens, etc.	Muscular rheumatism, myositis, etc.	Myogelosis, rheumatism, etc.	Myositis ossificans, etc.	Dystrophia musculorum progressiva, etc.	Myosarcoma, etc.
	<b>Excretion principle, enzymes intact, tendency towards a spontaneous cure, favourable prognosis</b>					<b>Condensation principle, enzymes damaged, tendency towards deterioration, dubious prognosis</b>

The homotoxic phases are arranged vertically, and the tissues affected by the homotoxins are arranged horizontally. Each phase can be related to practically any other through the vicariation phenomena.

### *Adverse reactions and interactions*

Most antihomotoxic medications contain micro doses or even nano doses of active components and therefore are in general considered non-toxic. Few side effects and contra-indications, no interactions with other medications classify homotoxicology as a complementary safe 'gentle' medicine.

Some studies reported that homotoxicology is safe when compared with placebo; no adverse reactions have been pointed out (Ferrara P. 2008; Ratiani L. 2012; Orellana Alvarellos G 2010). Also a review conducted by Ernst (2004) did not report important adverse reactions.

### *Methodology of the discipline in oncology*

Homotoxicology is generally used in oncology to relieve cancer symptoms and/or side effects of anticancer treatments. For example, in literature homotoxicology (Traumeel injection) has been reported for treatment of pain relief after breast cancer treatment (Orellana Alvarellos G 2010).

### *Glossary*

**Burgi Principle:** Burgi postulated that the simultaneous administration of different substances with a similar therapeutic action would create a synergetic effect that is more than the sum of the individual effects of all the single substances.

**Citric acid cycle compounds:** citrate, isocitrate, alpha-ketoglutarate, succinyl-CoA, succinate, fumarate, malate, oxaloacetate: mnemonic: "Citrate is a key substrate for mitochondrial oxidation".

**Krebs cycle:** the Krebs, or citric acid cycle is important in aerobic organisms as part of cellular respiration by which carbohydrates, fats, and proteins yield energy, H<sub>2</sub>O and CO<sub>2</sub>. Each cycle produces 3 CO<sub>2</sub>, 4 NADH, 1 FADH<sub>2</sub>, and 1 ATP from a molecule of pyruvate. Those reactions that converge on the citric acid cycle to 'fill up' intermediates are called anaplerotic reactions.

**Nosode:** homeopathic remedies prepared from a product of disease such as infected tissues or causal organisms.

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## **Anthroposophic Medicine**

### ***Definition and biological effects of anthroposophic medicine***

A comprehensive approach to patient in modern medicine was proposed by Rudolf Steiner *ante litteram*, starting with a cycle of lectures held in Prague in 1911. The whole human being is seen as central, with his diseases and questions. Anthroposophic medicine was developed since then as a scientific and clinical system, which combines mainstream medicine with Rudolf Steiner's anthroposophy. It provides an integrative diagnosis and therapy concept and is practised today in more than 60 countries. In describing health and disease, anthroposophic medicine recognises the interaction of a spiritual-existential individuality with the psychological and bodily dimensions. It is based on the cognitive methods and results of anthroposophy, with its practical applications in science and in the various fields of life and society. Its understanding is compatible with modern system theories in developmental biology and with holistic models of cancer (IVAA 2011; Kienle et al. 2013a).

Anthroposophic medicine has become an original medical system, characterized by a multimodal and interdisciplinary intervention of physicians, prescribing medicinal products and therapies, and therapists trained in anthroposophic health disciplines. The treatment and the therapeutic relationship are highly individualised and are seen as a process, where the self-healing resources of the body, the development of resilience and the empowerment of the patient are encouraged. A whole person and patient centered clinical is proposed. Learning-processes are part of the healing and self-development of the health professionals is a focus during education.

The medical system of anthroposophic medicine offers treatment for acute and chronic disease (Hamre et al. 2005, 2013) as well as suggestions for self-care, health promotion and prevention of illness, through lifestyle (Alfven et al. 2006) and coaching. Patients appreciate it and have a good compliance (Esch et al. 2008; Heusser et al. 2006ab). It has proven to be generally safe (Kienle et al. 2011) and cost saving (Kooreman et al. 2012). Anthroposophic medicine use in children is widespread, both in prevention and treatment and anthroposophic medicine is one of the complementary approaches used in paediatric oncology (Längler et al. 2012). In children, health protection is seen in close relationship to nutrition, lifestyle and education,

Anthroposophic medicine has been widely investigated, from the historical observation of experience to the actual high standards of research. Its concepts have inspired new cultural and practical issues in the methodology of research (Kienle et al. 2006). It is taught worldwide (IVAA 2012) and handbooks of anthroposophic internal medicine (Husemann et al. 1941-1978; Girke 2012) and in specialist domains, among which pediatrics (Soldner et al. 2013), have been published and are periodically updated.

Anthroposophic medicine is known and studied in cancer treatment (Kienle et al. 2003, 2013a, Patel et al. 2013) as an integrative medical system, forerunner of the recent concepts of integrated care in oncology, but is also known for the development of the anthroposophic injectable extracts derived from the mistletoe plant (*Viscum album* L.).

### ***History and worldwide diffusion data***

Anthroposophic medicine evolved historically from the work of the Austrian philosopher Rudolf Steiner (1861 - 1925) and the Dutch physician Ita Wegman (1876-1943), together with others colleagues from the 1920s. The first medical courses were held in Prague (1911) and Dornach (1920) (Steiner 1911-1924; Steiner et al. 1925). Since then, anthroposophic medicine spread at first to Middle European countries and later all over the world.

Concerning *diffusion*, it is not easy to have adequate figures of physicians practising anthroposophic medicine (anthroposophic medicine). Some are qualified as anthroposophic doctors by an international certificate, gained through official educational programs (certification is given by the Medical Section at the Goetheanum, CH-Dornach). Others are practitioners prescribing out of different levels of training. Anthroposophic medicine is prescribed by doctors only and practised by doctors and therapists in collaboration. According to von Ammon et al. (2012), among the approximately 305.000 registered CAM practitioners in the EU, 4.500 practice anthroposophic medicine (1/100.000 inhabitants in EU). Recognition of anthroposophic medicine has different levels among EU member states and Switzerland.

The last report of the International Federation of the Anthroposophic Medical Associations (IVAA, the international umbrella organisation which represents and coordinates the national anthroposophic doctors' associations, in regard to political and legal concerns) was published in July 2012 and is based mainly on

surveys conducted within the councils of most of its member associations (2009, 2011, 2012). In the report 2012 (IVAA 2012), the outstanding figures for anthroposophic medicine worldwide were as follows.

- In Europe anthroposophic medicine is practised by more than 2700 fully anthroposophic medicine trained licensed medical doctors in 22 EU member states, Norway and Switzerland. In addition anthroposophic medicine is prescribed by about 15,000 physicians with various levels of training (estimate, based on various data). Outside Europe about 500 fully anthroposophic medicine trained physicians and another 1.000 doctors work, with various levels of training.
- In Europe anthroposophic medicine is provided in 24 hospitals in 5 EU member states and Switzerland (14 of those have Accident&Emergency services, 2 of those are university teaching hospitals). Outside Europe there are still no fully working hospitals established.
- In Europe anthroposophic medicine is provided in >120 outpatient centres (physician and at least 1 anthroposophic therapist) in 14 EU member states, Norway and Switzerland. Outside Europe another 60 outpatient centres have been established.
- In Europe anthroposophic therapies are provided by >7000 anthroposophic therapists (“classical anthroposophic therapies”) and nurses in 25 EU members, in Norway and Switzerland. Outside Europe another 700 therapists offer anthroposophic therapies.
- In Europe anthroposophic medicine is provided in >500 institutes for people with learning difficulties in 19 EU member States, Norway and Switzerland, with several thousands of anthroposophic social workers. Outside Europe more than 1000 anthroposophic social professional are engaged in the work with people with learning difficulties.
- In Europe anthroposophic medicine is regularly taught at universities and medical schools in 7 EU member states and Switzerland (university chairs in Germany, Netherlands and Switzerland). Outside Europe regular anthroposophic medicine teaching at universities has been established in Brazil, Peru, the Philippines and in the United States.
- In Europe anthroposophic medicine-full training with certificate is provided for medical doctors in 7 EU member states and Switzerland. Outside Europe full training curricula in anthroposophic medicine have been established in Argentina, Brazil, Chile, Israel, Peru, The Philippines and in the United States.

Anthroposophic medicine is applied in primary and clinical care in different *settings*: practices, therapeutic centres, hospital departments, clinics, hospitals, university hospitals, aftercare clinics, homecare. There is a strong tendency to include in the same setting a staff of medical and therapeutic professional figures. The structures practising anthroposophic medicine follow the normal quality control systems of hospitals and institutes and can apply, in addition, an anthroposophic quality control system (AnthroMed®).

Anthroposophic medicine can be prescribed with alternative, complementary or integrated intention, according to indications and patients' preferences.

In Germany, Switzerland and Sweden, there are hospitals, providing acute medicine, internal medicine and various specialties, including oncology, such as the Gemeinschaftskrankenhaus Havelhöhe (Berlin, D), the Gemeinschaftskrankenhaus Herdecke (Herdecke, D), the Filderklinik (Filderstadt, D) the Vidarkliniken (Järna, S), the Paracelsus-Spital (Richterswil, CH) and the Ita Wegman Klinik (Arllesheim, CH).

Other institutions are specialised in cancer treatment (Klinik Öschelbronn, Öschelbronn, D; Lukas Klinik, Arlesheim, CH), internal medicine (Paracelsus-Zentrum für Anthroposophische Medizin, Bad Liebenzell-Unterlengenhardt, D; Klinik Öschelbronn, Öschelbronn, D), psychiatry (Friedrich-Husemann-Klinik, Buchenbach, D; Lievegoed Klinik, Bilthoven, NL), neurology and rehabilitation (Raphael Medical Center, Hildenborough, UK) or other.

In some conventional hospitals there are departments or services with anthroposophic medicine facilities, including oncology and/or palliative care (Regionalspital Emmental AG - Abteilung Komplementärmedizin, Langnau, CH; Ospidal Engiadina Bassa - Abteilung Komplementärmedizin, Scuol CH; Zentrum für Integrative Medizin Kantonsspital St. Gallen, St. Gallen, CH).

Other rehabilitation and inpatient healthcare centres, treating patients with cancer, are the Casa di Salute Raphael, Roncegno, I; the Rudolf Steiner Health Center, Ann Arbor, US; the Haus am Stalten, Steinen, D; the Raphael Medical Center, Hildenborough, UK, and the Casa di cura Andrea Cristoforo, Ascona, CH.

The detailed list can be found at [www.anthro-kliniken.de](http://www.anthro-kliniken.de) and in Kienle et al. (2013).

Anthroposophic medicine patients' organisations are present in 16 countries and merge in a federation counting around 50.000 patients (European Federation of Patient's Associations for Anthroposophic Medicine, EFPAM), concerned with health promotion themes and pluralism in therapeutic choice.

The training in anthroposophic medicine is a complementary extension to conventional education for professional figures such as physicians, nurses, physical therapists, psychologists and counselors (double competence). Other therapies, such as art therapies and eurythmy therapy, require a specific anthroposophic training and curriculum, lasting 4-6 years. Training is more diffuse in Europe, but education of anthroposophic medicine is available worldwide (IVAA 2011, 2012). A crucial focus in education is dedicated to self-development of physician and therapist, according to anthroposophy, to arouse skills in observation, diagnose, medical consultation and treatment.

### *Fundamentals*

Anthroposophic medicine extends and integrates conventional medicine with an anthroposophic perception of the human being. It includes in its assessment of the patient both the conventional diagnosis and a specific evaluation of the imbalances of the physical, biological, psychological, mental and spiritual dimensions.

It uses conventional, herbal and homeopathic medicinal products together with original anthroposophic medicinal products and offers, in addition, specifically developed anthroposophic therapies, prescribed as “pharmacoequivalents”. It represents a best practice example of integrative medicine as defined by the Consortium of Academic Health Centres for Integrative Medicine. The treatment approach and the use and selection of its medicinal products and therapies are individualised and aim to a development process within the patient, reinforced from various directions. An understanding of anthroposophic medicine and of its fundamental issues can be increased by referring to books concerning fundamentals (e.g. Husemann Wolff 1941-1978; Selg 2006), in references (IVAA 2011) and (IVAA 2012) and on the online references listed below. Health promotion measures and treatments aim to have an impact on health culture and prevention, as well as in curing disease. The official scientific journal for anthroposophic medicine is *der Merkurstab*.

Anthroposophic medicine has by definition a holistic approach, grounded in the anthroposophic image of human being. The definition was given by Rudolf Steiner in his written works (Steiner 1911-1924; Steiner and Wegman 1925). The integration of the physical, biological, mental and spiritual dimensions is described according to different sets of categories, which are used in diagnosis, in the pathogenetic descriptions of disease and in the association of remedies to symptoms or syndromes.

A first perspective sees the human being in four levels of organisation or shaping principles: a bodily level accessible to physical and instrumental examination; a life-forces level, describing vitality, healing processes and formative forces of the organism; a soul level, accessible to psychological/emotional description and the level of the spiritual individuality, the self-conscious, self-educating and active subject of a unique biography. A second perspective describes the interactions in health and disease between three morphological and functional systems: a nerve-sense system, a rhythmic system of balance in respiratory and circulatory organs, and a metabolic and locomotor system.

Disease can be described as an imbalance of the above systems, specific for the pathogenetic process of a disease and for the single patient history and constitution, or as a dislocation of a physiological process in space or time.

Another focus in anthroposophic medicine is the so called salutogenetic principle, i.e. the recognition and potential stimulation of the self-healing resources in the human organism.

Accordingly, the approach to patient is individualised, whole person oriented and patient-centred. The patient’s choice, empowerment and active participation in the healing processes are emphasised. Disease is considered as an event involving the whole biography. Accordingly, a cure project and a composition of interventions are offered to patients, depending on physician-patient agreement and on the available local resources. Emphasis is put on close caregiver-patient relationship, to support the coping efforts of the patient with the disease. Consultations are usually longer than conventional ones and this might be one of the reasons why patients seek CAM. In Germany health benefit programs have included the reimbursement of this additional physician time (Hamre et al. 2007c).

Anthroposophic medicine is a medical system, as the therapy is multimodal. Physicians and therapists work together in interdisciplinary relationships. Physicians can prescribe both anthroposophic medicinal products (AMPs) and therapeutic non-pharmacological interventions (NPIs), in an individual composition, according to the specificity of the disease and of the single person. Conventional therapeutic procedures are used as well, for anthroposophic medicine is meant to be an extension of conventional medicine. The anthroposophic medicine treatments can be therefore used, in the individual case and according to diagnose, with an alternative, complementary or integrative concept.

Another special focus of anthroposophic medicine is health promotion and prevention, particularly in infancy and adolescence, therefore developing an interactive perspective of medical approach with innovative methodologies in agriculture (biodynamic agriculture) and pedagogy (Waldorf education, curative education), arising from anthroposophic view of man and nature.

#### *Treatments - Anthroposophic medicinal products*

Anthroposophic medicinal products (AMPs) are produced according to anthroposophic pharmaceutical principles and processes, some of which they share with homeopathy and some of which are specific non-homeopathic processes that reflect the relationship between human beings and the nature kingdoms. They are manufactured according to the standards of Good Manufacturing Practice (GMP) and their quality is controlled by the criteria and parameters of official pharmacopoeias. The methods of production are specified in the German and Swiss pharmacopoeias and in the Anthroposophic Pharmaceutical Codex. Anthroposophic medicinal products are produced by dedicated manufacturers (Abnoba, Birken, Helixor, Novipharm, Weleda, Wala) and by expert pharmacies. As well as homeopathy, anthroposophic medicine uses dilutions and dynamisation proceedings. Usually the dilutions are decimal (1:10). Substances come from mineral, plant and animal realms and are mostly used in a dose range from ponderable to low-middle potency (D1 to D30). Original preparations come from special pharmaceutical processing of a composition of substance, as the so called “Dorons” or the anthroposophic *Viscum album* injectable extracts. Concepts and processings are related to the anthroposophic knowledge of human being. Oral and injectable preparations, rectal suppositories, vaginal tablets, ointments, oils and gels are used. A non-profit European scientific cooperation (European Scientific Cooperative on Anthroposophic Medicinal Products, ESCAMP) investigates, for scientific and regulatory purposes, questions regarding the system evaluation of anthroposophic medicine.

#### *Treatments – Non pharmacological interventions*

In addition to medicinal products, anthroposophic medicine prescribes originally developed therapies and instruments. They include external applications, medicinal baths, nursing techniques, physiotherapy and rhythmical massage, dietetics, a movement therapy (eurythmy therapy), therapeutic arts (music, drawing, painting, sculpture, speech), anthroposophic psychotherapy and biographical counseling, lifestyle coaching, psycho-educational groups.

Art therapy requires an inner and outer activity of the patient. The anthroposophic concepts apply the application of music, drawing, painting, sculpture, and speech, in order to influence bodily functions, physiological regulation of respiratory, heart and circulatory imbalance, emotional conditions and self-perception and awareness. Another active therapy is an originally developed movement therapy, called eurythmy therapy, which translates speech and music into gestures and movements, in order to stimulate, strengthen and regulate bodily functions and processes. Eurythmy therapy has specific prescriptions following the diagnosis and patients refer improvements also in self-awareness, sense of security and trust. Architecture and rhythms in time shaping are also cherished in order to create a “healing environment” in the therapeutic settings.

In anthroposophic medicine external therapies are often prescribed, such as embrocation or compresses, oil dispersion baths and nursing techniques. In the field of physiotherapy and massage, a rhythmical massage therapy has been developed, which employs the basic massage items in a rhythmical alternation of binding and loosening. In nutrition, along with the generally shared healthy diet concepts, anthroposophic physicians promote the use of biodynamic (“Demeter” trademark) quality food (Huber et al. 2011; Huber et al. 2012).

Counseling and psychotherapy have been extended in order to include the special focus given by anthroposophic medicine to the perspective of the spiritual nature of the human being, developing through a unique biography. Disease is seen as an event inside the entire biography. Some elements derived from general anthroposophy - such as the development of biography in seven year periods, the perspective of destiny in observing relationships and life in his social context, the basic exercises for inner development – are used for mindfulness and to help in finding meaning and sense to the course of disease and the biographical events.

#### *Concepts and hypothesis on the mechanisms of action of the anthroposophic medicine treatments*

In anthroposophic medicine, treatments are aimed both to the physical and to the other levels and mechanisms of action are not easily defined. Actual research investigates different ways to study

appropriately anthroposophic concepts in physiology and medicine. The mechanisms of action of the treatments are seen in relationship to the inner balance / imbalance of the organism processes and systems. The pharmacological and pharmacodynamic knowledge of the effects of substances in ponderable quantity and the homeopathic effects of the high-diluted substances (already discussed in the chapters “Homeopathy” and “Herbal medicine”) is extended to other aspects.

To let the facts emerge, some mechanisms of action have been studied recurring to biological, physiological and existential concepts. Investigations have gone towards biomarkers assessing, biological qualitative testings, rhythmological observations, person-centred questionnaires.

In a biological perspective, the well-known concepts of psychoneuroendocrinology (PNEI), based on the work of H. Selye in the 30's (Ader 2007; Selye 1976; Bottaccioli 2005), and of epigenetics (Russo et al. 1996; Biava 2008; Chahwan et al. 2011) can be helpful in thinking and studying the different levels of interaction of the body-soul-individuality system. The concepts of complex system theory (Nicolis et al. 1977; Prigogine 1978; Chapoutier 2009) and of system variability (Nani et al. 2007; Cysarz et al. 2013b) also lead to understand the balance and the epigenetic influences in the systems and to measure the variations of complex systems. One of the application fields is the evaluation of high dilutions and dynamisation/succussion procedures in plant models: variability seems to be one of the targets of homeopathic treatment effect (Betti et al. 2003, 2010; Nani et al. 2007). Variability is also studied in relation to heart rate (Cysarz et al. 2013a).

The influence of treatments on biological systems, such as the immune system, can be studied by examining its separate components as biomarkers, searching the minimal components combinations, which can show effects. The immune system, based on self/non-self distinction and substrate of higher regulation levels, is often taken as exemplary of the action of anthroposophic medicine treatments, especially in cancer. It is difficult to explore, monitor and predict and is therefore object of further studies (Orange 2010; Baars et al. 2012).

In the physiological domain, investigations concerns physiology, rhythmology, active reaction to stimulus, adaptive behaviours, compensations, behaviour patterns in time and space, constitutional assets and their evolution under treatment. The reactions of the human organism to a therapeutic stimulus or path are seen both as a reflex reaction and a regulation process towards a new higher balance. Aspects of vegetative regulation (sleep, cardiovascular, respiratory, orthostatic regulation, thermoregulation), of emotional behaviour and the ego competence in life shaping functions are taken in account. Circadian rhythms are considered as mirror of the imbalance and reconquered new balance during and after treatments. Rhythmology has been the theme of several anthroposophic medicine investigations (Kienle et al. 2006).

Concerning existential questions, the research groups of Kröz has published several papers, to define the different levels of questioning (vegetative, rhythmological, existential) and their integration in real life. Medical anamnesis is completed by the addition to conventional questionnaires for quality of life, clinical benefit and disease-specific questions, of own validated inventories, specifically developed for evaluation of health condition and treatment benefit from anthroposophic perspective. The first questionnaire in this direction was suggested by Rudolf Steiner (1920) and has been further developed. Questionnaires and analytic techniques are chosen to allow the specific anthroposophic issues to become more visible. These inventories are grounded on salutogenetic concepts and differentiate from coping questionnaires, which focus on avoiding/adapting to stressful situations and focus on active behavioural and physiological changes. In the context of health-related and disease-related quality of life, the inventories originated in anthroposophic medicine become interesting options for better understanding and evaluation of the mechanisms of action and the clinical benefit of single treatments or medical systems, with a focus on behavioural modifications.

In this regard, some studies addressed specific outcomes such as

- self regulation, sense of coherence and autonomic function
- heart rate dynamics and cardio-respiratory coordination
- life and formative forces.

#### *Self regulation, sense of coherence and autonomic function*

Questionnaires and epidemiological evaluation of autonomic function, self regulation and sense of coherence were found to be reliable tools to measure individual constitution, mind-body imbalances and psychosomatic abilities in healthy subjects and in patients with specific disease groups. Resilience development has been studied after the experience of the victims of the German concentration camps during the II world war.

Autonomic regulation deals with the composition of various elements reflecting the regulative state of vegetative functions. The validated inventory on autonomic regulation (aR inventory) measures chronobiological and autonomic functions such as rest/activity rhythms, dizziness, orthostatic regulation, thermoregulation, metabolism and digestion. It shows appropriate scores in health subjects and impairment in cancer patients and internal medicine patients with chronic disease. (Kröz et al. 2000, 2003, 2008b, 2011a, 2011b). Another tool to observe the balance of the physical, living, psychological and spiritual level is given by the Herdecke Quality of Life questionnaire (HLQ) (Kröz et al. 2008a).

Self regulation deals with competence and autonomy and is seen as a “problem solving capacity in terms of an active adaptation to stressful situations to restore well-being”. It has been associated with better outcome. The validated Self Regulation Questionnaire (SRQ) has been used to evaluate healthy subjects, internal medicine patients and cancer patients (Büssing et al. 2009; Kröz et al. 2011b).

Sense of coherence deals with the feeling of inner coherence and resilience and the physiological thermocoherence. The validated Internal Coherence Scale (ICS) has been used in cancer patients. It is also related to autonomic regulation and to reduction of anxiety/depression. The results are consistent with increase of physical and role functioning and global health obtained with EORTC-QLQ C30 (Kröz et al. 2009).

#### *Heart rate dynamics and cardio-respiratory coordination*

Impairment of circadian rhythms is associated with various clinical problems, has a negative impact on quality of life and immune regulation and has been associated in cancer patients with fatigue and poorer prognosis. It can be expressed e.g. by sleep disturbance, heart rate variability analysis or cardio-respiratory coordination. These parameters appear to be altered in various physiological and pathological conditions, such as stress, fatigue, cardiovascular diseases, diabetes or breast cancer and can be beneficially influenced by anthroposophic medicine therapies such as mistletoe extracts, Cardiodoron® (Onopordon Primula comp.), eurythmy therapy, speech therapy. (Cysarz et al. 2000, 2004, 2005, 2008, 2013; Bettermann et al. 2001, 2002; Hildebrandt 1999; Seifert et al. 2009, 2012, 2013; von Bonin et al. 2001). This could suggest an influence of some anthroposophic medicine treatments on the recovery of autonomous nervous and of the chronobiological regulation in human organism.

#### *Life and formative forces*

The impact in vitro and in biological models of potentised substances and of the succession procedures has been widely studied by the group of Betti and Nani in Italy (Betti et al. 2003, 2008, 2013; Nani et al. 2007) and by Baumgartner and Heusser in Germany (Baumgartner et al. 2009, Marschollk et al. 2010; Wolf et al. 2013)

We can use the idea of fields of forces, generating traces in physical forms, and suppose an influence of illness or illness-tendencies, which determinate in a similar way an inner imbalance in the field of life and formative forces. Methods have been developed to show these patterns through biological qualitative testing (capillary dynamolysis and sensitive crystallisation imaging). The tests add to conventional biochemical quantitative evaluations qualitative and processual information. When they are read, a qualitative description of the different form elements and their interactions is given. They are used e.g. to show the biological or biodynamic quality of medicinal plants or food. Traditionally they are also applied to show pathological tendencies in individual blood, as well as they can be added to patient treatment documentation. The qualitative evaluation can be implemented with a neural network approach and the visual evaluation can be standardised (Doesburg et al. 2007; Huber et al. 2010; Unluturk et al. 2011).

#### *Evidence Based Medicine and anthroposophic medicine*

Recent research about anthroposophic medicine has described a wide and complex and scientific clinical world. Evidences suggest that anthroposophic medicine is effective, safe, and cost effective in several conditions (Kienle et al. 2003, 2006, 2011, 2013a). Patient satisfaction is high (Kienle et al. 2006; Esch et al. 2008).

Use in children is safe and it is effective in disease treatment. Anthroposophic lifestyle and health care lead to reduced allergy and sparing use of antibiotics and vaccinations. Anthroposophic medicine is also used as a safe complement in paediatric oncology.

The amount of published work is huge and of different quality. First publications started in the 1910's. The great majority of the studies show positive results for anthroposophic medicine treatments and cover

quantitative and qualitative questions. Also the highest quality studies have given positive results. Best quality studies have been done in the last decades. The special needs of anthroposophic medicine and other CAM have generated new approaches in research methodology which contribute to general science and to innovative study designs.

The spectrum of research concerning anthroposophic medicine ranges from acute to chronic disease management, from maternity and infancy to elderly age, from health prevention to cure, from primary care to in-patients treatment and covers most fields of medicine. Research in anthroposophic medicine has been conducted in clinics and hospitals, in dedicated research institutes, in university departments and in clinical practices (see "References"). Prospective and retrospective studies and systematic reviews on different topics have been published, as well as Health Technology Assessment (HTA) reports on the anthroposophic medicine whole system. However the individualisation of treatments makes research with conventional methods more difficult, also good methodological quality studies are present and the overall positive results of reports confirm the clinical experience.

#### *Effectiveness, safety, costs*

Prospective trials (controlled and without control group) have shown efficacy of anthroposophic medicine as a whole system or of single medicinal products or non pharmacological interventions in many disease conditions, such as chronic disease, cancer, rheumatic diseases and osteoarthritis, acute upper airways infections, acute and chronic pain, fibromyalgia, hepatitis and chronic gastrointestinal inflammatory diseases, anxiety/depression, obstetrics/gynecology, endocrinology and wound healing. Practice relevance was high. Studies have been conducted in adults and in children. (Kienle et al. 2011).

Looking at the prospective controlled trials in all fields excluding cancer, 23 studies on anthroposophic medicine, involving 2773 patients have been published. RCTs are 10. All the studies gave in the great majority a positive result for anthroposophic medicine. Most gave a better and/or quicker outcome in at least one parameter. Concerning symptoms, in some studies anthroposophic medicine proved to be effective after long lasting disease or in conditions without response to conventional treatments. Comparison was versus no treatment, placebo or conventional medicine. Where anthroposophic medicine was compared to conventional medicine, the efficacy was comparable (lower in 1 study) but with lower side effects. 3 studies are about anthroposophic medicine as whole medical system, 17 about anthroposophic medicinal products (among which some of the most used, such as Cardiodoron®, Kephalodoron®, Iscador®, Scleron®, Wecesin®) and 3 about non pharmacological interventions (eurythmy therapy and nursing procedures). Improvements were evaluated in clinical or laboratory parameters or with general and disease-specific questionnaires.

In the following conditions anthroposophic medicine has given in prospective controlled studies a positive result: actinic keratosis (Huyke et al. 2009), acute ear and upper airways infections (Hamre et al. 2005), ageing with loss of memory and attention (Weckenmann 1979), bronchial asthma (Andriashvili et al. 2007), cardiovascular diseases, such as hypotension and post myocardial infarction (Fischer et al. 1985, Weckenmann et al. 1984, Mayrhofer 2007), fever in children (Ulbricht 1991), headache/migraine (Flemming et al. 1974), low back pain (Hamre et al. 2007f), prevention of chemorelated mucositis (Tiemann et al. 2006), improvement of pain or of wound healing after surgery for orthopaedic conditions (Jeffrey et al. 2002, Karow et al. 2008), recurrent infections in Chernobyl immunodepressed children (Chernyshov et al. 1997), stress (Kanitz et al. 2011), post-stroke (Wilkens et al. 2008), venous insufficiency (Weckenmann et al. 1987), umbilical wound healing (Janke et al. 1997, Guala et al. 2003). In 1 of the migraine studies, the anthroposophic medicine medication showed no advantage versus placebo (Krabbe et al. 1980). In 1 trial, an anthroposophic compositum reached clinical relevance only after 6 consecutive months (von Hagens et al. 2012). In 1 trial concerning osteoarthritis of the knee, the anthroposophic medicine medication was not superior to placebo in pain reduction, but was combined to higher reduction in pain medication (Huber et al. 2010). Using a combined anthroposophic medicine medication before and after dental surgery the results on pain, swelling and bleeding were comparable to the conventional treatment with painkillers and antibiotics, with supposed fewer side effects and reduced costs (Donati et al. 2012).

Observational studies also suggest a clinical benefit for anthroposophic medicine medications in several diseases (Kienle et al. 2011). One of the conditions of interest is allergic rhinitis. Treatment with and anthroposophic medicine classical medication (Gencydo®) could improve the symptoms of hay fever in 2/3 of the patients (Baars et al. 2005). The medication has been object of a range of studies from the clinical practice to in vitro experiments, to RCT (Gründemann et al. 2011, Baars 2008, Baars et al. 2011, 2012), to

determine efficacy and differentiate the administration routes. A large long-term study conducted in Germany, on chronic inflammatory rheumatic diseases treated with anthroposophic medicine, is on the way to publication. The pilot study has been published by Simon (1997).

Data bases for pharmacovigilance receive regular data from physicians, concerning general medicine (EVAMED) and cancer (Network Oncology). Safety and tolerability are high, as described below.

A positive impact of anthroposophic medicine on costs is described by several studies including economic analysis. A few studies describe a favourable cost structure and found cost-savings (Kienle et al. 2006, 2013a). Cost-effectiveness in comparison with conventional treatments has been described and needs larger observations. Reduction of hospitalisations for cancer and clinical improvement in patients with long term chronic diseases also contribute to cost savings (Hamre et al. 2006b; Hamre et al. 2010b; Studer et al. 2011a; Kooreman et al. 2012).

Education to management and socioeconomical research in CAM need to be implemented in medical education. An yearly Master-Course on “Health systems, traditional and non-conventional medicine” has started in 2011 at the Milan (I) University. It is thought for operators and decision-makers in health organisation concerning CAM, included anthroposophic medicine (management, administration, evaluation, and research) (Roberti et al. 2011).

### *Clinical research in anthroposophic medicine*

Performing clinical research in the anthroposophic medicine requires some additions to standard research. anthroposophic medicine is a therapy system, has in its background elaborate concepts, transcending biophysical models and has been used in real-life for one century, with good clinical experiences reported by doctors and patients.

Work and coworking of several institutes (publications, university projects, expert conferences, training courses) has built up in the last decades a research architecture, which combines different investigation methods (Hamre et al. 2009, Kienle et al. 2011a). RCTs have been and are planned and published, but they are more useful to examine specific questions and have limits in evaluating complex systems. The theme of the ethical conflict between individuality and RCT remains unsolved and need an extension (Heusser 1999; Kienle et al. 2006). The value of clinical judgment is encouraged and developed through cognition-based medicine (Kiene 2001). The depth of clinical experience is recognised and evaluated in scientific processes, such as the peer-reviewed data collections on single AMPs (Vademecum) and the clinical registers. The uniqueness of the patient history and process in treatment can as well find a scientific frame and come to medical community in the form of published case reports (Kienle et al. 2012). The uniqueness of physician / therapist experience can be described in the case reports and can be shared, peer-reviewed or evaluated in collective research projects (Vademecum, AMOS study). The pool of publications is evaluated in meta-analyses, reviews and HTA reports.

The references listed at the end of the chapter are exemplary and not exhaustive of the existing literature concerning anthroposophic medicine. Larger sources can be found in the AnthroLit and the TOPIC projects. Extensive lists are included in the reviews and in the research institutes websites.

The research strategies have to be adapted and implemented. The conventional research model evolves from the laboratory to the clinical use. The evaluation of anthroposophic medicine, coming from the clinical practice to clinical and preclinical studies, needs a reverse research model. Evaluation of anthroposophic medicine and of other CAM therapy systems “need to be integrative and cover the dimensions of: (1) therapeutic professionalism; (2) patient perspective and public demand; (3) conceptuality; (4) safety, effectiveness, and costs” (Kienle et al. 2011). Research needs also to reflect the routine clinical activity and aims to evaluate both the system and its components: single treatments or disease conditions. Hamre (2010) summarises in his papers the different issues of clinical research in relationship to the identity of anthroposophic medicine.

### *The anthroposophic medicine HTA report 2006-2011*

The most extensive evaluation of effectiveness, utility, costs and safety of anthroposophic medicine has been published by Kienle et al. (2006, 2011). 253/265 trials showed an improvement of disease in at least one relevant parameter. The updated review describes good clinical outcomes for anthroposophic medicine, only marginal side effects, high satisfaction of patients with regard to results and safety and presumably slightly less costs. Further high-quality evaluations are desirable. (Kienle et al. 2011).

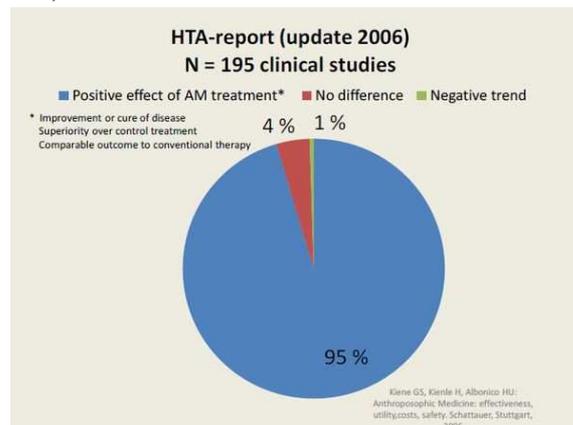
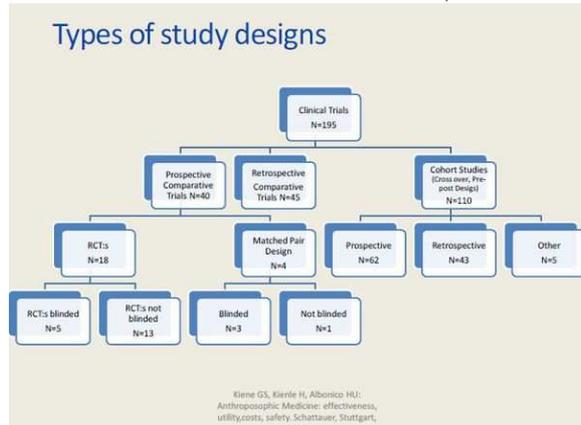
The Swiss government commissioned a Health Technology Assessment Report of five CAM, included anthroposophic medicine, as part of the PEK (Complementary Medicine Evaluation Programme). The HTA

report was first updated and published in 2006 (Kiene et al. 2006) and has been the first systematic appraisal of the scientific evidence on the efficacy/effectiveness, utility economics and safety of anthroposophic medicine. This first analysis examined 2090 studies, of which 195 were suitable for the chosen analysis criteria. An update, adding 70 new clinical studies was published in 2011 by Kiene et al., after the result of the Swiss referendum of 2009, which included in the constitution the recognition CAM. The methods for the systematic review were identified, according to the guidelines of the Swiss Federal Insurance Office and of the Swiss Federal Office of Public Health, and four clinical analysis domains were defined: 1) anthroposophic medicine as a whole system, 2) pain and wound care, 3) non pharmacological interventions and 4) cancer. Four databases and a specialised journal were searched and extensive expert consultations were used. Studies were selected according to predefined inclusion criteria, data were extracted, and methodological quality was assessed individually. Most studies showed a positive result for anthroposophic medicine. Methodological quality differed substantially, but the studies with better quality still showed a positive result. Practice relevance was high. (Kienle et al. 2011).

Altogether, 265 clinical studies investigated efficacy and effectiveness of the whole system of anthroposophic medicine, of single medications and NPIs, in various conditions:

- 74 prospective controlled trials, of which 38 randomized controlled trials and 36 prospective non randomised trials
- 49 retrospective trials with control groups
- 90 prospective trials without control groups
- 52 retrospective trials without control groups

The studies investigated a wide spectrum of anthroposophic medicine treatments in a multitude of diseases; the whole anthroposophic medicine system in 38 studies, non-pharmacological therapies in 10 studies, anthroposophic medicine mistletoe products in cancer therapy in 133 studies, and other anthroposophic medicine medications in 84 studies. (Kienle et al. 2011).



The AMOS outcome studies and the “seven practices study”.

One of the methodologically good and large studies in anthroposophic medicine is a pluriennial outcome study coordinated by H. Hamre, with the IFAEMM research group in Freiburg, called Anthroposophic Medicine Outcomes Study (AMOS) and has produced numerous publications (Hamre et al. 2004-2013). It was a prospective observational cohort study of patients treated with anthroposophic medicine in primary care in Germany, for chronic mental, musculoskeletal, respiratory and other diseases. In the study 151 anthroposophic physicians, 275 therapists and 1631 patients participated (Hamre et al. 2013). Anthroposophic treatment was associated with improvements of symptoms and quality of life.

In the last update, (Hamre et al. 2013) were evaluated 1.510 outpatients aged 1-75 years, starting anthroposophic treatment for chronic conditions in routine German outpatient settings with a 48-months follow up. Main outcomes were Symptom Score, SF-36 Physical and Mental Component scores in adults, and disease-specific outcomes in the six most common diagnosis groups: asthma, anxiety disorders and migraine, depression, attention deficit hyperactivity symptoms, and low back pain. Median disease duration at baseline was 3.5 years. From baseline to 48-month follow-up all ten outcomes improved significantly ( $p < 0.001$  for all pre-post comparisons). Standardised Response Mean effect sizes were large (range 0.84-1.24 standard deviations) for seven comparisons, medium for two comparisons (SF-36 Mental Component: 0.60, Low Back Pain Rating Scale: 0.55), and small for one comparison (SF-36 Physical Component: 0.39).

Symptom Score improved significantly with large effect sizes in adults and children, and in the four main anthroposophic therapy modality groups (art therapy, eurythmy therapy, rhythmical massage therapy, medical therapy). In a nested prospective non-randomised comparative study of patients with low back pain, patients treated with anthroposophic medicine had a significantly stronger improvement of quality of life, compared to patients receiving conventional treatment ( Hamre et al. 2007f).

Qualitative analysis of primary care showed positive effects and patients' satisfactions in chronic diseases also in a previous evaluation of seven therapeutic centres and medical practices, offering anthroposophic treatments in the United Kingdom (Ritchie et al. 2001). The research addressed three major questions: What is anthroposophic medicine as understood and interpreted by doctors, nurses and therapists working within general practice? How is anthroposophic medicine organised and delivered within primary care settings in the UK? What impact does anthroposophic medicine have on patients, both in terms of clinical outcomes and patient responses? AMPs and NPIs were evaluated in relation to patterns of use and outcome.

### *The clinical registers*

Two electronic networks are active in the anthroposophic medicine clinical practice context and are based in the Forschungsinstitut Havelhöhe (FIH) – Berlin (Matthes 2010). *EvaMed* (Evaluation anthroposophischer Medizin) is a prescription-based electronic system connecting in a network physicians expert in anthroposophic medicine (Jeschke et al, 2005, 2007). The project has been started in 2004 to evaluate the indications of anthroposophic medication, to monitor primary care and to describe pharmacovigilance and cost-effectiveness of anthroposophic medicine in general anthroposophic medicine practice. The *EvaMed* project has generated several publications on prescription patterns and safety in anthroposophic medicine (Jeschke et al. 2007, 2009a, 2009b, 2009c, 2010, 2011a, 2011b, 2012). Embedded in the *EvaMed* system, a second network is dedicated to the application of anthroposophic medicine in oncology and comparison to other CAM and conventional oncology: the Network Oncology (NO). The NO group has built up an international clinical cancer register for clinical efficacy, epidemiology, pharmacovigilance and cost-effectiveness of anthroposophic medicine in oncology (Schad et al. 2013).

### *The Vademecum experience*

In 2006 started a peer reviewed retrospective evaluation of clinical experience at international level. Data collection concern single medicinal products (single substance or compositum, oral, parenteral, external administration form, indication, dosage, duration of treatment, expected response, adverse reactions, contraindications; benefit or lack of benefit. The result is the *Vademecum* of anthroposophic medicine, at his 3<sup>rd</sup> German edition (GAÄD 2013). It contains 1543 indications for 559 anthroposophical medicine products, with 11.656 literature indications. Prescribed medications for cancer symptoms or side effects of cancer conventional therapies are found among the indications, but cancer treatment as such is not included and will be object of a further separate publication. The 2013 edition is published in German and English, Italian, Spanish and French translations have been or will be published before 2014, in paper and electronic searchable format. 210 physicians from 18 countries contributed to the last edition.

### *Clinical and fundamental research on NPIs*

A few studies have evaluated research on anthroposophic non pharmacological treatments.

Eurythmy therapy was effective in chronic diseases in adults (Hamre et al. 2007d) and children (Hamre et al. 2009), such as asthma (Hamre et al. 2009f), migraine (Hamre et al. 2010d), depression (Hamre et al. 2006d), ADHD (Majorek et al. 2004; Hamre et al. 2010c), anxiety and stress (Kanitz et al. 2011, Kienle et al. 2011e); and others. Positive effects in cancer related fatigue (Kröz et al. 2013) and neurorehabilitation (Kanitz et al. 2013ab) have been described. Inner correspondence and feeling of peacefulness after eurythmy therapy and yoga have been positively scored by Büssing et al. (2011). Reviews of eurythmy therapy in primary care and clinical studies have been published by Hamre et al. (2007b) and Büssing et al. (2008).

Art therapy proved to be effective in chronic diseases in adults (Hamre et al. 2013) and children (Hamre et al. 2009), for conditions such as depression (Hamre et al. 2010b), cancer related depression and fatigue (Bar-Sela et al. 2007, Kanitz et al. 2012; Kröz et al. 2013).

Effectiveness in chronic diseases was demonstrated for rhythmical massage (Hamre et al. 2007e). All NPIs seemed to be helpful in palliative care for cancer (Heusser et al. 2006ab).

Fundamentals of eurythmy therapy and speech therapy are under investigations and first results on physiology of rhythms have been published (Cysarz et al. 2004-2013; Seifert et al. 2009)

A few studies have been made regarding nutrition. The impact on human health by biodynamic food has been considered in a review (Huber et al. 2011) and the overview of published studies needs further development. The PARSIFAL study (14.000 children, 5 European countries) found that children receiving organic/biodynamic nutrition were found to have less allergies and a lower body weight (Alfven et al. 2006; Huber et al. 2011; Simões-Wüst et al. 2013). Insulin-resistance, relevant in diabetes, metabolic syndrome and cancer, is reduced by oat-diet and intestinal flora is improved (Zerm et al. 2013).

#### *Education, carer-patient relationship, spirituality*

Carer-patient relationship in anthroposophic medicine has been evaluated in relationship to spirituality issues. This is also a fundamental subject in medical training. Few publications concern issues related to new models and concepts in education, introducing from the beginning of medical training skills for development coming from anthroposophic medicine and based on non-reductionistic anthropology (Heusser 2012; Heusser et al. 2012; Neumann et al. 2011, 2012; Scheffer et al. 2010, 2011, 2012, 2013). The role of spirituality in patient perspectives and in the therapeutic relationships has been studied by Büssing et al. (2010-2013) in physicians, in patients with chronic pain, chronic disease and cancer. Specific questionnaires have been developed in this direction (SpREUK-SF10, Büssing 2010; SpNQ, Büssing et al. 2010). The preliminary results of a qualitative study with European doctors, active in integrative oncology and anthroposophic medicine, concerning psychological, biographical, and spiritual factors in integrative cancer care, has recently been presented by Kienle et al. (2013c) and stress the relevance of resilience, dignity, choice, emotional freedom from cancer in the caregiver-patient relationship.

#### *Innovations in research methodology*

Anthroposophic concepts in medicine have had a cultural and practical impact on research methodology and face the challenges of medical ethics and of the individual and whole system approach.

##### COGNITION-BASED MEDICINE

Cognition-based medicine (CBM) has been developed by H. Kiene and colleagues, to restore the value of physician experience and expertise and to implement evidence, with a methodology able to describe both individual and complex aspects of disease and treatment. Key elements are the criteria-based assessment of therapeutic causality at the level of the individual patient and the methodological professionalization of clinical judgment. CBM study designs expand the current range of clinical research, extending from criteria-based causality assessment in single cases to new forms of cohort evaluations. (Kiene 2001, 2005)

##### CASE REPORTS METHODOLOGY

Case reports describe the individual case and often contribute to discoveries and to the development of new treatments (Kiene et al. 2006). They can describe a complex treatment and a therapeutic process in time. 2090 single case reports have been sent for the first HTA report. Scientific quality is given by education of clinical judgment (Kiene et al. 1998, 2011; Kienle 2012) and by accurate methodology for describing events and effectiveness (Kiene 2001). This aim seemed to have captured international interest and led to the newly published CARE guidelines: an international consensus-based clinical case reporting guideline (Gagnier et al. 2013). Following this methodology, diverse Authors have published until now positive case report in anthroposophic medicine (e.g. cancer related fatigue and sc. mistletoe, Wode et al. 2009; Merkel cell cancer / breast cancer and high dose mistletoe, Orange et al. 2010; anxiety and eurythmy therapy, Kienle et al. 2011; primary cutaneous B-cell lymphoma, Orange et al. 2012; childhood diabetes and integrated system-oriented multidisciplinary anthroposophic medicine treatment, Kienle 2013; cutaneous squamous cell cancer and perilesional high dose mistletoe, Werthmann et al. 2013).

##### EVALUATION OF WHOLE SYSTEMS

Anthroposophic medicine, and the other CAMs need specific assessment strategies, combining and organising different high-quality research methods. A systemic approach is described by Kienle et al. (2011a), based on “well-conducted randomized and nonrandomized studies, cohort studies, qualitative research, high-quality case reports and case series, studies on patient perspective, safety analyses, economic analyses, etc. Good clinical judgment, a core epistemic element of medicine based on nonstochastic principles, should also be integrated and could reflect routine patient care.” (Kienle et al. 2011a, 2013a)

##### RESEARCH IN ULTRAHIGH DILUTION

In preclinical research, an issue has been the development of biochemical/biophysical techniques (Wolf et al. 2009, Baumgartner et al. 2009, Marschollk et al. 2010)) and of plant models, started with experiments of L. and E. Kolisko in the 1920s, and newly developed in the last decades to investigate quantitative and qualitative aspects of the ultrahigh / dynamisation (Betti et al. 2003-2013, Nani et al. 2007).

### *Utilizers*

Healthy people and patients who utilise anthroposophic medicine cannot be easily defined. Most surveys, especially concerning cancer, examine a complex of CAM or CAM techniques and few publications describe specifically anthroposophic medicine users in Europe. A profile of women in the 30s-50s, with high education, seem to prevail in some surveys, as well as patients with long duration of disease or severe diseases, like cancer, chronic pain or psychiatric disorders, and slightly differentiates in different countries. Families involved in children parenting and elderly are also good utilizers of anthroposophic medicine. Among major reasons and appreciations from patients are the avoidance of conventional treatments side effects, unmet needs, a longer consultation time, a tailored patient-centred approach, active engagement in the treatment, combination of conventional and anthroposophic medicine, the encouragement to personal growth and learning.

Patients preferences towards equivalent choices have also to be taken in account and can influence research. Mistletoe as a medication for cancer patients, e.g., is so popular in some European countries that patients refuse randomisation in clinical trials comparing VAE to other treatments.

### *Children*

Anthroposophic medicine has a special focus on children. Both education and lifestyle are involved in health promotion and in children body- and soul-spiritual development. The whole system of anthroposophic medicine has an impact on health and treatment of acute and chronic disease (Hamre et al. 2005, 2007a) and is safe (Hamre et al. 2007a; Längler et al. 2010). “Anthroposophic lifestyle” promotes healthy nutrition with biological/biodynamic food, rich in whole cereals and in lactobacilli for intestinal flora, moderates antibiotic and vaccination use and is not suppressive of childhood febrile infections. Anthroposophic education, borne for the children of the workers in the Waldorf-Astoria factory (called Waldorf schools or Steiner schools) is based on a whole-person understanding of children development, and is aimed to raise self-confidence and creativity in learning and to support healthy development phases. The anthroposophic lifestyle has been associated with reduction of the incidence of allergic diseases (Stenius et al. 2011; Lluís et al. 2013) and mistletoe treatment can reduce the incidence of recurrent infections in immunodepressed children (Chernyshov et al. 1997, 2000). NPIs are used in rehabilitation, treatment and prevention also by children. A statistically significant effects of Steiner school attendance for osteoarthritis (OR 0.69 [0.49-0.97]) and allergic rhinitis (OR 0.77, [0.59-1.00]) as well as for symptom burden from back pain (OR 0.80, [0.64-1.00]), insomnia (OR 0.65, [0.50-0.84]), joint pain (OR 0.62, [0.48-0.82]), gastrointestinal symptoms (OR 0.76, [0.58-1.00]) and imbalance (OR 0.60, [0.38-0.93]) has been described by Fischer et al. (2013), in a study on 1136 former Steiner school attendees and 1746 controls.

### *Adverse reactions and interactions*

Adverse effects related to anthroposophic medicine prescriptions are infrequent, also for injectables, considered essential in anthroposophic medicine practice, and for mistletoe in its different administration ways. In the AMOS study the clinical use of 949 anthroposophic medicinal products over 11,487 patients-months was well tolerated. The incidence of adverse reactions to AMPs was 3% of the AMP users and 2% of the AMPs used (Hamre et al. 2006). Side effects of NPIs are rarely reported and could lead to stop the treatment only for rhythmical massage (2%), never for eurythmy therapy or art therapy (Hamre et al. 2007). No severe side effects have been described Kienle et al. (2011) concluded after examining 265 studies in the reevaluation of the 2006 HTA report (Kienle et al. 2006). ) that side effects or other risks were rare and usually described to be mild or moderate. Studies regarding safety showed a good tolerability altogether.

Similar results have been obtained with patients self-reported side effects in the IIPCOS study, in 715 primary care patients with acute respiratory or ear infections treated with anthroposophic medicine incidence was 0.61% (2/327) of all different AMPs used, 0.28% (2/715) of patients, and 0.004% (3/73,443) of applications (Hamre 2005, 2006c, 2007a). Compared to conventional treatment, anthroposophic medicine treatments gave generally less (Hamre et al. 2005; Esch et al. 2008; Plangger et al. 2006) or comparable (Esch et al. 2008) rates of side effects.

Using the pharmacovigilance system of the EVAMED database (Matthes et al. 2008, Süsskind et al. 2012), 38 physicians of primary care described no serious adverse event. The rate per 10.000 prescriptions were 4,4 % for CAM drugs and 13% for conventional drugs in primary care (Süsskind et al. 2012) and 0,2% in hospitalised patients (Süsskind et al. 2011). Also the common plant medications obtained from chamomile

arnica and calendula resulted safe in 42.378 prescriptions (Jeschke et al. 2009a). Tolerability of *Viscum album* and *Helleborus niger* extracts are described in following paragraphs. Educational interventions have been used to improve physician reporting of adverse drug reactions in primary care (Tabali et al. 2008).

Use of injectable preparations of mineral and plant origin and organotherapeutics is widespread in anthroposophic medicine and appreciated by physicians. Surveys among physicians confirmed safety of injectables, with rare side effects (Baars et al. 2005; Kienle et al. 2006; Jong et al. 2012).

A systematic evaluation demonstrated that the reporting rate of ADRs associated with anthroposophic and homeopathic solutions for injection is very low. Most reported ADRs were listed, and one quarter consisted of local reactions. These findings suggest a low risk profile for solutions for injection as therapeutically applied in anthroposophic medicine and homeopathy. (Jong et al. 2012). Between 2000 and 2009, in total, 303 million ampoules for injection were sold, and 486 case reports were identified, corresponding to a total number of 1180 ADRs. Of all case reports, 71.8% (349/486) included ADRs that were listed (e.g. stated in package leaflet), and 9.5% (46/486) of the reports were classified as serious. The most frequently reported ADRs were pruritus, followed by angioedema, diarrhea and erythema. A total of 27.3% (322/1180) were localized reactions for example; application or injection site erythema, pain, swelling and inflammation. The overall reporting rate of ADRs associated with injections was less than 4 per 1 million sold ampoules and classified as very rare.

AMP prescriptions are safe and well tolerated. Evidence come from the quoted studies (physician and patient-reported) and from peer-reviewed physician-reported clinical experience (GAÄD 2013). The tolerability of several single AMP has been described in large populations, for long durations, both in adults and children, for with acute and chronic diseases, in primary care and in hospital treatments. Parents with children using anthroposophic medicine for cancer recommend it to other families.

### ***Methodology of the discipline in oncology***

Cancer treatment has been since the beginning one of the relevant matters in anthroposophic medicine. It is specially known for the mistletoe injectable extracts, initially developed by Rudolf Steiner and Ita Wegman starting from 1916-1917. The motif of a global approach, facing body and mind issues, and of a bridge-building perspective between conventional and anthroposophic medicine were present already in 1920 (Steiner 1920). Since then, anthroposophic cancer care has evolved, in clinical practice and in research, as a multimodal intervention and as an extension of conventional oncology.

Some of Rudolf Steiner's views about cancer anticipate actual themes: an inclusive concept in oncology, the relationship between the cancer cell and the organism, the influence of the soul and spiritual events on the living body, the role of fever and of acute inflammation as promoters of immunity, the essential qualities of lifestyle, art, movement, nutrition and environment. We know well today the importance of chronic inflammation and of the macro- and microenvironment in cancer. We start giving more attention again to the immune system in cancer prognosis and treatment. Concepts of healthy process dislocation, of imbalance in the organism systems and of imbalance between healthy (acute) inflammation capacity and cancer development are suggested. The role of biographical events and of soul attitudes is not clearly demonstrated and nevertheless is seen by patients and part of clinicians as a determining factor in genesis, prognosis and care.

Especially patients with chronic diseases and patients with cancer ask for complexity in treatment. In the institutions and therapeutic centres providing anthroposophic medicine, the proposal of intervention is interdisciplinary and comes from different directions. Cancer treatment adds to standard therapies the extracts from *Viscum album* L. and *Helleborus niger* L., together with anthroposophic medicinal products. An individual combination of treatments is offered in relation to local resources. Patients' perspective, preferences and satisfaction are taken in account (Kienle et al. 2013a) and spiritual needs are seen as relevant (Kienle et al. 2013c).

According to anthroposophic concepts, no intervention aims to a single effect and each treatment aims to the whole of the patient. However it is possible to describe objectives at different levels, to be shared in the discussion with cancer patients. Raising hope and health resources is considered part of quality of life. At the bodily level, the aims of the treatments (nutrition, medicinal products and non pharmacological interventions) are to enhance the immune system, nourish and support the constitution and the organs, promote cell differentiation, reduce the side effects of conventional treatments and contribute to tumor response. Medications, lifestyle coaching, rhythmical massage, eurythmy therapy are oriented to the

improvement and the recovery of physiological functions and of circadian rhythms. The different therapeutic arts are more oriented to the soul, exploring creativity and personal active resources, and help fighting passivity, anxiety and depression. Medicinal products, arts, biographical counseling, psychotherapy and meditation, all contribute to self regulation, resilience, inner growth and coping with the disease and the development of personal relationships.

Mistletoe therapy is often synonymous of anthroposophic medicine in cancer. Most of the published studies concern the mistletoe extracts. A few studies concern other medications and NPIs (art therapy, eurythmy therapy) in cancer or specific issues in cancer, such as fatigue (Bar-Sela et al. 2007; Kanitz et al. 2012, 2013ab, Kröz et al 2013). Some medications have been studied in other diseases and could be suggested for studies in specific cancer topics, such as Cardiodoron® (Cysarz et al. 2000; Mayrhofer et al. 2007; Weckenmann et al. 1984) for cardiooncological questions. There is an interest for psycho-educational groups arising from anthroposophic medicine concepts and introducing to multidimensional practices, to rehabilitate patients with specific diseases. Group work for patients empowerment have offered with positive results (Havelhöher Herzschule, [www.herzschule.org](http://www.herzschule.org); Portalupi 2012; Kröz et al. 2013).

Children with cancer and survivors can be seen as populations with special interest in comprehensive long-term treatments with anthroposophic medicine.

#### *Mistletoe (Viscum album L.) extracts*

The white berry mistletoe (*Viscum album* L.) is a hemiparasitic plant belonging to the family of Viscaceae. They flower and fruit in winter and grow on various host-trees without damaging the host. It is known to traditional medicine as alcoholic extract or herbal tea and it is found in complementary medications for hypertension or other indications. *Viscum album* extracts (VAE) have been originally introduced in cancer treatment only following the intuition of Rudolf Steiner, at the beginning of last century. History and documents date from the initial collaboration between Rudolf Steiner and Ita Wegman (Leroi 1987; Selg in press) and have evolved until today in the development of medicinal products, in clinical application and in research (Kienle et al. 2003, 2013a; Scheer et al. 2013). The first case report of a cancer treatment with an anthroposophic VAE dates from 1917, by dr. Ita Wegman (Walter 1953). They are actually one of the most commonly prescribed complementary cancer therapy in Central Europe (Heusser et al. 2006a; Kienle et al. 2007).

The anthroposophic VAE (Abnobaviscum, Helixor, Iscador/Iscar/*Viscum album* fermentatum, Iscucin, Isorel/Vysorel) are prepared mixing the extracts of the summer and winter plant, with an original processing (Heertsch 1985), by dedicated manufacturers, according to standardised procedures and GMP. They can be fermented or unfermented and are available from different hosts, such as almond (amygdali), apple (mali), ash (fraxini), birch (betulae), elm (ulmi), fir (abietis), hawthorn (crataegi), maple (aceris), oak (quercus), pine (pini), poplar (populi), lime tree (tiliae), willow (salicis). The choice is made according to tumor entity, gender and therapeutic intention.

Injectable, oral and external preparation are present. VAE are used mostly as ampoules for subcutaneous administration, but can also be administered in intravenous, oral, topical, intraperitoneal, intrapleural, intralesional use. Dosages vary from D30 to over 100 mgs, according to the therapeutic intention and to the product. Usually a dose escalating administration is chosen, with increasing dosage, according to individual response. Frequency of the subcutaneous administration is daily to once weekly. The duration is individual. Grossarth-Maticsek et al. (2001) observed a relationship of the duration of mistletoe treatment with the clinical benefit. The off-label intravenous administration is becoming more frequent and proved to be safe, also at higher dosages (Büssing 2006; Kienle et al. 2011d; Wiebelitz et al. 2013) and to prevent surgery-related immunosuppression (Büssing et al. 2005; Enesel et al.).

VAE have been studied in several clinical studies, in most tumor entities and stages and with different endpoints (survival, quality of life, reduction of side effects of conventional treatments, side effects, and cost-effectiveness). Few reviews reported the main features and evaluated the methodological quality of the studies. Preclinical research has investigated their components and their activity in vitro and in animal models (Kienle et al. 2003b). The studied components have proven to be active and are considered synergic in the whole extract.

Many substances have been found to be biologically active: lectines and viscotoxines (Urech et al. 2006, 2007; Stan et al. 2013), polysaccharides (Jäger et al. 2007), flavonoids (Deliorman et al. 2006), triterpene acids (Urech et al. 2005; Weissenstein et al. 2012) and others.

The mechanisms of actions have been intensively studied. Immunomodulation and cytotoxicity, mainly via apoptosis, are the more known activities. But also DNA-stabilising (Büssing et al. 1996, Kovacs et al.

2002), antiangiogenic (Elluru et al. 2009) and antiviral (Wiebelitz 2013) activities have been observed. VAE exert a protective effect on healthy bone marrow cells against chemical damage, reducing the cytotoxicity induced by methotrexate (Sekeroglu et al. 2012) and cyclophosphamide (Burkhart et al. 2010). The in vitro and in vivo experiments with VAE are numerous.

The immune system appears to be enhanced at several levels (increase and/or activation of neutrophils, eosinophils, T cells, natural killer cells, Th1 response, cytokines). Fever induction as an expression of immune enhancement and of health resources activation is seen as an aim in the anthroposophic mistletoe treatment (Orange 2010; Kienle 2012a) and VAE are also combined to hyperthermia. Albonico et al. (1998) observed that febrile infectious childhood fever were associated to lower risk of cancer in adulthood. The mistletoe properties are reviewed in Büssing 2000; Braedel-Ruoff et al. 2010; Orange 2010; Kienle et al. 2003, 2011, 2013.

Several clinical trials have been conducted on VAE. Many have good methodological quality, especially the most recent ones. Studies investigated VAE alone or the effectiveness of VAE added to conventional treatments. Randomised and non-randomised prospective trials investigated VAE in patients with bladder cancer, breast cancer, cervical cancer/dysplasia, endometrial cancer, gastric cancer, liver cancer, lung cancer, pancreas cancer, osteosarcoma, ovarian cancer, and reported mostly positive results in at least one endpoint. 4 retrospective studies described survival and treatment related quality of life in breast cancer, colorectal cancer, melanoma, pancreatic cancer and melanoma (Augustin et al. 2005 Friedel et al. 2009; Bock et al. 2004; Matthes et al. 2010; Ostermann et al. 2009). The results are described in the chapters related to the single tumor entities. The published reviews conclude for safety and improvement in quality of life (Kienle et al. 2003a; Kienle et al. 2007; Horneber 2008; Ben-Arye et al. 2010).

In 2013 a randomised study demonstrated a significantly prolonged survival with VAE in patients with advanced pancreatic cancer (Tröger et al. 2013). A benefit on survival was described until recently mainly by epidemiological studies (Grossarth-Maticek et al. 2001-2008), Ziegler et al. 2008, 2010) and is suggested by pilot studies.

Tumor remissions are not frequent and are mostly observed with high dosages or intralesional/intravenous/intraleural use. They have been described e.g. for pancreatic (Matthes et al. 2007), liver (Mabed et al. 2004), and breast cancer (Orange et al. 2010b), for lymphoma (Orange et al. 2012).

The most relevant evidence in studies with anthroposophic VAE concerns the improvement in quality of life and a protective effect against conventional treatment side effects. The main benefits consisted in improved coping, sleep, appetite, energy, fatigue, depression and anxiety, nausea, diarrhea, pain, neuropathy, ability to work and emotional and functional wellbeing, reviewed by Kienle et al. (2010). The reduction of chemotherapy side effects and the possibility of maintaining dosage and time schedules of chemotherapy are frequently observed adding VAE to single and polichemotherapeutic regimens (see chapter on quality of life).

Use of VAE has been associated to increased self-regulation (Grossarth-Maticek et al. 2001). A higher degree of spiritual quest is associated with increased CAM use, and higher expectations (Ben-Arye et al. 2012b)

VAE are safe, and side effects are minor. Although a number of different mistletoe extracts have been used in human studies, the reported side effects have generally been minimal and not life threatening (NCI PDQ 2013). Frequent and expected side effects are the dose-dependent local skin reaction and flu-like symptoms. Allergic reactions have been reported and are rare (Kienle et al. 2007; 2011b). VAE are safe also at high dosages. A systematic review of all 69 clinical studies and 48 animal experiments investigating higher dosages of VAE in animals and humans did not show immunosuppressive effects. Side effects were local reactions, dose-dependent flu-like effects and occasional allergic reactions. Altogether VAE seems to exhibit low risk but should be monitored by clinicians when applied in high dosages. (Kienle et al. 2011d)

No mutagenic or teratogenic effects are seen with VAE (Stein 2000; Stein et al. 2000; Kienle et al. 2003b) No interactions between VAE and chemotherapeutic agents are known. VAE do not inhibit cytochrome p450 (Engdal et al 2009; Doehmer et al. 2012). They do not interfere with the pharmacokinetic of gemcitabine and with VAE higher dosages of gemcitabine are tolerated (Mansky et al. 2010). In vitro VAE have shown synergic properties against neoplastic cells with other conventional drugs, such as paclitaxel (Pae et al. 2001), doxorubicine (Sabovà et al. 2010) or bortezomib (Freudlsperger et al. 2007). An advantage in cost-effectiveness with VAE is described at least in one study on cancer (Longhi et al. 2009) and in primary care (Kooremans et al. 2010) but needs further evaluations.

More information will come in the near future also from data base records. The Network Oncology (NO) Group, based in the Havelhöhe has built up an international clinical cancer register for clinical efficacy, epidemiology, pharmacovigilance and cost-effectiveness of anthroposophic medicine in oncology. It counts actually 10,405 patients with cancer, recorded in 6 years, in centers known for anthroposophic medicine. There is no difference in stage distribution with other epidemiological registers. 80% of the patients received mistletoe preparations and 63% received NPIs. One third of the patients received their 1st conventional treatment in a NO facility. (Schad et al. 2013).

Finally, VAE are used with positive results also in veterinary medicine (Biegel et al. 2013; Christen-Clottu et al. 2013).

#### *Hellebore (Helleborus niger L.) extracts*

Hellebores (*Helleborus niger* L. and *Helleborus foetidus* L.) are winter-flowering plants, belonging to the family of Ranunculaceae already known in traditional medicine. Anthroposophic medicine reintroduced hellebore use with original concepts, for indications in psychosomatic, internal medicine and oncohematology. It has been used to date as adjuvant treatment in cancer and haematologic malignancies in adults and children, rheumatic diseases (rheumatoid arthritis, arthrosis, and collagenoses), endometriosis, nephritic syndrome in children, anxiety and depression (Breitkreuz 2010, Debus 2010, Soldner 2010, Schnürer 2010, Wilkens 2010, GÄAD et al. 2013). No clinical trials have been performed to date.

The anthroposophic hellebore extracts are produced according to GMP by dedicated firms (Helixor, Wala, Weleda), to obtain the injectable and oral forms. Processing can be different. The aqueous extract of the winter whole plant is used in one case. With another method, the extracts are manufactured harvesting and extracting the plant at midsummer (flowers and stalks) and Christmas time (leaves, rhizome and roots). They are then mixed to obtain the final product with a special process, similar to the processing of mistletoe. The starting substance is then potentized and sterile-filtered. Of the two hellebores, *Helleborus niger* has been more frequently used and studied. The common name is Christmas rose.

Among the main components identified in *Helleborus niger* there are saponines, flavonoids and bufadienolide. Other components are lactone protoanemonines, ranuncosides (5-hydroxy laevulinic acid glucosides), aconitic acid and corituberin. Hellebore also contains the steroid hormone beta-ecdysone, known in entomology for its differentiating properties. (review in Jesse 2010). Beta ecdysone and saponines seem to be responsible for cytotoxicity and diuretic and anti-inflammatory effects. Protoanemonines show antibacterial effects (review in Schlodder 2010).

The common administration routes are the subcutaneous and the oral ones. Dilutions vary from D30 to D3. The injectable ampules are administered subcutaneously in decreasing dilution steps, with individual dose-finding and usually with daily to twice-weekly frequency.

In vitro experiments showed efficacy of *Helleborus niger* extracts against malignant cell lines from different origins: neuroblastoma (NXS2) (Delebinsky et al. 2012b), lymphoma (BJAB), leukaemia (NALM-6, Sup-B15 and REH) and melanoma (MEL-HO) (Jesse et al. 2008, 2009). The extract of the whole plant and of the roots have the most powerful effect. Apoptosis was found to be the major mechanism of cell killing (Jesse et al. 2008; Delebinski et al. 2012b). Black hellebore extracts were active also against ex vivo leukemia cells from children with ALL/AML and could overcome in vitro ex vivo resistance to antracyclines, vincristine and paclitaxel (Jesse et al. 2008, 2009). We lack significant *in vitro* demonstration of immunomodulatory actions (Büssing et al. 1998).

No toxicity has been seen in the clinical use. Only the accidental ingestion of the plant can be toxic (mucositis, cramps, nausea/vomiting, dizziness). The diluted anthroposophic extracts are safe and no undesired side effects have been described, even at the lowest (D1) dilutions (Schlodder 2010). As expected side effect, a transient local reaction at the injection site can be observed, at the higher concentrations. No studies concerning interactions have been found and no contraindications are known.

Clinical benefit is described only by casuistics and is recommended by clinical experience (GAÄD 2013). No clinical trials with hellebore extracts are present to date. Favourable course of disease are reported in breast cancer (Debus 2010), cancers of the urogenital tract and of nervous system (Wilkens 2010); lymphoma (Breitkreuz 2010; Debus 2010), lung cancer (Breitkreuz 2010; Debus 2010), melanoma (Debus 2010), rheumatic diseases (Schnürer 2010; Wilkens 2010) and other conditions (Breitkreuz 2010; Debus 2010; Schnürer 2010; Soldner 2010). Whole-brain radiotherapy and chemo-brain have also been described in case reports and represent a possible indication (Debus 2010). Clinical indicators suggesting the choice of anthroposophic hellebore extracts can be the presence of edema, inflammation, pain or fever, the

advanced cancer stage and the haematologic conditions in general (Schlodder 2006; Breikreuz 2010; Debus 2010). Trials investigating the efficacy of hellebore and the single indications are needed.

### **Conclusions**

According to the actual literature, anthroposophic medicine has proven to be safe, effective and can help in costs saving, in health and disease managements. Health promotion and prevention are relevant issues. The activation of health resources is an important aim of the treatments. Patients' preferences, compliance and satisfaction are high. Users are adults and children. International cooperation concerning anthroposophic medicine is present in Europe and at international level for scientific, educational, political and regulatory issues (IVAA, ESCAMP, EFPAM, ECHAMP). Physicians and therapists can receive trainings all over the world with 4-6 yrs. curricula and international certifications. Evidence of positive outcome and safety is present for the anthroposophic medicine in general and for cancer treatment. Adverse events are not frequent.

Anthroposophic medicine can safely contribute to cancer treatment, alone and in combination with conventional oncological treatments. It improves quality of life in patients with cancer and survivors, reduces side effects of conventional treatments, and possibly contributes to overall survival from cancer, tumor response and prevention. Anthroposophic medicine in cancer offers an individual integrates treatment for the whole person. *Viscum album* and *Helleborus niger* extracts are the medicinal products more used in patients with cancer. Further studies are currently ongoing concerning the specific endpoints of cancer care. Patients with cancer look for a comprehensive and individualised approach to disease and recovery. The offer of the complex intervention of anthroposophic medicine can meet some of their needs and can intensively implement the actual cancer standard treatments.

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### **Glossary**

**AMP:** Anthroposophic Pharmaceutical Products

**AnthroMed®:** AnthroMed® is the trade mark of the anthroposophic hospitals which are guaranteed by the quality control system for anthroposophic clinics. See <http://www.anthromed.de>.

**Anthroposophy:** 'Anthropos' and 'sophia' mean 'man' and 'wisdom' respectively in ancient Greek. The etymological meaning of the term 'anthroposophy' is 'wisdom of man'. Anthroposophy is defined in the Webster Encyclopedic Unabridged Dictionary of the English Language as 'A philosophy based on the teaching of Rudolf Steiner (1861–1925) which maintains that, by virtue of a prescribed method of self-discipline, cognitional experience of the spiritual world can be achieved'.

**Biography:** in the context of anthroposophic medicine, the term biography relates to the development of the individual in a lifetime from childhood to maturity and thereafter to physical 'decay' until death. During a lifetime each age has a specific physical, psychic and spiritual constellation leading to a differentiated understanding e.g. of the meaning and thus therapy of a disease in one age or another. During a lifetime the individual gradually takes hold of his or her inner self at the expense of physical vitality. This process may need professional counselling.

**Capillary dynamolysis:** it is a laboratory investigational method developed in the '20 by dr. Lily Kolisko. The method involves capillary dynamolysis on bibulous paper first with an aqueous extract of a plant sap. Followed by a metal salt, usually silver nitrate, which serves as indicator to develop the structured pattern. The pictures are evaluated qualitatively describing the different form elements and their interactions. The method is employed in blood testing and in quality evaluation of medicinal saps and food.

**Cognition-based medicine (CBM):** Cognition-based medicine (CBM) is a newly-developed

methodological system of scientific medicine (Helmut Kiene and colleagues). Its primary element is the criteria-based assessment of therapeutic causality at the level of the individual patient. Principles and criteria of single-case causality assessment have been analysed and explained. CBM enables a methodological professionalization of clinical judgment, as well as the explanation of physician experience and expertise.

**Eurythmy therapy:** Eurythmy therapy employs speech, gestures and music, translating them into a unique form of movement. Each consonant and vowel is connected to a particular movement. These exercises are specifically designed to stimulate, strengthen and even regulate every function and process of the human body. For more information see <http://www.hermeshealth.co.uk/euryth.htm#therapy>.

**Formative forces:** Structuring forces which give form and shape to mineral substances. In anthroposophic pharmacy raw materials are considered to be the result of the formative forces of the mineral, plant, and animal worlds. These forces are similar to the formative forces acting on the human organism.

**Life forces:** Life forces are vitality forces that make human beings grow, feel healthy and regenerate after straining, injury and illness. They enable self-healing and recovery.

**Metabolic system:** the metabolic system is that part of the body function that brings regeneration, cell growth and healing.

**Nerve sense system or catabolic system:** nerve sense system or catabolic system is that part of body system where body cells and substances are destroyed, as a basis for life function like awareness and cognition.

**NPI:** non pharmacological interventions.

**Rhythmic system:** a term used in anthroposophic anthropology and physiology that relates to the balancing rhythmic activities in human physiology between the awareness of the senses and nerves and the metabolic system. The rhythmic system acts in any organ and function, though is mainly located in the cardiorespiratory system.

**Salutogenesis:** the principle of concentrating on factors that support human health and well-being in contrast to factors that cause diseases. Salutogenesis is a term coined by Aaron Antonovsky, a Professor of Medical Sociology (see Aron Antonowsky, Unravelling the mystery of health. How people manage stress and stay well. Ann Arbor 1987). The 'salutogenic model' is concerned with the relationship between health, stress and coping.

**Self regulation:** the "ability actively to achieve well-being, inner equilibrium, appropriate stimulation, a feeling of competence and a sense of being able to control stressful situations", Grossarth Maticek 2001, 2008.

**Sensitive crystallisation:** it is a laboratory investigational method developed in the '30 by dr. Ehrenfried Pfeiffer. It is based on the principle that, when a salt (especially Copper chloride,  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ ) crystallises out of an aqueous solution, the crystal growth is influenced by the presence of other substances in the solution, such as blood or plant extracts. If a mixture of copper chloride solution with a small amount of blood or plant or food extract is allowed to crystallise on a level glass plate under controlled experimental conditions, an aggregate of crystals forms, which is specific for the sample that is used. Many investigations of blood have revealed empirically the relationships between various disease tendencies/processes and the phenomena of the blood crystallisation picture. The method is also used to evaluate the quality of plants for medicinal use and of biological / biodynamic food and wine. Literature: link to [www.kristallisationslabor.ch/3150.html](http://www.kristallisationslabor.ch/3150.html)

**Spiritual:** the anthroposophic understanding of the spiritual dimension is that each human being is a unique immortal individual. This individual undergoes a lifelong process of development in illness and in health. In the context of anthroposophic medicine, the term 'spiritual' mostly relates to the sources of development of

the individual personality, e.g. in a crisis leading to major sense of responsibility, goodness, social awareness, self-awareness and self-confident knowledge about one's origin and future.

**VAE:** *Viscum album* L. extracts.

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## Chapter 4

### **CAM and symptoms. Adverse effects of anticancer therapy and cancer related symptoms. Literature data and clinical experiences**

#### **Introduction**

Cancer patients are burdened by symptoms related to the disease itself or to the toxicities of treatments. That's why in this chapter both cancer related symptoms and the adverse reactions of current antitumor therapies are described.

The attention was focused on a group of symptoms chosen from those that affect a cancer patient and precisely: anxiety and depression, diarrhea, hot flashes, pain, edema and lymphedema, cancer related fatigue (CRF), insomnia, mucositis, nausea and vomiting, neuropathy, leucopenia, radiodermatitis, constipation and xerostomia.

Each symptom or pair of symptoms (as in the case of nausea and vomiting for instance) has been analyzed reporting the evidence found in the literature for the respective CAMs that are the object of this publication and in conformity with the criteria explained in Chapter 2.

Each paragraph on a symptom also lists the possible adverse reactions and the interactions with the anti-cancer medication.

These symptoms have been chosen for different reasons; the choice is primarily based on the most frequent demand of complementary treatments from the patients who have to face cancer-related symptoms. This is the case of some iatrogenic symptoms, such as nausea and vomiting with chemotherapy - oral complications that may cause significant patient discomfort, lead to poor nutrition and can also be responsible for delays or dosage limitations in antineoplastic treatments - or constipation with opioids.

We have also included radiodermatitis that is reported in more than 80% of patients with breast cancer undergoing post surgical radiotherapy; oral mucositis which directly results as an effect of radiotherapy and diarrhea that can be a consequence of the administration of Vinca alkaloids. Hot flashes are frequently experienced by cancer patients as sudden and transient episodes of sweating, palpitation and anxiety and are frequently associated with mood and sleeping disorders that can profoundly influence the quality of life of patients.

Other symptoms analyzed are the expression of the underlying disease as chronic fatigue, the most commonly reported symptom for people living with cancer or pain that according to the M. D. Anderson Cancer Center of Houston, is experienced by approximately 30% of people living with cancer. A systematic review also reports that the prevalence of cancer pain is found in 33% of patients after curative treatment, in 59% of patients following anticancer therapy and in 64% of people with metastatic cancer (advanced or final stage).

Cancer is highly threatening and understandably many patients are anxious in response to that threat; therefore, anxiety sometimes becomes a clinically important problem and may also be associated with depression.

Other criteria of this chapter include the division of the evidences between adults and children as the pediatric management of the disease requires a very different approach and cannot be assimilated to the intervention in adult patients.

When considering CAMs resources in the management of symptoms directly connected with anticancer therapies, great attention should be paid to avoid the interference of complementary treatments with the efficacy of conventional anticancer protocols. This very crucial aspect has been carefully considered in our work.

Finally, as cancer may quickly impair the quality of life, also this issue and the contribution of CAMs in this field is the object of a specific chapter.

## Main adverse effects of anticancer drugs

### *Hot flashes*

Vasomotor symptoms are often present in cancer patients. They are complex physiological events appearing with sudden and transitory perspiration episodes, palpitations and agitation and are often connected to mood and sleep disorders which affect patients' quality of life very negatively. Furthermore, they can reduce the compliance of the patient in antiestrogenic and antitestosterone therapies.

These symptoms are prevalent in 51-81% of women with breast cancer, 69-76% of men with prostate cancer and 85-90% of patients with carcinoid syndrome.

Other oncological patients who may manifest vasomotor symptoms are those suffering from medullary thyroid carcinoma, pancreatic cancer and clear cell renal cancer.

Although the pathogenesis of vasomotor disorders is still unknown, there are various options to treat them. In patients with breast or prostate cancer, hormone therapy is normally contraindicated as estrogens can promote the cancer growth, particularly in mammary and prostatic neoplasia (L'Espérance, Frenette, Dionne, & Dionne, 2013).

Hormone treatments are connected to numerous unfavorable reactions. Progestogenics may cause diarrhea, weight gain, rash and hypertension; tibolone may cause stomach pain, hypertrichosis and metrorrhagia; cyproterone may cause sleepiness, asthenia and photosensitivity.

In these patients some treatments are effective, such as antidepressants, (venlafaxine, paroxetine, citalopram and fluoxetine), antihypertensive drugs (clonidine) and anticonvulsivants (gabapentin and pregabalin).

The studies on these drugs did not report significant differences from a placebo treatment.

The 2013 Guidelines of CEPO (Comité de l'évolution des pratiques en oncologie) recommend the use of the following therapies for vasomotor disturbances in patients with breast cancer:

1. Patients with breast cancer treated with Tamoxifen therapy:

venlafaxine, citalopram, clonidine, gabapentin, pregabalin (grading B recommendation)

Avoid paroxetine and fluoxetine because they may reduce the effects of tamoxifen.

2. Patients with breast cancer not treated with Tamoxifen:

- venlafaxine, citalopram, clonidine, gabapentin, pregabalin (grading B recommendation)

Fluoxetine seems not be effective (grading D).

These recommended drugs, besides not necessarily being effective, also have side effects which can negatively influence the quality of life.

Venlafaxine, paroxetine and citalopram are often connected with dry mouth, constipation, headache, anorexia and taste alteration, asthenia, nausea, sleepiness, palpitations.

Clonidine may result in sleep disorders. Gabapentin and pregabalin may result in sleepiness, vertigo, blurred visions, increase in appetite and weight gain, cognitive problems and problems of attention and coordination (Fisher & Johnson, 2013; L'Espérance, Frenette, Dionne, & Dionne, 2013).

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### *Nausea and vomiting*

Vomiting and especially nausea are still the most frequent unfavorable reactions during chemotherapy, despite recent progress in the last ten years.

Not all the chemotherapeutics have the same pro-emetic effects. The definition of emetic effect connected to each chemotherapeutic agent is essential in order to draw the guidelines which could be useful for nausea and vomiting's prophylaxis.

The official classification provides 4 chemotherapeutic drugs categories: high, moderate, low and minimal emetogenic risk.

These 4 chemotherapeutic categories coincide with different percentages for nausea and vomiting (>90%; 30-90%; 30-10%; <10%).

In each chemotherapeutic class, different anti-emetics have been recommended:

high risk: combination of a neurokinin 1 (NK1) receptor antagonist, a 5-hydroxy-triptamine (5HT3) receptor antagonist and desametasone;  
medium risk: combination of a NK1 receptor antagonist (or a 5TH3 receptor antagonist if not available) and desametasone;  
low risk: desametasone.

In low chemotherapeutics risk, nausea and vomiting prevention is not recommended.

Lorazepam and diphenhydramine could be associated to the above mentioned therapies if these are not effective, but they are not recommended as single anti-emetics (Olver et al. 2011; Roila et al., 2010).

Despite the anti-emetic prophylaxis, there are unfortunately cases of refractory emesis. Furthermore, the most commonly used drugs in prophylaxis are not lacking in side effects.

5HT3 receptor antagonists may induce headache, asthenia, stomach pain and constipation, and they are connected to the extended QT interval. This risk is higher for ondansetron (Charbit & Alvarez, 2008; Mckechnie & Froese, 2010). The unique drug in this class that is considered to have no effects on QT is palasetron (Mason & Moon, 2013).

NK1 Receptor-antagonists can cause hipertransaminasemia and inhibition of CYP3A4 (Hesketh et al. 2003).

Unfavorable reactions caused by desametasone depend on the dose and duration of therapy and include insomnia and hyperglycemia (Jordan, Kasper, & Schmoll, 2005).

Lorazepam and antihistamine, in addition to not been effective in monotherapy, could cause mental confusion, nervous excitement and somnolence, dry mouth, blurred vision (Jordan et al. 2005; Olver et al. 2011).

Dopamine receptor antagonists (phenothiazines, butyrophenones, metoclopramide) have demonstrated to be effective only with chemotherapeutics with medium and moderate emetic risk.

They are also connected to extrapyramidal symptoms, sedation, vertigo and headache (Jordan et al. 2005).

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## Cancer pain therapy

According to a systematic literature review, pain has a prevalence varying from 33% in patients after curative treatments to 59% in patients in anti-cancer treatment and to 64% in patients with metastatic cancer, advanced or in final stage (Van den Beuken – Van Everdingen 2007).

Factors that influence the development of chronic pain in cancer survivors who completed the treatment, include peripheral neuropathy caused by chemo or radio-therapy, chronic brachial plexopathies, pelvic pain after radiotherapy and post-surgical pain (Sun 2008).

Pain has a large specific prevalence for types of cancer. Furthermore, another systematic review of literature showed that nearly half of cancer patients were under-treated (Deandrea 2008). Recent studies conducted in

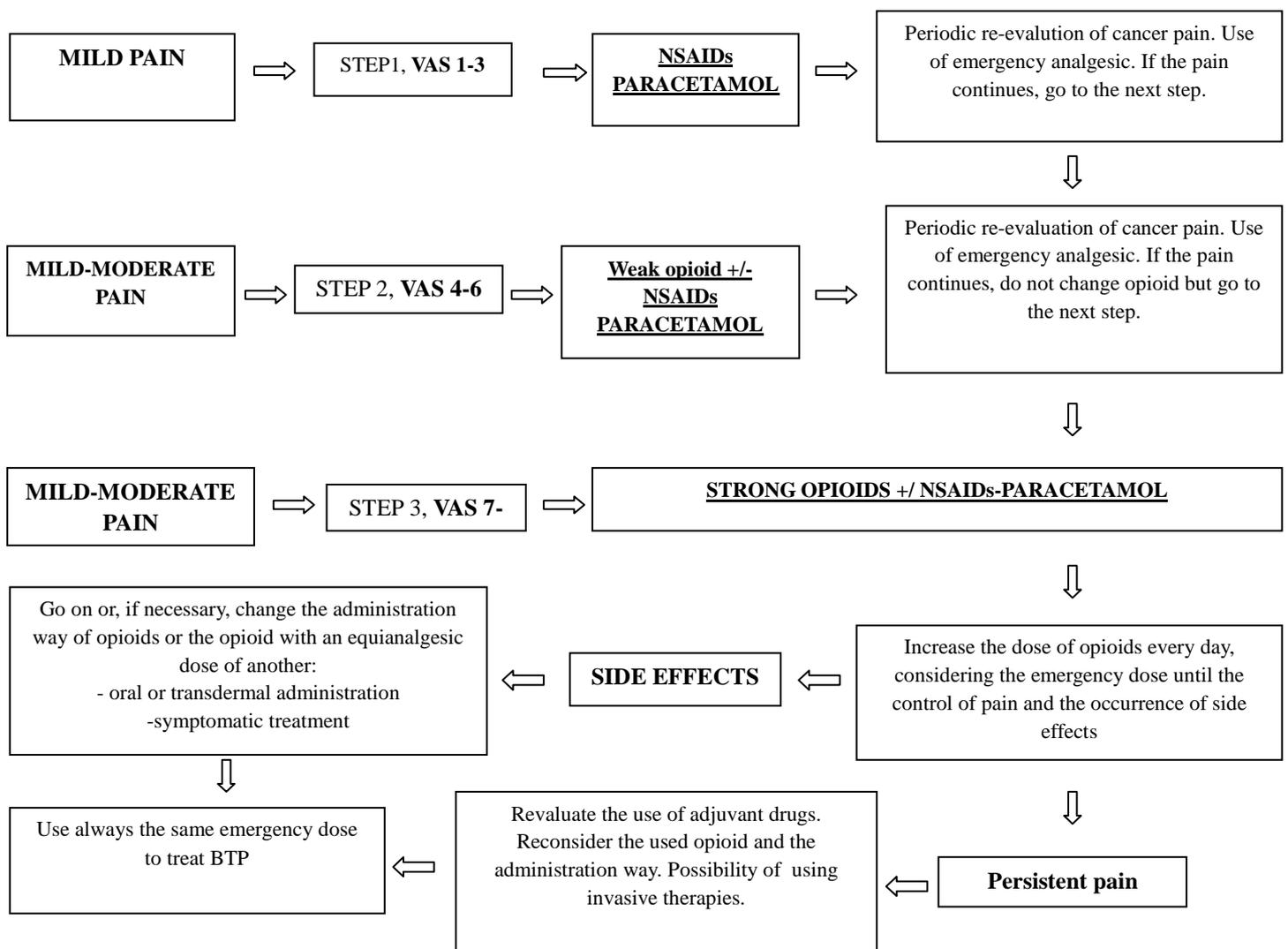
Italy and Europe (Costantini 2009, Breivik 2009) confirmed this data, showing that the different types of pain or pain syndromes (Higginson 2010, Morselli 2009) were present in all phases of cancer (early and metastatic) and were not adequately treated in a significant percentage of patients, from 65% to 82,3%.

In spite of the published Guidelines and educational programs on cancer pain evaluation and treatment, in every illness phase pain continues to be a substantial source of worry for public health in patients with either solid or haematological cancers. Cancer pain may be presented as an important worldwide health care problem considering that cancer incidence was 12,667,470 new cases in 2008 and, based on projection, will be >15 million in 2020 (Frankish 2003).

The correct and regular self-evaluation of pain intensity through validated instruments is the first step to effectively achieve an individualized treatment. Moreover, the pain quality evaluation improves the therapeutic choice. According to the literature, the majority of advanced cancer patients have at least 2 types of cancer-related pain attributable to a variety of aetiologies.

Chronic pain therapy should be prescribed regularly and not only “if needed”. It could be a good practice to prescribe a therapy that could be given in a simple way and easily managed by patients and their families, particularly in cases of domiciliary care. Oral administration of drugs seems to be the more eligible to satisfy this requirement. The evaluation and treatment of breakthrough pain (BTP) could also be an optimal therapeutic conduct.. In 1986, the World Health Organisation (WHO) proposed a strategy for the treatment of cancer pain based on a sequential choice of analgesics, from non opioids, to weak opioids, and then to strong opioids, which is considered the best treatment even today.

The choice of analgesic therapy in patients with cancer pain is based on the therapeutic scale proposed by the WHO (see the chart).



Though each mentioned drug is a good solution to treat pain, none of them is lacking in side effects. Analysing classes of useful drugs used as analgesics, it is actually possible to see how each of them has possible complications that should be considered in order to avoid them or to reduce their severity.

### **Non-steroidal anti-inflammatory drugs**

The extended use of non-steroidal anti-inflammatory drugs (NSAIDs) could involve gastrointestinal risks: in controlled randomized studies on cancer patients a gastric disease frequency up to 15% has been observed, up to 9% of gastric bleeding and up to 3% of perforation.

Ketoprofene, ketorolac and piroxicam are associated with a higher risk of gastrointestinal toxicity compared to other NSAIDs. All the COX-2 inhibitors are contraindicated in patients with ischemic heart disease, artheriopathies and cerebrovascular diseases (EMEA public statement: European Medicines Agency announces regulatory action on Cox-2 inhibitors EMEA /62838/2005). Some conventional NSAIDs may also be associated with thromboembolic reactions when used at the maximum dose recommended for long term. Diclofenac 150 mg/die and ibuprofene 2.400 mg/die have the same profile of thrombotic risk as the selective Cox-2 inhibitors. Epidemiological evidences suggest that naproxene 1.000 mg/die and ibuprofene 1.200 mg/die are not associated to the increase in the risk of myocardial infarction. In patients chronically treated with ASA it's important to consider the interaction with ibuprofene. Patients in therapy with NSAIDs with high risk of gastrointestinal complications should receive a prophylaxis with a standard dose of proton pump inhibitors or a double dose of histamine H2-receptor antagonists.

### **Weak opioids**

The use of these drugs causes nausea and vomiting, constipation, anorexia, asthenia and vertigo in the majority of patients. A recent meta-analysis revealed that there are no significant differences between the use of non opioid analgesics alone and the use of single weak opioid. Other studies demonstrate instead that the efficacy of these opioid is limited by their "roof effect": over a certain threshold dose the effects of analgesics do not increase and only the adverse effects of drugs persist. Many authors suggest even the abolition of the second step in the scale of WHO, in favour of an early use of morphine in low doses.

#### *Codeine*

sub-optimal doses of codeine and paracetamol in formulations marketed in Italy (not permitted to reach the codeine effective maximum dose 360 mg/die without administered paracetamol toxic doses).

#### *Tramadol*

possible occurrence of severe psychiatric reactions (mood alterations: euphoria, occasionally dysphoria; variations in activity: generally suppressed, occasionally increased; and changes in cognitive and sensory capacity: decisional perceptual capacity disorders, hallucinations, confusion) if the maximum dose is exceeded (400 mg/day adult 300 mg patients > 75 years).

### **Strong opioids**

Very frequent adverse effects are: constipation, nausea and vomiting, urinary retention, itches and toxicity to central nervous system (sleepiness, cognitive alterations, confusion, hallucinations, convulsions and, more rarely, hyperalgesia and allodynia).

Morphine is the most commonly used drug through various ways of administration. Alternative opioids can be used in patients who have morphine intolerable adverse effects. Nevertheless, the replacement of morphine with another major opioid is just one of the possible approaches to treat adverse effects. Other possibilities are: to reduce the dose of morphine (adding a non opioid analgesic and/or an adjuvant); to treat the adverse events with symptomatic drugs; to change the manner in which the morphine is administered.

#### *Fentanyl*

Transdermic fentanyl is an effective analgesic in treating severe pain and can be used in patients with stabilized algic state who are not able to swallow an oral form, as an alternative to subcutaneous morphine. Plasters guarantee an analgesic effect for 3 days. An increase in cutaneous temperature (fever, shower, etc.) may cause an increase of absorption and consequently of adverse effects.

The oral transmucosal administration of fentanyl may have a faster reaction compared to fast-release morphine in treating episodic intense pain in patients already treated with major opioids. It is advisable to start with 200 mcg dose as the episode of breakthrough pain appears, also more times a day.

### *Hydromorphone*

Hydromorphone could be an alternative to oral morphine. The formulation of administering once a day may result particularly convenient to patients who have a poor compliance to repeated morphine doses or poor analgesia or side effects.

### *Methadone and transdermal buprenorphine*

These are also very good drugs. Methadone can be used in severe pain therapy and buprenorphine in moderate-severe pain, though their use is also associated to the typical adverse effects of opioids.

### *Oxycodone*

Oxycodone should be considered as an efficacious alternative to morphine in patients who cannot tolerate it. It is similar to morphine in terms of analgesics and side effects.

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## **Treatment of the side effects of chemo- and radiotherapy: homeopathy**

Homeopathic, homotoxicological, and anthroposophic treatment are used, especially in Western countries, as a support in the treatment of adverse effects of chemotherapy, radiotherapy and hormone therapy. The symptoms paragraphs are mainly connected with homeopathy, except 2 cases (mucositis and pain) which are dedicated to homotoxicology, as indicated in the title.

A systematic review (Kassab S, 2009) was conducted on the clinical research evidence of homeopathy in the treatment of adverse effects of anticancer therapy.

There are homeopathic RCTs for the treatment of patients with a clinical or histological diagnosis of cancer where the intervention was aimed at preventing or treating symptoms associated with cancer treatments. All age groups and all stages of disease were included.

Eight controlled trials (7 placebo controlled and one trial against an active treatment) with a total of 664 participants met the inclusion criteria. Three studied adverse effects of radiotherapy, 3 the adverse effects of chemotherapy and 2 studied menopausal symptoms associated with breast cancer treatment.

Two studies with low risk of bias demonstrated benefit: one with 254 participants demonstrated the superiority of topical calendula over trolamine (a topical agent not containing corticosteroids) for the prevention of radiotherapy-induced dermatitis, and another with 32 participants demonstrated the superiority of Traumeel S\* (homotoxicology) over placebo as a mouthwash for chemotherapy-induced stomatitis. Two other studies reported positive results, although the risk of bias was unclear, and 4 further studies reported negative results.

Type of study	Therapeutic protocol	N. patients and disease	End points criteria	Results	Author, year
Randomised, patient and outcome assessor blind, placebo controlled trial	Clinical homeopathy a) homeopathic Arnica 5CH b) placebo both administered as 3 granules 4 times a day, 3 days before and 3 days after treatment for 2 chemotherapy cycles	29 women with breast cancer undergoing intravenous chemotherapy Age: 54.41 years (range of 7.61 years)	Pain produced by injection or hematoma graded by patient on a vertical line between 0 (no pain) and 160 (intense pain) 2. Venous tone assessed by the number of hematomas 3. Venous accessibility graded from one (first attempt easy) to ten (five and more than five attempts)	Significant improvement from baseline in the treatment group; there were no statistically significant differences between active and placebo groups	Bourgois, 1984
Prospective randomised placebo controlled trial with 3 parallel arms	Clinical homeopathy a) homeopathic Cobaltum 30 CH b) homeopathic Causticum 30 CH c) placebo Each treatment taken as 3 pills each morning during radiotherapy	82 participants with head and neck, pelvic or thoracic cancers undergoing a course of radiotherapy	Radiation reaction profile, a symptom list with 18 items (one blank) each graded 0-3. On this measure, a total of 0-5 indicates very minimal reaction, 6-10 moderate but tolerable reactions, 11 and above severe degree of reaction usually resulting in interruption of the therapy. Scores recorded once weekly during the course of radiotherapy	Average grading of radiation reactions: placebo 8.5, Cobaltum 4.7, Causticum 5.4 The authors reported “about 30%” overall reduction in the degree of reactions in both groups taking homeopathic medicines compared with placebo. No adverse effects were reported.	Kulkarni, 1988
Prospective randomised double blind (subject and observer blind) placebo controlled trial with 2 parallel arms	Clinical homeopathy a) homeopathic medicines - Belladonna 7 CH 3 granules twice daily and X-ray 15 CH, 3 granules once daily b) placebo	66 women after conservative surgery for breast cancer treated with radiotherapy Age: mean 52.7 years, range 28.3 to 70 (7.0 in text, presumed error) years	Skin reactions to radiotherapy assessed by physician observers using ordinal and nominal scales as follows: The efficacy of the treatment was calculated on the Index of Total Severity (sum of the scores of the four parameters) weekly during radiotherapy, and during recovery, 15 and 30 days after the end of the radiotherapy	Analysis of the data on Total Severity during recovery, showed a statistically significant benefit of the active medicines over placebo. The homeopathic medicines had particular effectiveness on the heat of the skin	Balzarini, 2000
Prospective randomised placebo controlled trial with 2 parallel arms	Homotoxicology a) Traumeel S (proprietary complex homeopathic medicine)	32 participants with malignant diseases who had undergone allogeneic or autologous stem cell transplantati-on	WHO grading for mucositis, 5 point scale (0-4) used to grade stomatitis. The 2 main treatment comparisons, as specified in the protocol, were of the area under the curve (AUC) for stomatitis symptoms, and the time to first worsening of stomatitis symptoms. A subjective scoring system assessing the	The mean AUC scores were 10.4 in the Traumeel S group and 24.3 in the placebo group (Wilcoxon rank-sum score, 167.5; expected score, 232.5; $p < 0.01$ ). The log-rank test indicated that a statistically significant difference (chi-square test, 13.4 with 1 degree of freedom; $p < 0.001$ ) between the 2 groups	Oberbaum, 2001

			degree of pain, dryness and dysphagia	in the time to worsening of symptoms. In those patients whose symptoms worsened, the median time to worsening was 4.7 days in the Traumeel S group and 4.0 days in the placebo group	
Prospective randomised single blind (outcome assessor blind) controlled trial	Clinical homeopathy: a) Calendula extract ointment. b) Trolamine topical agent  Topical agents were used at the onset of radiotherapy, twice daily or more depending on occurrence of dermatitis or pain until completion of radiotherapy. No other creams, lotions or gels were allowed.	254 women (18-75 years) with non metastatic breast cancer treated with lumpectomy or mastectomy with or without adjuvant post operative chemotherapy or hormonal treatment.		The occurrence of acute dermatitis of grade 2 or higher was 41% (95% CI, 37 to 46) in the calendula group and 63% (95% CI, 59 to 68) in the trolamine group (p<0.001) Pain: the mean maximal pain evaluated on the VAS was 1.54 (95% CI, 1.2 to 1.89) in the calendula group and 2.10 (95% CI, 1.72 to 2.48) in the trolamine group (p p= 0.03) Compliance to application of creams as evaluated by the physicians: considered good for 84% of patients receiving calendula and 92% of those receiving trolamine (p = 0.047) Allergic-type reactions: none in the calendula group, 4 in the trolamine group (pruritis and urticaria)	Pommier, 2004
Prospective randomised placebo controlled trial with 2 parallel arms	Individualised homeopathy a) individualised homeopathy; 5 consultations and prescriptions in various forms b) placebo	53 women treated for breast cancer, who had more than 3 hot flashes/day, did not have metastatic disease, were not on other treatments for hot flashes, did not have severe concurrent illnesses, and not undergoing, or about to receive, any adjuvant chemotherapy	Primary outcome measure MYMOP - a change of 0.8 was considered a clinically relevant change. Secondary outcome measures: Menopausal Symptom Questionnaire Patient diaries of frequency and severity of hot flushes EORTC QLQ C30 (European Organisation for Research and treatment of Cancer Quality of Life Questionnaire C30) HADS (Hospital Anxiety and Depression Scale) FAQ (Final assessment Questionnaire) GHHOS (Glasgow Homeopathic Hospital Outcome Scale)	85% (45/53) of women completed the study. No evidence of a difference between groups for either MYMOP activity Clinically relevant improvements in symptoms and mood disturbance observed in both groups over the study period. Adverse effects reported by approximately one quarter of women in both groups	Thompson, 2005
Prospective randomised placebo	Homotoxicology On day 2, if symptomatic	65 women in chemotherapy for breast cancer	Intensity of nausea questionnaire Vomiting Quality of Life	68.2% of patients in the homeopathy group required additional conventional treatment compared with 59.1% in the	Daub, 2005

<p>controlled trial with 2 parallel arms</p>	<p>(conventional antiemetics were used for the first day)  a) Vomitusheel S a) proprietary complex homeopathic medicine containing Ipecacuanha D2 (1.1 mg), Aesthusea D2 (1.1 mg), Nux vomica D2 (1.1 mg), Apomorphium hydrochloricum D4 (1.65 mg), Colchicum D4 (2.75 mg), Ignatia D4 (3.3 mg) given as a suppository and Gastricumeel - a proprietary complex homeopathic medicine containing Argentum nitricum D6 (30 mg), Acidum arsenicosum D6 (30 mg), Pulsatilla D4 (60 mg), Nux vomica D4 (60 mg), Carbo vegetabilis D6 (60 mg), Antimonium crudum D6 (60 mg) given as oral tablets  b) Sambucus nigra D3 oral tablets used as the placebo  If symptoms did not resolve within two hours conventional antiemetics were</p>	<p>Age: 28-67 years</p>	<p>Side effects</p>	<p>control group. There was no significant difference between the two groups (p=0.6)</p>	
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	given The placebo was another homeopathic medicine that the authors chose because “no antiemetic properties had been described”				
Prospective randomised subject, care provider, statistician blind placebo controlled trial with 3 parallel arms		83 women with a history of carcinoma in situ or Stage I to III breast cancer who had completed all surgery, chemotherapy and radiotherapy (women taking Tamoxifen were also included) who had hot flushes for at least one month, with an average of at least three hot flushes per day in the week prior to beginning treatment  Age: mean 55.5 years	Hot flash severity score (frequency times severity of hot flushes from symptom diary) at entry to the study and at 1, 2, 3, 6, 9 and 12 months after randomisation Secondary outcome measures Total number of hot flushes Kupperman Menopausal Index (KMI) SF-36 (Short Form 36) quality of life score FSH (Follicle Stimulating Hormone) level before and after treatment	There was no significant difference found in the primary outcome measure, the hot flush severity score, although there was a positive trend in the single remedy group. A statistically significant improvement in general health score in both homeopathy groups ( $p < 0.05$ ) on the SF-36 after 1 year was found. There were no statistically significant differences between the three groups in the KMI score or in individual symptoms of the KMI score except for an increase in headaches in the group taking the homeopathic combination at 6 and 12 months. The general health score of the SF36 was significantly increased in both homeopathy groups compared with placebo. There was an increase in the number and severity of hot flashes in the subgroup not taking Tamoxifen and receiving the proprietary combination (post hoc)	Jacob, 2005

### **Conclusions of the literature and authors**

The review found preliminary data in support of the efficacy of topical Calendula for prophylaxis of acute dermatitis during radiotherapy and Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis. The trials need to be replicated. There is no convincing evidence for the efficacy of homeopathic medicines for other adverse effects of cancer treatments. Further research is required.

\*Traumeel S: Oral drops: contains: medicinal ingredients: Arnica montana D2 5 g; Calendula officinalis D2 5 g; Hamamelis virginiana D2 5 g; Bellis perennis D2 2 g; Echinacea D2 2 g; Echinacea purpurea D2 2 g; Aconitum napellus D3 10 g; Hypericum perforatum D2 1 g; Chamomilla D3 8 g; Millefolium D3 5 g; Belladonna D4 25 g; Mercurius solubilis Hahnemanni D8 10 g; Hepar sulfuris calcareum D8 10 g; Symphytum officinale D8 8 g. Non-medicinal ingredients: ethanol, purified water

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## Anxiety and depression

### *Anxiety and depression and acupuncture/TCM*

There have been few studies regarding anxiety and depression on oncology; these symptoms are studied more as an aspect of lifestyle or together with other symptoms (pain, hot flashes, etc.). Several studies conducted on non-oncological patients however suggest that acupuncture but also auricular acupuncture and acupression are effective in treating depression and anxiety. There are very few side effects in comparison to conventional treatments. These promising results have led to extending these studies to cancer patients.

Sagar (2008) reviewed the literature for symptom control in cancer patients and reported 5 RCTs regarding anxiety in non-oncological patients: a RCT of auricular acupuncture for dental anxiety in 67 patients compared auricular acupuncture with intranasal midazolam, placebo acupuncture, and no treatment for reducing dental anxiety. The auricular acupuncture group and the midazolam group were significantly less anxious at 30 min. in comparison to patients in the placebo acupuncture group. In conclusion, both, auricular acupuncture and intranasal midazolam were similarly effective for the treatment of dental anxiety. In an other study a combination of auricular and body acupuncture decreased preprocedural anxiety and increased intraprocedural analgesia in patients undergoing lithotripsy, where 29 patients were treated with preprocedural auricular acupuncture intervention combined with intraprocedural electroacupuncture stimulation versus sham control group (preprocedural sham auricular acupuncture intervention combined with intraprocedural sham electroacupuncture stimulation, n = 27).

In other studies, acupuncture has been studied and found to be of benefit in reducing anxiety for prehospital transport settings (17 patients with auricular acupression at the relaxation point and 19 patients at a sham point); the anxiety of mothers whose children were scheduled to undergo surgery (acupuncture group or sham acupuncture control group) and 30 patients scheduled to undergo colonoscopy (acupuncture group, sham, or no acupuncture). The conclusion is that suppression of anxiety by acupuncture is associated with an increase in the pain threshold.

The same review maintains that some studies indicate that acupuncture treatment may be an equally effective alternative to drugs in patients suffering from mild depression. It reports a systematic review of 9 RCTs of acupuncture in the treatment of depression and concludes that despite the odds ratios of existing literature suggesting a role for acupuncture the evidence thus far is inconclusive due to the inferior quality of the studies.

A Cochrane review (Smith 2005) concludes that there is insufficient evidence to determine the efficacy of acupuncture compared to medication, or to wait list control, or sham acupuncture, in the management of non-oncological depression. However, because pharmaceutical antidepressants are not usually effective until 2 weeks after starting therapy, their combination with acupuncture may enable more rapid results with reduced side effects.

A later revision Cochrane (Smith et al. 2010) contains data from 30 studies with 2,812 participants included in the meta-analysis comparing acupuncture with sham acupuncture, no treatment, pharmacological treatment, and other structured psychotherapies. The following modes of treatments were included: acupuncture, electroacupuncture or laser acupuncture. Primary outcomes were reduction in the severity of depression measured by self rating scales or by clinician rated scales and an improvement in depression defined as remission versus no remission.

There was a high risk of bias in the majority of trials. The acupuncture delivered in the trials varied in terms of points selection, frequency of treatments and total numbers of treatments administered. There was insufficient evidence of a consistent beneficial effect from acupuncture compared with a wait list control (thought in two trials with 94 participants, there was evidence of a reduction in the severity of depression in the acupuncture group) or sham acupuncture control (2 trials with 56 participants). Two trials found acupuncture may have an additive benefit when combined with medication compared with medication alone. A subgroup of participants with depression as a co-morbidity experienced a reduction in depression with manual acupuncture compared with selective serotonin reuptake inhibitors SSRIs (RR 1.66, 95%CI 1.03, 2.68) (3 trials, 94 participants). The majority of trials compared manual and electroacupuncture with medication and found no difference between groups. The authors found insufficient evidence to recommend the use of acupuncture for people with depression. The results are limited by the high risk of bias in the majority of trials meeting inclusion criteria.

A recent review (Chandwani et al. 2013) analyzes stress correlated to cancer treated with complementary and alternative medicine. Of the techniques considered (yoga, meditation, tai chi chuan, etc.) the authors cite 5

studies that involve acupuncture, concluding that it can relieve anxiety, fatigue, and distress associated with advanced cancer.

Garcia et al. in their review (2013), report that although acupuncture is frequently used for anxiety and stress management, relatively few studies have evaluated its use for these symptoms in patients with cancer. Six trials met the inclusion criteria. Five of them (Nedstrand 2007 - Frisk 2012 see hot flashes paragraph; Feng 2011, Melhing 2001 and Walker 2010 reported in the table; had positive outcomes but were unblinded and, thus, assessed as having high ROB (risk of bias). One negative trial (Balk 2009 see in fatigue paragraph) with high ROB was blinded but underpowered (26 people; 15 acupuncture and 11 sham).

Type of study	Therapeutic protocol	N. patients and disease	Endpoint criteria	Results	Author, year
RCT <ul style="list-style-type: none"> <li>massage and acup.+ usual care</li> <li>usual care</li> </ul>	- massage (standard and acupressure-type foot massage)  -acupuncture LV3 LI4 Yin Tang 2 sessions	n.150 eligible n.138 randomly assigned (93 group 1; 45 group 2) postoperative cancer stage	Subscales of the Profile of Mood States Short Form (POMS-SF)	decrease in depressive mood of between groups(P=0.003)	Mehling, 2007
pilot single armed prospective clinical trial	acupuncture HT7 PC4 LV5 GV24 + generals points 12 sessions over 8 weeks, twice weekly first 4 weeks, weekly last 4 weeks. Follow up at weeks 9 and 12	n.40 enrolled n.32 assessed  ovarian and breast cancer	Rotterdam Symptom check list (RSCL) Subscales of the Profile of Mood States – Total Mood Disturbance (POMS-TMD,D) QOL	significant improvement over time for patients with anxiety (P =0.001) and depression (P = 0.02)	Dean-Clower, 2010
single-arm observational study	acupuncture BL13 BL14 BL15 BL18 BL20 BL23 LU7 KI6 Ren4 SP6 He6(Yanglao) KI7 LI11 8 sessions	n. 54 recruited n.50 completed treatments  breast cancer	Women’s Health Questionnaire (WHQ)  Hot Flashes and Night (HFNSQ)	significant statistical and clinical improvements anxiety/fears (p=0.001)	de Valois, 2010
RCT 1) acupuncture 2) venlafaxine	1) acupuncture KI3 BL23 SP6 GB20 DU14 DU20 ST36 LV3 HT7 PC7 Ren6 LU9 for 12 weeks twice for 4 weeks weekly for 8 weeks	n.50 randomized (25 group 1, 25 group 2) breast cancer	Beck Depression Inventory-Primary Care (BDI-PC)	both groups exhibited significant decreases in depressive symptoms (BDI Scores p< 0.001) Venlafaxine group experienced 18 incidences of adverse effects (e.g., nausea, dry mouth, dizziness, anxiety) acup. no negative adverse effects	Walker, 2010
RTC acup. fluoxetine	acupuncture ST40 SP9 SP10 SP6 Yintang (EX-HN3) DU20 Sishencong (EX-HN1) PC6 ear Shenmen (TF4)	n.80 randomly assigned (40 group 1, 40 group 2) suffering malignant tumour	Self- rating Depression Scale (SDS), Hamilton Depression Rating Scale (HAMD), Pittsburgh Sleep Quality Index (PSQI) after treatment for 30 days	Scores SDS HAMD significantly lower than control group (P < 0.05)	Feng, 2011

## Conclusions of the literature and the authors

There are few studies and with small numbers on anxiety and depression in cancer care and therefore even if they are promising, their quality is low; for this reason it is not possible to draw conclusions regarding the validity of acupuncture. In some studies conducted on non-oncological patients, these symptoms are benefitted by treatment with acupuncture and auricular acupuncture. Despite this, the Cochrane review (2010) states there was a high risk of bias in the majority of trials and that there was insufficient evidence of a consistent beneficial effect from acupuncture compared with a wait list control or sham acupuncture control. It is to be noted that recent literature considers sham acupuncture not as an actual placebo but as a form of acupuncture, which in various studies obtains results which are similar to true acupuncture. The majority of trials compared manual and electro acupuncture with medication and found no difference between groups.

In clinical practice patients suffering from anxiety and depression, at least mild or not severe, benefit greatly from treatment with acupuncture but also auricular acupuncture, moxibustion and massage and these are among the disturbances that are most frequently treated. This is understandable considering the base of acupuncture referred to in the introduction it has been demonstrated that there is an increase in the neurotransmitters that affect the psyche like endogen opioids (endorphins, dinorphins and encephalins).

The Guidelines SIO (2009) do not attribute a grading for the treatment of anxiety and depression. On the basis of the same criteria, the authors of TNIM have evaluated that the adequate grading is 2B (weak recommendation, moderate quality evidence).

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### Anxiety and depression and herbal medicine

Several medicinal plants are traditionally used in the treatment of anxiety-depressive states and sleep disorders, but only a few have been studied with appropriate clinical trials in cancer.

The medicinal plants both used in anxious-depressive states and studied in cancer progression are *Hypericum perforatum* (St. John's wort), *Crocus sativus* (Saffron), Lavender (*Lavandula officinalis*) essential oil; the other herbal medicinals commonly used in anxiety and depression but not studied in oncology include *Melissa officinalis*, *Passiflora incarnata*, *Rhodiola rosea* (see Cancer Related Fatigue paragraph) and *Valeriana officinalis*(see Fig.1).

Furthermore, substantial evidence indicates that *Piper methysticum*, also known as kava kava, reduces anxiety and stress; however, it has been implicated in liver failure and is therefore not clinically recommended; also, following hepatotoxicity reports, the preparations based on kava kava root extracts have been withdrawn from the European market.

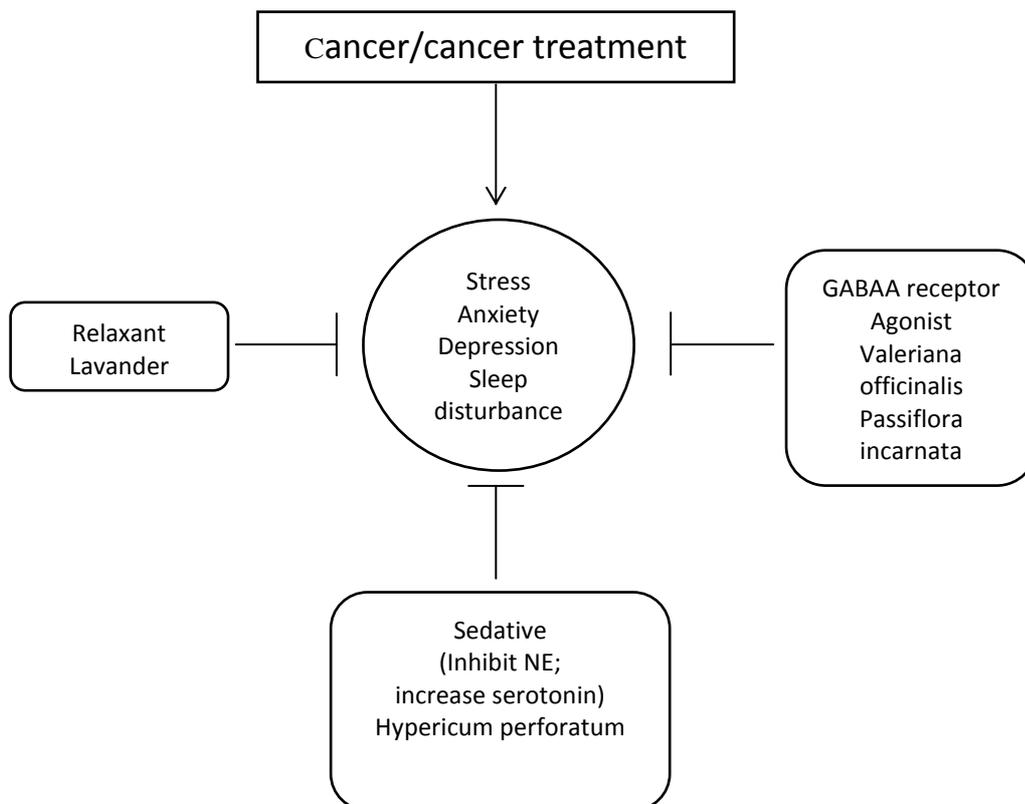


Fig.1. The officinal plants most used in anxiety and depression. (reformulated by Chandwani KD. 2012).

### **Crocus sativus**

*Crocus sativus* (CS), also known as Saffron, is a Mediterranean plant of the Iridaceae family growing spontaneous also in Italy. Throughout history, uses against cancer and depressive mood were regularly identified while a Traditional Chinese Medicine text from the Mongol dynasty mentions that "...long-term ingestion causes a person's heart to be happy" (Dwyer AV. 2011).

Some recent preclinical and clinical studies (see Tab.1) indicate that stigma and petal of CS have antidepressant effect. These studies were well designed and analysed but larger studies are necessary to confirm the data.

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Pilot double-blind randomized trial	CS: 30 mg Imipramine: 100 mg  Period: 6 weeks	30 patients	Compare CS and imipramine in the treatment of mild to moderate depression  Criteria: HAM-D	CS treatment is as effective as imipramine in the treatment of mild to moderate depression (F = 2.91, d.f. = 1, p= 0.09).	Akhondzadeh S, 2004
Double-blind, randomized and placebo-controlled trial	CS: 30 mg  Period: 6 weeks	40 patients	Evaluate the CS (petal) action in the treatment of mild-to-moderate depression  Criteria: HAM-D	CS produced a significantly better outcome on HAM-D than placebo (d.f.=1, F=16.87, p<0.001)	Moshiri E, 2006
Pilot double-blind randomized trial	CS: 30 mg  Fluoxetine: 10 mg  Period: 8 weeks	40 outpatients	Compare the effect of CS petal and fluoxetine in the treatment of depressed outpatients  Criteria: DSM-IV, HAM-D	CS was found to be effective similar to fluoxetine in the treatment of mild to moderate depression (F=0.03, d.f.=1, p =0.84).	Akhondzadeh BA, 2007

Tab.1. Legend: CS (*Crocus sativus* petal), HAM-D (Hamilton depression rating scale), DSM- IV (Diagnostic and Statistical Manual of Mental Disorders).

**Dosage:** Typical daily dosages of CS hydroalcoholic extract are 30 mg administered once or twice daily and standardized in 0.60-0.70 mg of safranale/day. A trial comparing the efficacy of CS petal with the stigma, suggests they are equally effective in the treatment of mild-to-moderate depression (Blasti AA.2008).

**Side effects:** It has been reported that CS inhibits platelet adhesion; therefore its use is contraindicated in pregnancy and in patients in anti-aggregant treatment. In addition, it has been suggested that crocin and safranal, the two major components of CS, inhibit reuptake of dopamine, norepinephrine and serotonin.

### Hypericum perforatum

*Hypericum perforatum* (HP), also known as St. John's wort, is a perennial weed common to the western United States, Europe and Asia recommended for the treatment of mild-to-moderate depression and anxiety. The HP antidepressant's mechanism lies in its ability to inhibit the synaptosomal reuptake of serotonin, norepinephrine, and dopamine and several RCTs show the effectiveness of HP extract treatment in anxiety and depression (See Tab. 2).

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Randomized, double blind and placebo-controlled trial.	HP: 600 mg  Period: 6 weeks	184 outpatients with somatization disorder (ICD-10 F45.0), undifferentiated somatoform disorder (F45.1), and somatoform autonomic dysfunction (F45.3).	Evaluate the treatment of somatoform disorders with St. John's wort  Criteria: SOMS-7, somatic subscore of the HAMA, somatic subscore of the SCL-90-R, CGI	HP daily is statistically effective and safe in the treatment of somatoform disorders (p=0.006)	Müller T, 2005
Double-blind, randomised, multicentre, placebo-controlled study	HP: 900 mg  Citalopram: 20 mg  Period: 6 weeks	388 outpatients suffering from moderate depression	Compare the efficacy and safety HP (STW3-VI) and citalopram in patients with moderate depression  Criteria: HAM-D, GCI	Data shows a statistical significant therapeutic equivalence of HP STW3-VI to citalopram (p< 0.0001) and the superiority of HP over placebo (p< 0.0001)	Gastpar M, 2006
Randomized double-blind clinical trial	HP: 900 mg  Fluoxetine: 20 mg  Period: 8 weeks	53 patients with mild or moderate depression	Evaluate the action of HP versus fluoxetine in the treatment of mild to moderate depression  Criteria: HAM-D, GCI	Patients receiving HP had the low remission rates (12%, p = 0.016) compared to fluoxetine (34.6%) and placebo (45%)	Moreno RA, 2006
Randomized, double-blind, placebo-controlled, multi-center trial	HP: 123 patients to 600 mg, 127 patients to 1200 mg  Period: 6 weeks	332 adult outpatients with mild or moderate major depressive episode	Evaluate the efficacy of HP (WS 5570) compared to placebo in patients with major depression.  Criteria: DSM-IV, HAM-D	Patients in the HP treatment groups showed a consistently more effective response than placebo. The number of patients who experienced remission was higher in the HP1200 mg/day (p< 0.001)	Kasper S, 2006
Double-blind, randomized, placebo controlled long-term trial.	HP: 900 mg  Period: 26 weeks	426 out-patients	Evaluate a continuation and long-term maintenance treatment HP (WS 5570) after recovery from an acute episode of moderate depression  Criteria: HAM-D, GCI	HP (WS 5570) showed a beneficial effect in preventing relapse after recovery from acute depression. (p=0.034)	Kasper S, 2008
Open study	HP: Tablet 255–285 mg standardized to hypericin 0.3%	1,541 patients	Evaluate the HP in the treatment of depressive symptoms in outpatients	HP are effective as an antidepressant in the management of depression in daily practice	Melzer J, 2010

		and hyperforin content of 2–3%, capsule 425 mg standardized to hypericin 0.1–0.3% Period: 1 year		Criteria: ICD-10		
Randomised, double-blind, controlled study	multicentric, placebo-	HP:900 mg  Citalopram: 20 mg  Period: 6 weeks	154 patients	Determine a duration of response after treatment of mild to moderate depression with HP (STW 3-VI), vs. citalopram  Criteria: HAM-D	HP (STW 3-VI) is more efficient in lowering the relapse (14.8%) and recurrence rates of responders, when compared to citalopram (25.9%) and placebo (17.4%)	Singer A, 2011
Randomized clinical trial		HP:810 mg  Citalopram: 20 mg  Period: 12 weeks	59 participants	Investigate the efficacy of HP, citalopram, or placebo for acute treatment of Minor Depression (MinD)  Criteria: Minor depression was defined according to DSM-IV criteria. HAM-D, GAF, MOS	Data do not support the hypotheses that citalopram and HP statistically differentiate from placebo-treatment in MinD (p=0.771)	Rapaport MH, 2011
Randomized, controlled study	double-blind,	HP: 900-1500 mg sertraline: 50-100 mg  Period: 26 weeks	124 participants	Evaluate the effect HP (LI-160) vs. sertraline and placebo in major depressive disorder  Criteria: HAM-D	Comparisons between all treatments were non-significant (p=0.61)	Sarris J, 2012

Tab.2. Legend: HP (*Hypericum perforatum* extract), HAM-D (Hamilton depression rating scale), GAF (Global Assessment of Functioning), MOS (Medical Outcomes Study), GCI (Global Clinical Impression scale), SOMS-7 (Somatoform Disorders Screening Instrument-7 days).

**Dosage:** Typical daily dosages of standardized HP extracts range from 600 to 1800 mg, titrated to 0.3-0.5% in hypericin, for the treatment of mild-to-moderate depression. The dose is typically divided into two or three throughout the day. It may take 2-4 weeks to notice clinical results (EMA 2008, Monograph. 2004). HP can be found in dietary supplements but normally is prescribed as drug (with medical prescription) or galenic preparation.

**Side effects:** to date, the studies comparing the use of HP with other antidepressant drugs were not associated with any serious adverse event. The side-effect rate is estimated of 2.4 percent, without severe side effects but only the expected mild side effects like gastrointestinal upset, increased anxiety, minor palpitations, fatigue, restlessness, dry mouth, headache, and increased depression.

The most common side effect of the HP is the transient photosensitivity that, generally, occurs more commonly at higher doses than the standard range in use. Fair-skinned individuals should take precautions when exposed to the sun while taking HP. It is advisable that elderly people taking HP use protective eyewear when exposed to the sun. There is no specific indication about the HP use in pregnancy and lactation but a study published by da Conceição AO et al (2010), shows that HP and hypericin can increase the trophoblast internal Ca(2+) concentration through regulating the protein expression of the Ca(2+) transport system, and their intake during pregnancy is still a point of concern (da Conceição AO, 2010).

**Drug interactions:** HP affects the pharmacokinetics of many drugs by inducing cytochrome P450 (CYP) isozymes, such as CYP1A2, CYP3A4, CYP2C19, CYP2C9, and the P-glycoprotein (P-gp) transporter. The use of HP preparations is not recommended in people who are taking immunosuppressants (e.g. tacrolimus to prevent transplant rejection) or cardiovascular drugs (e.g. verapamil). Concomitant use of HP extract with selective serotonin reuptake inhibitors like citalopram, fluoxetine, paroxetine and sertraline may cause serotonin syndrome as well as the use of HP may interfere with tricyclics. Literature data show that HP influences the serum level of other classes of drugs (see table 3). Finally, it is known that the metabolic interactions between HP and drugs are not always unfavorable and sometimes there are benefits (e.g., reduction of irinotecan toxicity and increase in clopidogrel responsiveness) (Rahimi R. 2012, Lawvere s. 2005, Monograph, 2004).

<b>Drug</b>	<b>Possible clinical result of interaction with HP</b>
Adrenergic Vasopressors (ephedrine and phenylephrine)	Decreased
Anesthetics	Delayed emergency
Atorvastatin	Reduced efficacy
Bupropion	Persistent orofacial dystonia
Buspirone	Serotonin syndrome
Chlorzoxazone	Increased
Cyclosporine	Lowering of blood levels / Organ rejection
Digoxin	Decreased
Eletriptan	Serotonin syndrome
Gleevec	Decreased
Gliclazide	Decreased
Imatinib	Decreased
Indinavir	Decreased
Irinotecan	Decreased
Ivabradine	Decreased
Loperamide	Brief episode of acute delirium
Methadone	Decreased
Midazolam	Decreased
Nefazodone	Nausea, vomiting, headache
Nevirapine	Decreased
Nifedipine	Decreased
Omeprazole	Decreased
Oral contraceptive	Bleeding
Paroxetine	Decreased anticoagulant effect
Pravastatin	Decreased
Prednisone	Maniac episode
Sertraline	Nausea, vomiting epigastric pain, anxiety, confusion
Simvastatin	Decreased
Tacrolimus	Decreased
Tamoxifen	Decreased
Theophylline	Decreased
Tibolone	Acute hepatitis
Tryptophan	Serotonin syndrome
Venlafaxine	Serotonin syndrome
Verapamil	Decreased
Warfarin	Decreased INR
Zolpidem	Decreased

Tab. 3. Table of pharmacological interactions of *Hypericum perforatum*.

## Lavender Essential Oil

The genus *Lavandula* is native to the lands surrounding the Mediterranean Sea and Southern Europe, Northern and Eastern Africa, Middle Eastern countries, Southwest Asia and Southeast India. The various lavenders have similar ethnobotanical properties and major chemical constituents; the major components of Lavender oil were identified as 51% Linalyl acetate and 35% Linalool measured by gas chromatography. In literature, the Lavender Essential Oil (LEO) was used predominantly in anxiety and insomnia treatment by oral administration, inhalation or massage. In addition to psychological effects, the LEO inhalation also showed a physiological effect through the action exerted on the Central Nervous System via the limbic system and in particular, through the amygdale and hippocampus. Linalool and Linalyl acetate are also rapidly absorbed through the skin and detected in plasma after topical application with massage, reaching peak levels after approximately 19 minutes and causing depression of a CNS.

Aromatherapy massage with EO has been shown to relieve symptoms of anxiety in the immediate after math of the therapy and patients perceive aromatherapy massage with EO as positive and beneficial (Serfaty M. 2012, Wilkinson SM. 2007). We identified 3 clinical trials which have investigated the efficacy of an oral lavender oil preparation (a patented active substance produced from *Lavandula angustifolia* flowers by steam distillation consisting of the main active constituents Linalool 36.8% and linalyl acetate 34.2%, the trade name shown in literature articles). This was administered in gelatin capsules once daily at a dose of 80 mg/day, in subsyndromal (mixed) anxiety disorder, generalized anxiety disorder as well as in restlessness and agitation (see Tab. 4). The action mechanism of LEO is to inhibit the voltage dependent calcium channels in synaptosomes, primary hippocampal neurons and stably over-expressing cell lines in the same range such as the established anxiolytic pregabalin (Schuwald AM. 2013).

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, Year
Multi-center, double-blind, randomized study	LEO: 80 mg  Lorazepam: 0.5 mg  Period: 6 weeks	77 patients	Compare the effect of Lavender oil preparation Silexan to Lorazepam for generalized anxiety disorder  Criteria: HAMA SAS SF-36 CGI	The results demonstrate that silexan is as effective as lorazepam in adults with Generalized Anxiety Disorders LEO showed no sedative effects	Woelk H, 2010
Randomized, double-blind, placebo controlled trial.	LEO: 80 mg  Period: 10 weeks	221 patients	Evaluate the effectiveness of orally LEO preparation in the treatment of 'subsyndromal' anxiety disorder  Criteria: HAMA, PSQI CGI SF-36	LEO had a significant beneficial influence on quality and duration of sleep and improved general mental and physical health without causing any unwanted sedative or other drug specific effects. (p<0.001)	Kasper S, 2010
Phase II RTC	LEO: 80 mg  Period: 6 weeks	50 patients with neurasthenia (ICD-10 F48.0), post-traumatic stress disorder (PSD; F43.1), or somatization disorder.	Evaluate the effects of Silexan in patients with neurasthenia, post-traumatic stress disorder or somatization disorder  Criteria: SCL-90-R D-S SF-36	Waking-up frequency (p = 0.002), Waking-up duration (p< 0.001) and morning tiredness (p=0.005) were reduced, while efficiency of sleep (p = 0.018) and mood (p = 0.03) improved. The data justify the LEO use in human disorders with accompanying restlessness caused by sub-threshold anxiety	Uehleke B, 2012

Tab.4. Legend: LEO (Lavender Essential Oil), SCL-90-R (Symptom Checklist-90-Revised), D-S (von Zerssen's Depression Scale), SF-36 (36-item Short Form Health Survey Questionnaire), VAS (Visual Analogue Scale), HAMA (Hamilton Anxiety Scale), PSQI (Pittsburgh Sleep Quality Index), GCI (Global Clinical Impression scale), SAS (Self-rating Anxiety Scale).

**Dosage:** The oral dose of Lavender essential oil is 80 mg/day while, for the inhalation treatment and massage, a final solution at 1-2% and 1% (Soden K. 2004) of Lavender essential oil in suitable vehicle is used.. LEO can be prescribed as medication over the counter or galenic preparation.

**Side effects:** There are some reports of adverse effects after application of lavender; nevertheless the available data suggests that short-term therapy with lavender is relatively safe. Furthermore, rare cases of gynecomastia resolved after discontinuation of treatment were reported.

Lavender should be also used cautiously or avoided in patients with known allergy to Lavender. Gastrointestinal adverse events, such as nausea and dyspepsia, after receiving Silexan were reported. Its use should be avoided during pregnancy (Koulivand PH. 2013).

For completeness, we describe briefly the properties of medicinal plants not studied in oncology that could be used by expert physicians.

*Passiflora incarnata* is traditionally used to relieve the symptoms of mental stress and promote sleep; its concomitant use with synthetic sedatives such as benzodiazepines is not recommended. In literature some side effects like hypersensitivity, vasculitis, nausea and tachycardia are reported.

For *Passiflora incarnata* are admitted the following compositions (Directive 2001/83/EC): herbal substance fragmented or cut, dried aerial parts, herbal preparations powdered, herbal substance for tea preparation liquid extract (1:8 in 25% ethanol, 1:8 in 45% ethanol, 1:1 in 25% ethanol or 1:1 in 70% ethanol) and corresponding dry extracts. The posology is 1-2 g of herbal substance as powder 1-4 times daily; these herbal medicines could be used in infusion or liquid extract with appropriate dilutions (EMA, 2008).

Even *Melissa officinalis* is a traditional herbal medicinal product for the relief of mild symptoms of mental stress and to aid sleep; moreover, it is indicated for symptomatic treatment of mild gastrointestinal complaints including bloating and flatulence. No side effects or overdoses are reported.

*Melissa officinalis* is indicated in traditional medicine for uses exclusively based upon long-standing with the follows formulations: Herbal substance cut, dried, herbal preparations like powdered herbal substance, tincture (1:5; extraction solvent ethanol 45% V/V or m/m) and liquid extract (1:1; extraction solvent ethanol 45% V/V/ or m/m) or dry extracts correspondent. The dosages recommended are 1.5 – 4.5 g of cut or powdered herbal substance, 2-6 ml of tincture and 2 – 4 ml of liquid extract for 1-3 times daily (EMA, 2007).

The traditional and the well-established use of *Valeriana officinalis* suggests this herbal medicinal product for the relief of sleep disorders and of mild symptoms of mental stress (see Insomnia paragraph). The oral use is recommended for adults and is not recommended in adolescents and children below the age of 18 years, due the lack of adequate data. Gastrointestinal symptoms (e.g. nausea, abdominal cramps) are the unique side effects known after ingestion of valerian root preparation.

The well-established use suggests 1-2 doses half to one hour before bedtime, without exceeding 500 mg of valerian extract and to achieve an optimal therapeutic effect, the continued use over 2-4 weeks is recommended. Today there are only limited data on pharmacological interactions with other medicinal products and no clinical evidence supports its use for anxiety or distress in cancer (EMA, 2009).

Finally, also *Rhodiola rosea* is active in the anxiety-depression states and its use in oncology may be interesting for both Cancer Related Fatigue (see related paragraph) and anxiety treatment.

**Summary table**

<b>Plant</b>	<b>Clinical indications</b>	<b>Grading</b>	<b>Dosage</b>	<b>Recommendations</b>
<i>Crocus sativus</i>	Mild-to-moderate depression	1B	Hydroalcoholic extract: 30 mg, (0.60-0.70 mg of safranale/day)	
<i>Hypericum perforatum</i>	Mild to moderate depression and insomnia	1A	Dry extract: From 600 to 1800 mg of extract, titrated to 0.3-0.5% in hypericin	Be cautious due to important drug interactions
<i>Lavender</i> spp.	Generalized anxiety disorder and insomnia	1B	cps: 80 mg/day Inhalation: final solution 1-2% Massage: final solution 1% Aromatherapy: (1:2) Essential lavender oil in water into an ultrasonic ionizer aromatherapy diffuser	Be cautious about internal administration
<i>Melissa officinalis</i>	Mild symptoms of mental stress, sleep and gastrointestinal disorders	T	Dry extract: 1.5 – 4.5 g, Tincture: 2 – 6 ml, Liquid extract: 2 – 4 ml (1-3 times daily)	
<i>Passiflora incarnata</i>	Depression, anxiety and insomnia	T	Dry extract: 1-2 g (1-3 times daily)	
<i>Rhodiola rosea</i>	Mild-to-moderate depression and Cancer Related Fatigue	T	Dry extract: 200 to 600 mg/day	
<i>Valeriana officinalis</i>	Mild symptoms of mental stress, sleep disorders	T	Dry extract: 500 mg of extract	

Legend: T = Traditional use

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### *Anxiety and depression and homeopathy*

A systematic review (Pilkington K. et al., 2006) was conducted to evaluate the clinical research evidence of homeopathy in the treatment of anxiety. Efforts were made to identify unpublished and ongoing research using relevant sources and experts in the field. Relevant research was categorised by study type and appraised according to study design. Clinical commentaries were obtained for studies reporting clinical outcomes.

A comprehensive search demonstrates that the evidence on the benefit of homeopathy in anxiety and anxiety disorders is limited. A number of studies of homeopathy in such conditions were located but the RCTs report contradictory results, are underpowered or provide insufficient details of methodology.

Several uncontrolled and observational studies reported positive results, including high levels of patient satisfaction but due to the lack of a control group, it is difficult to assess the extent to which any response is due to homeopathy. Adverse effects reported appeared limited to 'remedy reactions' and included temporary worsening of symptoms and/or reappearance of old symptoms.

Adler et al. (2009) aimed at investigating the non-inferiority and tolerability of individualized homeopathic medicines (Q-potencies) in acute depression, using fluoxetine as active control. Ninety-one outpatients with moderate to severe depression were assigned to receive an individualized homeopathic medicine or fluoxetine 20 mg day<sup>-1</sup> (up to 40 mg day<sup>-1</sup>) in a prospective, randomized, double-blind double-dummy 8-week, single-center trial.

Primary efficacy measure was the analysis of the mean change in the Montgomery & Asberg Depression Rating Scale (MADRS) depression scores, using a non-inferiority test with margin of 1.45. Secondary efficacy outcomes were response and remission rates. Tolerability was assessed with the side effect rating scale of the Scandinavian Society of Psychopharmacology. Mean MADRS scores differences were not significant at the 4th ( $P = .654$ ) and 8th weeks ( $P = .965$ ) of treatment. Non-inferiority of homeopathy was indicated because the upper limit of the confidence interval (CI) for mean difference in MADRS change was less than the non-inferiority margin: mean differences (homeopathy-fluoxetine) were -3.04 (95% CI -6.95, 0.86) and -2.4 (95% CI -6.05, 0.77) at 4<sup>th</sup> and 8<sup>th</sup> week, respectively.

Table 1 Summary of studies

Study	Study design	Sample	Inclusion criteria	Homeopathy intervention (Tx)	Control intervention (Ct)	Outcome measure(s)	Results	Methodology comments and Jadad score*	Clinical comments
<b>Randomised controlled trials</b>									
Albeu and Jobert <sup>22</sup> (French)	RCT	50 hospitalised children (6 months–14 years) Selection process unclear Tx = 23 Ct = 24	Post-operative agitation (anxiety)	Aconite No. of doses not stated	Placebo (verum)	Not stated except for 'improvement' (physician assessment according to Linde <i>et al</i> <sup>14</sup> )	'Effective with 95% good results' Negative outcomes: not mentioned	Randomisation: unknown Allocation concealment: unknown Blinding: not mentioned Power: unknown Attrition rate: unknown Jadad score: 2	On abstract only: Intervention and control appropriate. Outcomes unclear Very high response rate
Baker <i>et al</i> <sup>23</sup>	RCT 3-arm	70 of 113 Australian university student volunteers Tx = 21 Ct 1(R) = 18 Ct 2(P) = 23 [completers only]	Test anxiety Score of 50+ on Benson RTA	Traditionally prepared <i>Argentum nitricum</i> 12 × Twice daily for 4 days	1. Rationally prepared <i>Argentum nitricum</i> 12 × 2. Placebo Alcohol/water mixture as per treatments	Benson Revised Test Anxiety Scale (RTA) TAS 36-item A. <i>nitricum</i> questionnaire Pre and post (1 week later)	No significant difference found between treatments on either RTA or TAS Negative outcomes: not mentioned	Randomisation: adequate Allocation concealment: adequate Blinding: adequately powered Attrition rate: 8 (11%) Jadad score: 4	Intervention, placebo and outcomes appropriate High-quality study
Bonne <i>et al</i> <sup>24</sup>	RCT	44 selected from 247 adults recruited via adverts Tx = 22 Ct = 22	Generalised anxiety disorder (DSM-IV diagnosis) HAM-A > 20 HAM-D < 18	Individualised homeopathy (single remedy, all dilutions > 10 <sup>-30</sup> ) 10 weeks	Placebo 'Non-medication impregnated globules'	HAM-A HAM-D BSI P GWBI BDI STAI subjective distress (VAS)	Significant improvement in most measures including HAM-A in both groups. No significant difference between groups Negative outcomes: no aggravations observed	Randomisation: unknown Allocation concealment: adequate Blinding: adequate Power: calculation suggested target of 60 Attrition rate: 5 (11%) Jadad score: 3	Intervention, control and outcomes appropriate but follow-up short for GAD.
Hariveau <sup>25</sup> (French)	RCT 2 centres	84 (no statement on numbers in each group)	Reactive anxiety-depression	Lithium Microsol 3–4 ampoules per day, twice daily 30 days	Lorazepam 2–4 mg per day, twice daily	Measures not stated—sleep, delay in sleep onset, heart rate, 'emotionalism'	Outcomes measured after 30 days, measures used not described Negative outcomes: not mentioned	Randomisation: unknown Allocation concealment: unknown Blinding: not mentioned Attrition rate: unknown Jadad score: 1	Not sent for clinical commentary—no English abstract
Heulley <sup>26</sup>	RCT (non-blinded)	N = 60 setting and recruitment unknown Tx = 30 Ct = 30	Currently under consultation for depression, postmenopausal involution or thymo-effective dystonia	Non-individualised L72 (constituents not specified) (20 drops 4 times daily for 31 days) dose increased if required	Diazepam (dose and frequency unknown)	Ratio of pre and post scores for selected items on HAM scale	'L72 as effective as diazepam on all measures' Negative outcomes: drowsiness (1 case for L72, 2 for diazepam)	Randomisation: unknown Allocation concealment: unknown Blinding: open study Power: not mentioned Attrition rate: unknown Jadad score: 1	Intervention appropriate Control unclear Outcomes inappropriate Diagnostic classification a problem

Table 1. (continued)

Study	Study design	Sample	Inclusion criteria	Homeopathy intervention (Tx)	Control intervention (Ct)	Outcome measure(s)	Results	Methodology comments and Jadad score*	Clinical comments
McCutcheon <sup>27</sup>	RCT	77 recruited via students and health food store	Above average anxiety scores (score of 18+ on part one of pre-test STA)	Anti-Anxiety,* 15 days	Placebo	STAI	No significant differences in STAI or pulse rate between groups. Significantly less sleep loss in homeopathy group. Negative outcomes: not mentioned. Homeopathic preparation significantly improved test anxiety compared with placebo. No difference between groups for either activity or profile scores.	Randomisation: unknown. Allocation concealment: adequate. Blinding: not reported. Attrition rate: 5 (6%) Jadad score: 4	Intervention, control and outcomes appropriate but sleep disturbance is not a core symptom of anxiety
Stanton <sup>28</sup> (details reported in Baker et al <sup>23</sup> original report unavailable)	RCT	Tx = 38 Ct = 39	Test anxiety	20 drops 4 times daily Argentum nitricum 12 x	Placebo	Resting pulse Sleep loss Test Anxiety Scale		No details available Jadad score: ?	Not sent for clinical commentary
Thompson et al <sup>29</sup>	RCT	53	Symptoms of oestrogen withdrawal (including anxiety)	Individualised prescribing (60 minute initial consultation plus four 20 minute follow-up consultations) Duration 16 weeks	Matched placebo tablet, granule or liquid	Primary: MYMOP  Secondary: HADS Menopausal Symptom Questionnaire EORTCQLQ-C30	Clinically relevant improvements in symptoms and mood for both homeopathy group. Negative outcomes: approx 25% in each group	Randomisation: adequate. Allocation concealment: adequate. Blinding: adequate. Power: post hoc calculations suggested 65–175 per group required. Attrition rate: 5 from homeopathy group, 3 from placebo, reasons documented. Jadad score: 5	Large number (71) of homeopathic medicines used, intensive follow-up
<b>Uncontrolled studies (anxiety disorders)</b>									
Davidson et al <sup>31</sup>	UC study	12 patients at US hospital or homeopathic hospital. Recruitment process unclear	Social phobia, panic disorder, residual attention-deficit disorder, major depression, chronic fatigue syndrome	Full psychiatric assessment and homeopathic interview then individualised prescribing	N/A	CGI plus self-rated SCL-90 in the hospital, BPS in the medical practice. Measures taken at variable intervals	58% (7) recorded a 50% reduction on the CGI scale	Not randomised, controlled or blinded.	Intervention and outcomes appropriate
Clover et al <sup>30</sup>	Case series	50 cancer patients referred to UK homeopathic hospital	Cancer-related symptoms (including anxiety)	Individualised homeopathy	None	HADS Rotterdam Symptom Checklist (RSCL)	Improvements on the psychological distress subscale of RSCL	Compliance unknown Co-interventions—partial (drug and dose reported not frequency)	Control/placebo N/A Very relevant, excellent preliminary report

Table 1. (continued)

Study	Study design	Sample	Inclusion criteria	Homeopathy intervention (Tx)	Control intervention (Ct)	Outcome measure(s)	Results	Methodology comments and Jadad score*	Clinical comments
McCutcheon <sup>27</sup>	RCT	77 recruited via students and health food store	Above average anxiety scores (score of 18+ on part one of pre-test STAI)	Anti-Anxiety, * 15 days	Placebo	STAI	No significant differences in STAI or pulse rate between groups Significantly less sleep loss in homeopathy group Negative outcomes: not mentioned Homeopathy preparation significantly improved test anxiety compared with placebo No difference between groups for either activity or profile scores.	Randomisation: unknown Allocation concealment: adequate Blinding: adequate Power: not reported Attrition rate: 5 (6%) Jadad score: 4	Intervention, control and outcomes appropriate but sleep disturbance is not a core symptom of anxiety
Stanton <sup>28</sup> (details reported in Baker et al <sup>23</sup> original report unavailable)	RCT	Tx = 38 Ct = 39	Test anxiety	20 drops 4 times daily <i>Argentum nitricum</i> 12 x	Placebo	Resting pulse Sleep loss Test Anxiety Scale		No details available Jadad score: ?	Not sent for clinical commentary
Thompson et al <sup>29</sup>	RCT	53	Symptoms of oestrogen withdrawal (including anxiety)	Individualised prescribing (60 minute initial consultation plus four 20 minute follow-up consultations) Duration 16 weeks	Matched placebo: tablet, granule or liquid	Primary: MYMOP Secondary: HADS Menopausal Symptom Questionnaire EQRT/COLQ-C30	Clinically relevant improvements in symptoms and mood for both homeopathy group. Negative outcomes: approx 25% in each group	Randomisation: adequate Allocation concealment: adequate Blinding: adequate Power: post hoc calculations suggested 65–175 per group required Attrition rate: 5 from homeopathy group, 3 from placebo, reasons documented Jadad score: 5	Large number (71) of homeopathic medicines used, intensive follow-up Outcomes clinically significant in both groups Adverse events appear more common than in other trials. No details of nature of adverse events given
<b>Uncontrolled studies (anxiety disorders)</b>									
Davidson et al <sup>31</sup>	UC study	12 patients at US hospital or homeopathic hospital. Recruitment process unclear	Social phobia, panic disorder, residual attention-deficit hyperactivity disorder, major depression, chronic fatigue syndrome	Full psychiatric assessment and homeopathic interview then individualised prescribing	N/A	CGI plus self-rated SCL-90 in the hospital, BSPS in the medical practice. Measures taken at variable intervals	58% (7) recorded a 50% reduction on the CGI scale 50% (6) recorded a 50% reduction on the SCL-90 or BSPS scale Negative outcomes: none reported	Not randomised, controlled or blinded. Compliance unknown	Intervention and outcomes appropriate Control/placebo N/A Very relevant, excellent preliminary report
<b>Uncontrolled studies (anxiety in physical or medical conditions)</b>									
Clover et al <sup>30</sup>	Case series	50 cancer patients referred to UK homeopathic hospital	Cancer-related symptoms (including anxiety)	Individualised homeopathy	None	HADS Ritterdam Symptom Checklist (RSCL) (RSCL)	Improvements on the psychological distress subscale of RSCL	Not randomised or blinded	Intervention, outcomes appropriate (latter for quality of life)

*In cancer care:*

Güthlin C et al. (2010) compared the characteristics of 2 cancer patient cohorts: one was treated in a homeopathic cancer care clinic and the other in a conventional oncology care (CC) outpatient clinic. Six-hundred and forty-seven patients were included in this cross-sectional cohort study and had to fill in questionnaires: health-related quality of life (QoL) (Functional Assessment of Cancer Therapy-General Scale), depression and anxiety (Hospital Anxiety and Depression Scale), fatigue (Multidimensional Fatigue Inventory) and expectancies toward treatment. Clinical data were extracted from medical records. This study presents the comparison of both cohorts.

Rostock M. et al. (2011) conducted a research on classical homeopathy in cancer patients in a prospective observational study considering: quality of life, impairment by fatigue, anxiety and depression.

The cancer patients were divided in 2 differently treated cohorts: one cohort with patients under complementary homeopathic treatment (HG; n = 259), and the other with conventionally treated cancer patients (CG; n = 380). For a direct comparison, matched pairs with patients of the same tumour entity and comparable prognosis were to be formed. Main outcome parameter: change of quality of life (FACT-G, FACIT-Sp) after 3 months. Secondary outcome parameters: change of quality of life (FACT-G, FACIT-Sp) after a year, as well as impairment by fatigue (MFI) and by anxiety and depression (HADS).

Type of study	Therapeutic protocol	N. patients and disease	End points criteria	Results	Author, year
Randomized controlled double-blind trial	Individualized homeopathic medicines Q-potencies in acute depression, using fluoxetine as active control	91 outpatients with moderate to severe depression	Primary efficacy measure was the analysis of the mean change in the Montgomery & Asberg Depression Rating Scale (MADRS) depression scores, using a non-inferiority test with margin of 1.45. Secondary efficacy outcomes were response and remission rates. Tolerability was assessed with the side effect rating scale of the Scandinavian Society of Psychopharmacology	There were no significant differences between the percentages of response or remission rates in both groups. Tolerability: no significant differences between the side effects rates, although a higher percentage of patients treated with fluoxetine reported troublesome side effects and there was a trend toward greater treatment interruption for adverse effects in the fluoxetine group	Adler, 2009
Cross-sectional cohort study	First cohort: cancer patient group treated in a homeopathic clinic (Orselina, Switzerland). Second cohort: patient group receiving treatment at a conventional outpatient oncology unit	Six-hundred and forty-seven patients	Questionnaire: health-related quality of life (QoL) (Functional Assessment of Cancer Therapy-General Scale), depression and anxiety (Hospital Anxiety and Depression Scale), fatigue (Multidimensional Fatigue Inventory) and expectancies toward treatment	Patients in the homeopathy cohort were younger, better educated and more often employed than patients in the CC cohort. The most pronounced differences indicated longer disease histories and different diagnostic and clinical pretreatment variables.	Güthlin C et al. 2010
Prospective observational study	Individualised homeopathic treatment	Cohort 1 (HG): 259 patients under complementary homeopathic  Cohort 2 (CG): 380 patients treated with conventionally cancer care	Main outcome parameter: change of quality of life (FACT-G, FACIT-Sp) after 3 months. Secondary outcome parameters: change of quality of life (FACT-G, FACIT-Sp) after a year, as well as impairment by fatigue (MFI) and by anxiety and depression (HADS).	For fatigue, anxiety and depression no relevant changes were found. 120 patients of HG and 206 patients of CG met our criteria for matched-pairs selection. Due to large differences between the two patient populations, however, only 11 matched pairs could be formed. This is not sufficient for a comparative study	Rostock M. et al., 2011

Table 1. Homeopathic studies on Anxiety and Depression.

### **Conclusions of the literature and authors**

Considering the research in the depression field that compares homeopathic drug versus fluoxetine in depression, there were no significant differences between the percentages of response or remission rates in both groups. Indeed there were no significant differences between the side effects rates, although a higher percentage of patients treated with fluoxetine reported troublesome side effects and there was a trend toward greater treatment interruption for adverse effects in the fluoxetine group. This study illustrates the feasibility of randomized controlled double-blind trials of homeopathy in depression and indicates the non-inferiority of individualized homeopathic Q-potencies as compared to fluoxetine in acute treatment of outpatients with moderate to severe depression. In the oncological field, on the basis of the review, it is not possible to draw firm conclusions on the efficacy/effectiveness of homeopathy in anxiety.

If demonstrated to be effective, homeopathy could have benefits in terms of adverse effects and acceptability to patients. In the prospective study, an improvement in quality of life was observed as well as a tendency of fatigue symptoms to decrease in cancer patients under complementary homeopathic treatment. Considerably larger samples are necessary to find matched pairs suitable for comparison in order to establish a definite causal relation between these effects and homeopathic treatment. Consequently, further investigation is needed.

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### *Anxiety/depression and anthroposophic medicine*

Cancer patients are particularly vulnerable to depression and anxiety. An improvement of anxiety and depression in patients with cancer treated with *Viscum album* L. extracts has been described in the context of studies concerning quality of life.

A systematic review (Kienle et al. 2010) described a significant improvement of mood disturbances, among other items of quality of life. Improvements were shown also with the whole system approach to cancer offered to in-patients of anthroposophic medicine hospitals (Heusser et al. 2006; Carlsson et al. 2005, 2006). Concerning mood disturbances, the anthroposophic medicine whole system approach and the non-verbal and artistic exercising therapies can offer a promising opportunity and a different proposal or even a bridge to opening up communication on a verbal level. Anthroposophic medicinal products and non pharmacological interventions are regularly used in clinical practice in the treatment of anxiety and depression. Only one study concerns specifically depression in patients with cancer, and describes the improvement of depression from art therapy combined to chemotherapy.

A systematic review (Kienle et al. 2010) of 26 RCTs and 10 non-RCTs investigated the influence of *Viscum album* L. extracts (VAE) on quality of life in patients with cancer. Improvements in anxiety and depression were described by most of the studies. Anxiety and depression appeared to be improved in studies considering *Viscum album* extracts in combination with conventional oncological treatments, e.g. in few RCTs and in 3 retrospective comparative epidemiological cohort studies on pancreatic (Matthes et al. 2009), breast (Bock et al. 2004), and colorectal (Friedel et al. 2009) cancer.

In relation to the psychoemotional impact of surgery for cancer, depression was significantly improved ( $p < 0.0001$ ) by postoperative treatment with VAE (Schumacher et al. 2003) and anxiety decreased with perioperative administration of VAE (Enesel et al. 2005).

The reparative effect of anthroposophic medicine on anxiety and depression in cancer can be especially seen in the context of a multimodal administration of interventions. The published studies on anthroposophic medicine as whole system described improvements in anxiety and depression.

Some publications described the quality of life of women with breast cancer treated in the anthroposophic clinic Vidarkliniken, Järna, S, compared in matched pairs to conventionally treated patients.

The perceived quality of life, including emotional functioning and depression has been evaluated over 5 years (Carlsson et al. 2006). Data from admission, after 1 year and after 5 years were used for the comparisons. On admission to the study the women in anthroposophic care perceived their emotional functioning to be lower than that of the women in the conventional treatment group. Twenty-six women within anthroposophic care and 31 women within conventional medicine survived 5 years. Effect size estimation favored the anthroposophic group in 7 of the subscales mostly measuring emotional functioning. Coping was also improved by anthroposophic global treatment (Carlsson et al. 2005).

Mental adjustment to cancer is defined as the cognitive and behavioral responses made by an individual to the diagnosis of cancer. The Mental Adjustment to Cancer scale (MAC) can be used for evaluation and contains 5 subscales measuring 5 coping strategies (fighting spirit, helpless/hopeless, anxious preoccupation, fatalism and avoidance). In this study, the 4 latter subscales were combined into a single variable representing passive and anxious coping behavior (PAC). The women in the group treated with anthroposophic medicine showed more PAC compared with their matched "twins" on admission to the study. The results showed that PAC decreased over time in the group treated with anthroposophic medicine and that the active choice of anthroposophic care could be seen as a possible way of coping with emotional distress in this group or women with breast cancer.

Heusser et al. (2006) described the treatment of 144 in-patients with various epithelial advanced cancers, in the Lukas Klinik (Arlesheim, CH) dedicated to anthroposophic oncological treatment. Patients were evaluated with EORTC QLQ-C30, HADS und SELT-M. In relation to anxiety and depression, a marked increase in 'emotional functioning' and 'basic mood' and a decrease in 'anxiety' and 'depression' scores were observed during hospitalisation ( $p < 0.0001$ ). Among others, quantitatively, the most pronounced improvement occurred in the dimensions 'emotional functioning' and 'basic mood'.

The considerable rise in the emotional scores corresponded to these patients' prior expectancy of emotional well-being, described as a major reason for choosing the Lukas Klinik for palliative treatment (Von Rohr et al. 2000).

Mood disturbances and stress affect bodily, soul and spiritual resilience and internal regulation. In relation to cancer, autonomic regulation and self regulation seem to be a prognostic factor in breast cancer survivors (Kröz et al. 2013b) and self regulation has been associated also to improved survival in some cancers (Grossarth-Maticek et al. 2001; Kröz et al. 2011). Psychological distress possibly predicts recurrence and

survival in breast cancer patients (Groenvold et al. 2007) and is often associated to cancer-related fatigue. A prospective observational study comparing 90 women with breast cancer and 80 healthy women suggests that high autonomic regulation and self regulation seem to have a protective influence on anxiety and depression (Kröz et al. 2013b).

Considering some single approaches, eurythmy therapy has shown in healthy adults (Kanitz et al. 2011) a potentially positive influence on distress and coping. Case reports described clinical courses of improvement of anxiety, in relation to eurythmy therapy (Kienle et al. 2011) and anthroposophic psychotherapy and medications (Lees et al. 2013). But only art therapy has been studied specifically in a non-randomized, open phase II clinical trial in patients with cancer (Bar Sela et al 2007). Sixty cancer patients on chemotherapy participated once-weekly to anthroposophic art therapy sessions. Nineteen patients who participated in  $\geq 4$  sessions were evaluated as the intervention group, and data of 41 patients who participated in  $\leq 2$  sessions were used to compare basic details. Hospital Anxiety and Depression Scale (HADS) was completed before every session, relating to the previous week. The anxiety score was in the normal range from the beginning, but depression decreased during the treatment. In the intervention group, the median HADS score for depression was 9 at the beginning and 7 after the fourth appointment ( $p = 0,021$ ), suggesting further studies.

Some studies described the results of anthroposophic treatment for anxiety disorders and depression in general (e.g. Hamre et al. 2007abc; Hamre et al. 2013). They may be of interest also for dealing with mood disturbances in patients with cancer and for considering patterns of treatment and possibly cost-effectiveness. A prospective cohort study of 64 consecutive adult outpatients starting anthroposophic treatment for anxiety disorders under routine conditions was conducted by Hamre et al. (2009). Main outcomes were anxiety severity (physician and patient ratings 0–10), the Self-rating Anxiety Scale (0–100), the Center for Epidemiological Studies Depression Scale, German version (CES-D, 0–60), and the SF-36 Mental Component Summary. The anthroposophic treatment modalities used were medications (56% of patients), eurythmy therapy (41%), art therapy (30%), and rhythmical massage therapy (3%). Patients with anxiety disorders under anthroposophic treatment had long-term improvements of symptoms and quality of life. In the first 6 months after enrolment, 55% of the study patients had no standard therapy (psychotherapy, anti-anxiety medication). Some patients with anxiety disorders will not profit from standard therapies; other will discontinue standard therapies due to adverse reactions or reject them because they are passive (medication) or can be felt as intrusive or too verbal (psychotherapy). The proportion of responders at six-month follow-up (patients with 50% improvement of Anxiety Severity from baseline: 57%–58%) was of the same order of magnitude as responder rates in trials of anti-anxiety medications or psychotherapy.

Concerning depression, 97 outpatients with symptoms of depression lasting minimum 6 months, from 42 medical practices in Germany, participated in a prospective cohort study (Hamre et al. 2006). Median number of art/eurythmy/massage sessions was 14 (interquartile range 12–22), median therapy duration was 137 (91–212) days. Anthroposophic therapies were followed by long-term clinical improvement. All outcomes improved significantly between baseline and all subsequent follow-ups, and were maintained until last follow-up. At 12-month follow-up and later, 52%–56% of evaluable patients (35%–42% of all patients) were improved by at least 50% of baseline CES- D (Center for Epidemiological Studies Depression Scale) scores. CES-D improved similarly in patients not using antidepressants or psychotherapy during the first six study months (55% of patients).

Therefore *Viscum album* L. extracts and the whole system of anthroposophic medicine can help to improve anxiety and depression in cancer patients, with a value to be given to non pharmacological intervention as special assets, for an active, practising and motivating participation to cure of the patient himself.

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## Cancer related fatigue (CRF)

### *Cancer related fatigue and acupuncture/TCM*

The Guidelines of Filshie and Hester (2006) indicated as a specific condition to consider for the acupuncture treatment not treatable fatigue.

Lu et al. (2008) reviewed some pilot not controlled clinical studies which show improvement in patients with fatigue correlated to chemotherapy. In patients with persistent asthenia who completed cytotoxic therapy and not anaemic, acupuncture resulted in an improvement of 31,3%.

According to the Guidelines of the Society for Integrative Oncology (SIO) (Deng et al. 2009), the acupuncture treatment is recommended in cancer-related fatigue (CRF) as a support to therapy (recommendation level 2 C, weak recommendation, evidence of low quality) but further studies are necessary (RCTs).

In a review by Kirshbaum (2010), among the interventions that seem to be helpful, in addition to the current practice, a large choice of complementary therapy is proposed, among them also acupressure and acupuncture.

Garcia et al. (2013) published a review about various symptoms, among them the fatigue. Three studies on fatigue were included. All were assessed as having high risk of bias (ROB). Two studies with negative outcomes were underpowered (n. 26: 15 acupuncture and 11 sham; n. 12: 5 acupuncture plus lifestyle education and 7 usual care). The latter study also had problems with recruitment. In a third study with positive outcomes (n. 38; 13 acupuncture, 12 acupressure, and 13 sham acupressure), there were questions about possible group differences at baseline.

A systematic review (Finnegan et al. 2013) was conducted to appraise the effectiveness of CAM interventions (acupuncture, massage, yoga, and relaxation training) in ameliorating CRF and evaluated it through randomized controlled trials (RCTs) or quasi-experimental design. Twenty studies were eligible for the review, of which 15 were RCTs, 3 of them regarded acupuncture (reported in the Table: Molassiotis 2007, Balk 2009, Johnston 2011). The review identified some limited evidence suggesting hypnosis and ginseng may prevent the increase in CRF and acupuncture and that biofield healing may reduce CRF following cancer treatments. However, trials varied greatly in quality; most of them were methodologically weak and at high risk of bias. Consequently, there is currently insufficient evidence to conclude with certainty the effectiveness or not of CAM in reducing CRF.

Also Posadzki et al. (Korea 2013) published a review: 14 databases were searched from their respective inception to November 2012. RCTs of acupuncture or electroacupuncture for the treatment were considered for inclusion. The risk of bias/methodological quality was assessed using the method suggested by the Cochrane Collaboration. Seven RCTs met the eligibility criteria; most of them were small pilot studies with serious methodological flaws. All the studies can be seen in the table, except 2 studies that were not found in literature: a pilot study by Oh (2009), a single blind 2 arm RCT on 18 patients treated with acupuncture (LU9, SP3, Ki2, TE6) and a study (Deng 2010) conducted using Park sham acupuncture (telescoping blunt-edged needle). Five studies had the sham acupuncture as control group (Park sham needles were used in 3 studies, in 1 sham acupressure and 1 sham needles in 1 sham needles near points used in TA), and 2 studies compared acupuncture versus usual care. Four of the RCTs showed the effectiveness of acupuncture or acupuncture in addition to usual care over sham acupuncture; 3 RCTs showed no effect of acupuncture and electroacupuncture over other treatments (1 Park sham, 2 usual care). The authors concluded that the quantity and the quality of RCTs were too low to draw meaningful conclusions.

Finally He et al. (2013) in the review and meta-analysis examined the efficacy of alternative therapies including acupuncture and moxibustion in RCTs published before December 2012. The quality of the included studies was assessed basing on the Cochrane handbook. A total of 7 studies involving 804 participants were eligible. Four of these studies deal with the acupuncture treatment versus control group (Molassiotis 2007, Balk 2009, Molassiotis 2012, Smith 2013, seen the table). The other 3 studies are in Chinese and deal with moxibustion. The conclusion is that up to the search date, there have been few high quality RCTs to evaluate the effect of acupuncture and moxibustion, especially moxibustion. Yet acupuncture and moxibustion still appeared to be efficacious auxiliary therapeutic methods for CRF.

Here a few particularly interesting studies are reported: a RCT of Molassiotis et al. (2007) on 47 patients randomized in 3 groups (15 with acupuncture treatment; 16 with acupressure on the same points, 16 with a false acupressure treatment). After 2 weeks of treatment the RCT demonstrated a significant improvement (36%) in the acupuncture group, an improvement of 19% in acupressure group compared to the false acupressure group (0,6%) and 2 weeks after the conclusion of the treatment, even lower values.

The authors conclude that the results support the use of acupuncture in the treatment of post-chemotherapy fatigue.

In 2012 also Molassiotis et al. have conducted a pragmatic, randomized, controlled trial comparing acupuncture with enhanced usual care in 302 patients with breast cancer (75 patients to usual care, 227 to acupuncture plus usual care). After 2 weeks, in 240 patients the difference in the mean general fatigue score, between those who received the intervention and those who did not, was -3.11 ( $p < .001$ ). The intervention also improved all other fatigue aspects measured by MFI (Mental Fatigue Index), including Physical Fatigue and Mental Fatigue (acupuncture effect, -2.36 and -1.94, respectively, both at  $p < .001$ ). The authors conclude that acupuncture is an effective intervention for managing the symptoms of CRF and improving patients' quality of life.

Finally Molassiotis et al. (2013) re-randomized breast cancer patients who participated in a randomized trial of acupuncture (2012) for CRF management: 65 patients received an additional four acupuncturist-delivered weekly sessions; four self-administered weekly acupuncture sessions (self-needling, n.67) or no acupuncture (n.65). Maintenance acupuncture did not yield important improvements beyond those observed after an initial clinic-based course of acupuncture.

Type of Study	Therapeutic Protocol	N. patients and disease	Endpoints criteria	Results	Author, year
Observational study	acupuncture twice per week 4 weeks bilaterally ST36 SP8 SP9 LI11 unilaterally CV6 CV4  acupuncture once per week for 6 weeks ST36 SP6 CV6 CV4 KI3 KI27	37 patients registered in 2 cohorts 31 completed treatments  cancer patients in chemotherapy	Brief Fatigue Inventory (BFI)	Mean improvement following acupuncture was 31.1% no difference in improvement following once-weekly and twice- weekly treatments	Vickers, 2004
RCT 1) acupuncture 2) acupressure 3) sham acupressure	1)LI4 SP6 ST36 six 20-min sessions over 2 weeks 2)LI4 SP6 ST36 acupressure daily thereafter for 2 weeks on their own 3)L12 GB33 BL61	47 cancer patients randomized (15 group 1, 16 group 2,16 group 3)	Multidimensional Fatigue Inventory (MFI)	At the end of treatments: 36% improvement in fatigue levels in the acupuncture group, the acupressure group improved by 19% and the sham acupressure by 0.6%	Molassiotis, 2007
RCT double-blind placebo-controlled trial  1) true acupuncture 2) sham acupuncture	1)acupuncture KI3, SP6 LI4 ST36 Ren6/CV6 once to twice per week during the 6-week of radiation therapy 30 min. per session 2)Park sham needles at the same points	27 patients enrolled 23 completed treatments cancer patients receiving external radiation therapy	Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACIT-F)	both true and sham acupuncture groups improved fatigue  difference between groups not statistically significant  no adverse events	Balk, 2009
pilot single armed prospective clinical trial	acupuncture 12 sessions over 8 weeks  ST36 SP6 LI11 LI4 LV3 SP9 Yintang GV20 CV6 Shenmen  K3, TW5, GV14, LU9 (fatigue)	40 patients enrolled 26 completed treatments  advanced ovarian and breast cancer	Severity Scale (0-10)	significant improvement over time for patients with fatigue (P = .0002)	Dean-Clower, 2010

<p>pilot RCT</p> <p>1) acupuncture+ usual care 2) usual care only</p>	<p>1) Education (self care training, exercise, nutrition, etc.) for 4 weekly and 8 weekly 50-minute acupuncture sessions Acupuncture points LI4, SP6, ST36, KI3 + additional points 2) usual care</p>	<p>13 patients (7 group 1, 6 group 2) breast cancer</p>	<p>Brief Fatigue Inventory (BFI)</p>	<p>compared to usual care control, the intervention was associated with a 2.38-point decline in fatigue as measured by the BFI (<math>p &lt; 0.10</math>).</p>	<p>Johnston, 2011</p>
<p>RCT</p> <p>1) acupuncture with usual care 2) usual care</p>	<p>1) ST36, SP6, LI4, Alternative points: GB34, SP9 once a week for 6 weeks 2) usual care received a booklet with information about fatigue and its management</p>	<p>302 patients randomized 227 group 1, 75 group 2; 181, 65 evaluated) breast cancer</p>	<p>Multidimensional Fatigue Inventory (MFI)</p>	<p>significant reduction in fatigue for acupuncture group compared with control after 2 weeks (<math>p &lt; 0.001</math>), and improvement in patients' quality of life</p>	<p>Molassiotis, 2012</p>
<p>randomized sham controlled trial</p> <p>1) true acupuncture TA 2) sham acupuncture SA</p>	<p>once weekly for 6 weeks 1) acupuncture CV6 CV4 and bilaterally KI3 ST36 SP6 LI11 HT6 and auricular point antidepressant 2) sham needles near points used in TA</p>	<p>101 patients randomized 74 evaluated (34 group 1, 40 group 2) cancer patients in chemotherapy</p>	<p>Brief Fatigue Inventory (BFI)</p>	<p>BFI scores fell by about one point between baseline and follow-up in both groups with no statistically significant difference between groups</p>	<p>Deng, 2013</p>
<p>RCT re-randomized (Molassiotis, 2012)</p> <p>1) acupuncture delivered by therapists 2) self acupuncture/self-needling 3) no acupuncture</p>	<p>1) ST36, SP6, LI4, 4 weeks weekly sessions 2) ST36, SP6, LI4, administered weekly self-acupuncture 3) no acupuncture 4 weeks weekly sessions</p>	<p>197 patients re-randomized (65 group 1, 67 group 2, 65 group 3) 151 patients analysed (56, 46, 49) breast cancer</p>	<p>Multidimensional Fatigue Inventory (MFI)</p>	<p>a non-significant trend in improving fatigue in the combined acupuncture arms (<math>p = 0.07</math>).</p>	<p>Molassiotis, 2013</p>
<p>RCT</p> <p>1) acupuncture 2) sham acupuncture 3) waiting list</p>	<p>1) KI3 KI27 ST36 SP6 CV4 CV6 2) sham acupuncture Park device, in no acupuncture points 6 sessions of acupuncture over 8 weeks 3) waiting list</p>	<p>84 eligible patients 30 randomized (10 group 1, 10 group 2, 10 group 3) breast cancer</p>	<p>Brief Fatigue Inventory (BFI)</p>	<p>a significant reduction in fatigue for women receiving acupuncture compared with control after 2 weeks, mean difference (<math>p = 0.05</math>)</p>	<p>Smith, 2013</p>

## Conclusions of the literature and the authors

According to the Guidelines of the Society for Integrative Oncology (SIO 2009), it is not possible to conclude whether the acupuncture could be used to improve asthenia in cancer patients. The recommendation level is 2 C (weak recommendation, low or very low quality evidence).

However Filshie J. and Hester J. in 2006 and the latest literature (He reviews 2013 and RCTs by Molassiotis 2007, 2012, 2013) suggest that both acupuncture and moxibustion are effective auxiliary therapeutic methods for CRF, as the current practice confirms. All the authors agree that other high quality studies are needed.

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### Cancer related fatigue and herbal medicine

Herbal medicines used in the treatment of Cancer Related Fatigue (CRF) are mostly adaptogens, substances that have the capacity to normalize body functions and strengthen systems compromised by stress. Belong to this group: *Astragalus propinquus*, *Eleutherococcus senticosus*, *Panax ginseng*, *Panax notoginseng*, *Panax quinquefolius*, *Paullinia cupana*, *Rhodiola rosea* and *Schisandra sinensis*.

Among these, only the species of ginseng, *Paullinia cupana* and *Rhodiola rosea* have been studied in the treatment of CRF; however some evidences suggest that the other adaptogens are active in mild fatigue although not studied in CRF.

The beneficial effect of adaptogens is related to regulation of homeostasis via several mechanisms of action associated with the hypothalamic-pituitary-adrenal axis and the control of key mediators of stress response such as molecular chaperones, stress-activated c-Jun N-terminal protein kinase, transcription factors, cortisol and nitric oxide (NO).

### Ginseng

Ginseng is a perennial plant included in genus *Panax* and family Araliaceae. Among eleven different species of ginseng, three species, i.e., *P. ginseng* (PG, commonly called as ginseng, Korean ginseng or Asiatic ginseng), *P. quinquefolius* (PQ, commonly called as American ginseng) and *P. notoginseng* (PN, commonly called as Chinese notoginseng or San-chi or Tien-Chan) are the most commonly used at present (Kim HJ. 2013).

Ginsenoside is believed to be the active compound of ginseng herbs and widely used for the pharmacological examination of effects of ginseng ranging from the role as a traditional nourishing stimulant to anticancer reagent. The major active components are divided in two groups in relation to their chemical structure: protopanaxadiol and protopanaxatriol. The nomenclature of ginsenosides is by the designation Rx, where x represents the retention factor (RF) value from the sequence of spots on TLC from bottom to top. The level of ginsenosides can vary depending on steeping time and type of preparation. The ginsenoside concentration can vary from approximately 64-77%. In PG, up to 40 distinct ginsenosides have been identified by thin layer chromatography and methanol extraction experiments (Monograph. 2009).

The three species of ginseng have many of the same ginsenosides but in different ratios, in this context the researchers found that two types of ginsenosides (Rb1 and Rg1) are necessary to enhance activity performance in mice and without either of these ginsenosides, the extracts were not effective. Both *Panax ginseng* and *Panax quinquefolius* have both of them but the first has more Rg1, while the second has more Rb1 (Barton DL. 2010).

Recent research supports the hypothesis that ginsenosides are activated by intestinal bacteria through deglycosylation and esterification; also, the fermentation activity of intestinal bacteria enhances some of the desirable effects of ginseng (Park BG. 2013).

Protopanaxadiol and protopanaxatriol glycosides are absorbed into the blood or lymph and transported to target tissues for esterification with stearic, oleic, or palmitic fatty acids.

The most recent clinical trials about the CRF treatment with *Panax* genus are summarized in Tab. 1.

Type of study	Therapeutic protocol	N.patients and disease	End point and Criteria	Results	Author, year
Randomized, double-blinded, placebo-controlled trial	PG: 1000 mg  Period: 3 - 8 years	643 chronic atrophic gastritis patients	Effect of long-term administration of Korean red ginseng extract on incidence of human cancers  Criteria: RRs CI	The administration of red PG powder for 3 years exerted significant preventive effects on the incidence of non-organ-specific human cancers in males (p = 0.03)	Yun TK, 2010
Pilot study, randomized, double-blind, dose-finding evaluation	PQ (5% Ginsenoside): 750 mg 1000 mg 2000 mg	282 patients	Effect of PQ to improve cancer-related fatigue  Criteria:	The two highest doses of PQ did appear to decrease fatigue more than did a placebo, as	Barton DL, 2010

	Period: 49 days		BFI SF-36 PSQI GIC LASA	measured by various scales of fatigue, vitality, and well being. ( $p \leq 0.08$ )	
Randomized, double-blind trial, N07C2.	PQ: 2000 mg  Period: 4 and 8 weeks	364 patients	Effect of PQ in improving Cancer-Related Fatigue  Criteria: MFSI-SF	Data support the benefit of PQ, 2000 mg daily, on CRF over an 8- week period. No discernible toxicities associated with the treatment. ( $p = .003$ )	Barton DL, 2012
Randomized, controlled trial	PQ: 400 mg  Period: 3 months	293 subjects with early- stage, untreated CLL	Effect of PQ extract (CVT- E002) to reduce respiratory infection in patients with chronic lymphocytic leukemia  Criteria: ARI CTC-NIC	PQ was well tolerated. It did not reduce the number of infection days or antibiotic use; however, there was a trend toward reduced rates of moderate to severe ARI	High KP, 2012

Tab.1. Single clinical studies on *Panax* spp. in cancer patients. Legend: PG (*Panax ginseng*), PQ (*Panax quinquefolius*), ARI (Acute Respiratory Infection), CI (Confidence Interval), CTC-NCI (Common Toxicity Criteria-NCI), GIC (Global Impression of Change), LASA (Linear Analogue Self-Assessment Scale), MFSI-SF (Multidimensional Fatigue Symptom Inventory-Short Form), POMS-FS (Profile of Mood State), PSQI (Pittsburgh Sleep Quality Index), RRs (relative risks), SF-36 (Medical Outcome Scale Short Form-36).

**Dosage:** Ginseng root can be chewed, taken as a powder, liquid extract, decoction, or infusion. The recommended daily intake is 1–2 g/day of Asian ginseng (4–5% ginsenosides). The EMA suggests an adult dosage of 250 mg daily of PG powder standardized to 4% ginsenosides (8 mg ginsenosides daily), up to 8 doses daily up to 3 months or otherwise according to medical advice (EMA 2013).

**Side effects and toxicity:** In general, ginseng has a good safety record. The common adaptogenic ginsengs are generally considered to be relatively safe even in large amounts. To many people, ginseng tastes a bit sweet and is usually well tolerated. The root of *Panax ginseng* appeared nontoxic to rats, dogs, and humans. In mice, a lethal oral dose of purified ginseng was determined to be higher than 5 g/kg, equivalent to about 0.4 g/kg of oral ginseng given to an adult man.

The effects described as “ginseng abuse syndrome” are long-term side effect of ginseng that is related to a consumption far exceeding the recommended daily intake.

Both American and Asian ginsengs are stimulants and may cause nervousness or sleeplessness, particularly if taken at very high doses. Other reported side effects include high blood pressure, insomnia, restlessness, anxiety, euphoria, diarrhoea, vomiting, headache, nosebleed, breast pain and vaginal bleeding.

These side effects usually decrease after a few days. Asian ginseng may lower levels of blood sugar especially in people with diabetes. Therefore, diabetic patients who are taking anti-diabetic drugs should be cautious with ginseng and monitor their blood sugar levels closely. Because ginseng has an estrogen-like effect, women who are pregnant or breastfeeding should take it at recommended doses (Kim HJ. 2013).

**Drug interactions:** Several studies show that ginsenosides induced the CYP1A1, CYP1A2 and CYP3A4 expression. (Liu R. 2012, Malati CY. 2012, Bilgi N. 2010, Wanwimolruk S. 2009). Data suggest that after

oral administration, naturally occurring ginsenosides may influence hepatic P450 activity in vivo via ginseng's intestinal metabolites (Liu R. 2012, Qi LW 2011).

The Tab. 2 summarizes the human clinical trials conducted to date, to study the ginseng drug-interactions. They are limited in number, have small experimental group, different experimental designs and inconsistent results; therefore, further studies are needed.

*Panax ginseng*: Patients taking PG in combination with CYP3A substrates with narrow therapeutic ranges (like Imatinib an inhibitor of bcr-abl tyrosine kinase enzyme use in chronic myelogenous leukaemia) should be monitored closely for adequate therapeutic response to the substrate medication (Malati CY. 2012, Bilgi N. 2010).

Furthermore, the P-glycoprotein (P-GP), an intestinal enterocyte drug transporter, is responsible for pumping drugs out of the body, thus serving to decrease drug bioavailability. Imatinib is a P-GP substrate; therefore, its plasma concentration may be dependent on P-GP activity. PG has been shown to inhibit P-GP; as a result, the intestinal absorption and bioavailability of imatinib could theoretically increase with concurrent ginseng ingestion. This drug-herb interaction involving drug transporters may act in synergy with the interaction on CYP3A4, further potentiating imatinib's hepatotoxic effect (Bilgi N. 2010, Malati CY. 2012).

Fishbein AB et al. evaluated the synergy between PG and 5-fluorouracil (5-FU), and explored the mechanism of their anti-proliferative effects. The authors show an in-vitro positive anti-proliferative effect of Rd and Rg3 ginsenosides on human colorectal cancer cells (Fishbein AB. 2009).

*Panax notoginseng*: Liu R. et al. in a study *in vitro* show that PN could induce CYP1A2, which may affect the disposition of medicines primarily dependent on the CYP1A2 pathway (Liu R. 2012, Wang Y. 2008).

*Panax quinquefolius*: No studies show drug interactions of PQ with any drugs. Only two studies suggest that PQ does not alter zidovudine and indinavir pharmacokinetics (Andrade AS. 2008, Lee LS).

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Randomized, double-blind, placebo-controlled trial	PQ: 2gr  Warfarin: 5 mg  Period: 4 weeks	20 healthy patients	Action of American ginseng to reduce warfarin's effect in healthy patients:  Criteria: INR plasma warfarin level	The data suggest that PQ reduces warfarin's anticoagulant effect. When prescribing warfarin, physicians should ask patients about ginseng use. (P = 0.0012)	Yuan CS, 2004
Randomized, open-label, controlled study	PG:  Warfarin: 2 mg (first week) and 5 mg (second week)	25 patients newly diagnosed with ischemic stroke	Interaction between warfarin and PG in ischemic stroke patients  Criteria: PT INR	The data suggests that coadministration of PG and warfarin in ischemic stroke patients does not influence the pharmacologic action of warfarin	Lee SH, 2008
Multi-center, double-blinded, randomized controlled clinical trial	PN 600mg + Aspirin 50 mg	140 patients of ischemic stroke in anterior cerebral	Action of radix/rhizome PN extract for ischemic stroke	Low dose of aspirin combined with PN ameliorated neurological deficit (p<0.0001) and	He L, 2011

	Period: 7 months	circulation	Criteria: ESS BI	activities of daily living (p=0.0178) after treatment compared with aspirin alone	
Single-center, crossover, single-sequence, open-label study	PG: 1000mg Midazolam: 8 mg Fexofenadine: 120 mg  Period: 28 days	20 healthy participants	Analysis of PG, midazolam and fexofenadine interaction in plasma concentrations	PG appeared to induce CYP3A activity. Patients taking PG in combination with CYP3A substrates with narrow therapeutic ranges should be monitored closely	Malati CY, 2012

Tab.2. Single clinical studies on Panax spp. in drug interactions. Legend: PG (*Panax ginseng*), PN (*Panax notoginseng*) AUC<sub>0-8</sub>(Area Under Curve 0-8 h), PT (Prothrombin Time), BI (Barthel index), ESS (European Stroke Scale), t<sub>1/2</sub> (half-life), INR (International Normalized Ratio).

### Paullinia cupana

*Paullinia cupana* (PC), also known as Guarana is a plant native to the Amazon basin. Traditionally, extracts of roasted seeds have been used in medicinal drinks as stimulants, tonics and aphrodisiacs. It is interesting to note that the PC has shown favorable effects on memory and cognition in a small randomized, placebo-controlled study of young volunteers (Kennedy DO. 2004).

del Giglio et al. (2011) show as PC may be used in CRF treatment. The authors process a meta-analysis of three clinical trials showing that in 137 patients, mostly with early breast cancer undergoing either radiation or chemotherapy, PC was effective in comparison with the placebo (del Giglio A. 2011).

PC seeds contain 4-8% of caffeine, as well as trace amounts of theophylline and theobromine together with large quantities of alkaloids, terpenes, tannins, flavonoids, starch, saponins, and resinous substances. The xanthine alkaloids (caffeine, theophylline, theobromine) are believed to contribute significantly to PC's psychostimulant activities in clinical studies. Even though caffeine content in PC is large relative to other plants such as coffee, black tea and mate, the amount of caffeine present in the dosages of 75 to 100 mg used in the studies of this meta-analysis may be insufficient to explain the anti-fatigue activity of this plant. Other activities of PC yet unknown may be responsible for anti-fatigue effects clinically observed in patients with cancer (del Giglio A. 2011).

Moreover Subbiah MT et al. (2008) have identified in the fraction containing catechins, epicatechins, and their dimers, the fraction responsible for anti-platelet aggregator activity in PC seeds.

The clinical studies on cancer patients treated with CP for chronic fatigue, require larger samples (Tab.3).

Type of study	Therapeutic protocol	N.patients and disease	End point and Criteria	Results	Author, year
Double-blind randomized study, with crossover between experimental arms	CP arm: 75 mg daily per os and then switch to placebo  Period: 2 cycles of radiotherapy (35 for each treatment)	36 patients with breast cancer undergoing adjuvant radiation therapy	evaluate the effectiveness of guarana in the treatment of post-radiation depression and fatigue  Criteria: BFI, CFS	the data show that patients with breast cancer undergoing radiation therapy derive any advantage with guarana over placebo for both fatigue and depressive symptoms	Da Costa Miranda V, 2009
Phase II randomized, double-blind, placebo controlled crossover trial.	CP: 100 mg  Period: 49 days	75 patients	To study the effect of PC in improving fatigue in breast cancer patients	CP significantly improved the FACIT-F, FACT-ES, and BFI global scores compared to	de Oliveira Campos MP, 2011

			undergoing systemic chem.	placebo (p < 0.01)	
			Criteria: FACIT-F FACT-ES BFI PSQI CFS HADS	and did not produce any adverse events	

Tab.3. Single clinical studies on *Paullinia cupana* in adults. Legend: PC (*Paullinia cupana* extract), FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue), FACT-ES (Functional Assessment of Chronic Illness Therapy-Endocrine Symptoms), BFI (Brief Fatigue Inventory), (PSQI) Pittsburg Sleep Quality Index, CFS (Chalder Fatigue Scale), HADS (Hospital Anxiety and Depression Scale).

**Dosage:** The dosage reported in del Giglio's meta-analysis is 75 mg of unmanipulated dry extract, per os once daily or 50 mg per os twice daily, while the EMA report suggests a maximum dosage of 450 mg up to 5 times per day. (EMA. 2011, del Giglio A. 2011).

**Side effects and toxicity:** At the doses indicated, the PC did not worsen sleep quality, cause anxiety or depression and any other side effect (EMA. 2011, del Giglio A. 2011).

**Drug interactions:** Rodrigues M et al. (2012) have reported the first drug interaction of PC with amiodarone in adult rat. Amiodarone, the most widely prescribed antiarrhythmic agents for the treatment of atrial fibrillation and ventricular arrhythmias has also been associated to important clinical drug interactions.

The authors clearly evidenced a significant decrease (73.2%) in the peak plasma concentration of the drug following the simultaneous coadministration of the PC extract and amiodarone, as well as a reduction of 57.8% in the extent of systemic drug exposure. It is probable that PC extract or its components interact reducing significantly the bioavailability of the drug after simultaneous coadministration in a single dose (Rodrigues M. 2012).

The community herbal monograph from EMA shows that the patients taking MAO-inhibitor drugs should use *Paullinia* semen with caution. (EMA. 2012)

### **Rhodiola rosea**

*Rhodiola rosea* (RR) belongs to the plant family Crassulaceae and the genus *Rhodiola*, and has been used in China and Russia for over 1000 years. It grows on the mountain regions up to 3500 to 5000 m above sea level throughout the Arctic, Europe and Asia and has shown to improve mood, alleviate depression and cancer related fatigue as well as treating opioid addiction. The effects are potentially mediated by changes in serotonin and dopamine levels due to monoamine oxidase inhibition and its influence on opioid peptides such as  $\beta$ -endorphins. Additionally, *Rhodiola rosea* and/or its major active ingredients have been reported to induce cell-cycle arrest and apoptosis in human breast cancer cells, reduce high-altitude sickness and mental problems (Chan SW, 2012).

The investigations on the phytochemistry of RR root have revealed the presence of about 140 compounds, such as monoterpene alcohols and their glycosides, aryl glycosides, cyanogenic glycosides, phenylethanoids, phenylpropanoids and their glycosides, flavonoids, flavonlignans, proanthocyanidins and gallic acid derivatives (Panossian A. 2010). Extracts of the roots of RR have been found to favorably affect a number of physiological functions including neurotransmitter levels, central nervous system activity, and cardiovascular function. It is being used to stimulate the nervous system, decrease depression, enhance work performance, and eliminate fatigue. Most of these effects have been ascribed to constituents such as salidroside (rhodioloside), rosavins, and p-tyrosol. It has also been found to be a strong antioxidant and anticarcinogen due to the presence of several phenolic compounds.

A recent article (Zubeldia JM et al. 2010) reports the possibility to use RR in Cancer Related Fatigue treatment. The authors propose it as a viable alternative treatment for the symptoms (e.g. CRF) of short-term hypothyroidism in patients with thyroid cancer that are subjected to periodic surveillance like serum thyroglobulin measurements followed by radioiodine administrations for diagnostic and therapeutic

purposes. The procedures require adequately elevated blood levels of thyroid-stimulating hormone (TSH) that can be achieved by approaches inducing profound state of hypothyroidism and resulting in physical and mental complaints that may interfere severely with the patient's daily activities.

RR also finds other applications not yet studied in cancer patients e.g. anxiety and depression treatment. The traditional use of *Rhodiola rosea* in the treatment of generalized anxiety disorders is well established for a long time even though and the first pilot study was carried out by Bystritsky A et al. (2008).

In a pilot study 10 patients with generalized anxiety disorder were administered 340 mg of RR extract daily for 10 weeks containing 30 mg of each of the following 8 biomers: rosavin, rosarin, salidroside, rosin, rhodalgin, acetyl rhodalgin, rosaridin, and rosaridol. The data show significant decreases in mean HARS (Hospital Anxiety and Depression Scale) scores at the endpoint ( $p=0.01$ ). (Bystritsky A. 2008) (see anxiety and depression paragraph).

**Dosage:** The recommended daily intake for a dry extract (extraction solvent ethanol 67-70% v/v) is 144 - 400 mg. The use in children and adolescents under 18 years of age is not recommended (EMA. 2011).

**Side effects and toxicity:** RR has a very low level of toxicity. In rat toxicity studies, the LD<sub>50</sub> was calculated to be 28.6 mL/kg, approximately 3360 mg/kg. The equivalent dosage in a 70-kg man would be about 235 g. Therefore, the usual clinical doses of 200 to 600 mg/day have a huge margin of safety. RR should be taken early in the day because it can interfere with sleep or cause vivid dreams (not nightmares) during the 1st few weeks. Side effects are relatively uncommon but could include allergy, irritability, insomnia, fatigue, and unpleasant sensations, especially at high doses. It is contraindicated in excited states.

**Drug interactions:** RR should not be used in individuals with bipolar disorder, who are vulnerable to becoming maniac when given antidepressants or stimulants. RR does not appear to interact with other medications, although it may have additive effects along with other stimulants (Khanum F. 2005).

#### Other herbs

*Astragalus propinquus* is mainly used in traditional Chinese medicine in complex with other plants, also in the treatment of CRF (see traditional Chinese medicine).

Among the adaptogens not studied in CRF, *Eleutherococcus senticosus* and *Schisandra chinensis* increase endurance and mental performance in patients with general fatigue and weakness.

*Eleutherococcus senticosus* (ES), also known as *Acanthopanax senticosus* or Ciwujia, and previously known as Siberian ginseng, is an herbal medicine native to the far Eastern areas of the Russian taiga and the Northern regions of Korea, Japan, and China (Monograph. 2006).

Its active ingredients are typically concentrated in the root and mainly consist of chemically distinct glycosides called eleutherosides A-M.

ES preparations have been traditionally used as tonic for the relief of symptoms in case of decreased performance such as fatigue and sensation of weakness, exhaustion, tiredness and loss of concentration, also as a prophylactic and restorative tonic for enhancement of mental and physical position, and as adaptogen to increase body resistance to stressful exposures for many decades. Since the clinical documentation is not fully satisfactory and no controlled clinical studies in well-defined clinical conditions are available, the use of ES preparations has to be regarded as traditional.

For adolescents over 12 years of age, adults and elderly the daily dosage recommended is 0.5-4 g as comminuted herbal substance as herbal tea, 0.75-3 g of powdered herbal substance, 2-3 ml of liquid extract. The dosage of dry extracts (ethanol 28-70% v/v), dry aqueous extract (15-17:1) and tincture are respectively 0.5-4 g of dried root, 90-180 mg and 10-15 ml.

In general, only minimal adverse events have been reported like insomnia if taken too close to bedtime. In two studies on atherosclerotic patients, some cases of insomnia, shifts in heart rhythm, tachycardia, extrasystoles, and hypertonia were reported. Another study on 55 patients with rheumatic heart disease showed that 2 of them reported headaches, pericardial pain, palpitations, and elevated blood pressure at high dose levels of the extract (EMEA. 2008).

*Schisandra chinensis* (SC) Baill. (Schisandraceae) is a well-known herb used in traditional Chinese medicine (TCM) as anti-tussive, tonic, and sedative agent and to treat general fatigue, neurasthenia, and spontaneous sweating and to improve the liver function of patients with viral hepatitis. The dried fruits of SC have been used for several thousand years in China. The main constituents of SC are schizandrin derivatives, and the active principles are lignans with a dibenzocyclooctadiene skeleton.

SC preparations used in official medicine are: Tinctura prepared in 95% ethanol (40-60 drops daily), infusion using air-dried fruits and water (1:20, w/v, 300 mL daily), fructum air-dried fruits and seed powder (1-3g daily), before lunch and evening meal, over a period of 20–30 days and seed extract in 95% ethanol (1:1, w/v) administered in a single dose of 0.05 or 0.2 mL/kg. (Panossian A. 2008). Su T. et al. (2013) have studied the drug interactions of SC in rat with three probe substrates (theophylline, dapsone and chlorzoxazone) analyzing the plasma levels of the probes and the gene expression of CYP1A2, CYP2E1 and CYP3A4 after single or multiple SC administration. The data show that the treatment with single or multiple doses of either extract of SC respectively induces and inhibits the CYP3A4 and CYP1A2 activity, while the CYP2E1 activity is induced after treatment with a single dose and inhibited after multiple doses.

### Summary table

Plant	Clinical indications	Grading	Dosage
<i>Eleutherococcus senticosus</i>	General fatigue and weakness, exhaustion, tiredness and loss of concentration, for enhancement of mental and physical position	T	0.5-4g/day as comminuted herbal substance as herbal tea
Panax spp.	Symptoms of asthenia such as fatigue and weakness	1A	1-2 g/day of powder standardized to 4-5% ginsenosides
<i>Paullinia cupana</i>	Symptoms of asthenia such as fatigue and weakness	2B	450 mg up to 5 times a day
<i>Rhodiola rosea</i>	Symptomatic treatment of mild depressive episodes and asthenia such as fatigue and weakness	2C	200 to 600 mg/day
<i>Schisandra chinensis</i>	General fatigue, neurasthenia, spontaneous sweating and hepatic dysfunction	T	Tinctura: 40-60 drops daily Infusion 1:20 w/v: 300mL daily Fructum air-dried fruits and seed powder: 1-3g daily

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### *Cancer Related Fatigue (CRF) and homeopathy*

Weatherley-Jones E et al. (2004) used a triple-blind design (patient and homeopath blind to group assignment and data analyst blind to group until after initial analyses to reduce the possibility of bias due to data analyst) and randomly assigned patients to homeopathic medicine or identical placebo.

One hundred and three patients meeting the Oxford criteria for CFS were recruited from 2 specialist hospital outpatient departments. Patients had monthly consultations with a professional homeopath for 6 months. Main outcome measures were scores on the subscales of the Multidimensional Fatigue Inventory (MFI) and proportions of each group attaining clinically significant improvements on each subscale. Secondary outcome measures were the Fatigue Impact Scale (FIS) and the Functional Limitations Profile (FLP). Ninety-two patients completed treatment in the trial (47 homeopathic treatment, 45 placebo). Eighty-six patients returned fully or partially completed post-treatment outcome measures (41 homeopathic treatment group who completed treatment, 2 homeopathic treatment group who did not complete treatment, 38 placebo group who completed treatment, and 5 placebo group who did not complete treatment). Seventeen of 103 patients withdrew from treatment or were lost to follow-up.

Patients in the homeopathic group showed significantly more improvement on the MFI general fatigue subscale (one of the primary outcome measures) and the FLP physical subscale but not on other subscales. Although group differences were not statistically significant on four out of the five MFI subscales (the primary outcome measures), more people in the homeopathic medicine group showed clinically significant improvement. More people in the homeopathic medicine group showed clinical improvement on all primary outcomes (relative risk=2.75, p=.09).

### **Conclusions of the literature and authors**

There is weak but equivocal evidence that the effects of homeopathic medicine are superior to placebo. Results also suggest that there may be non-specific benefits from the homeopathic consultation. Further studies are needed to determine whether these differences hold in larger samples.

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### *Cancer related fatigue and anthroposophic medicine*

Fatigue is one of the major symptoms declared by cancer-patients and survivors; it reduces consistently the quality of life, remains more often underestimated and unrelieved, and finds rare treatment options in conventional oncology. It is the most frequent burden for cancer patients and is described as a persistent sense of exhaustion, incompletely relieved by rest that affects physical, mental, spiritual and social condition. In the anthroposophic perspective, fatigue appears as a condition involving all levels of human being and suggests the requirement of multimodal interventions. Improvement of fatigue represents a significantly relevant aim of the therapeutic approach, regarding quality of life and the global well-being of patients with primary and advanced cancer and of survivors.

In anthroposophic oncology the multimodal medical system of anthroposophic medicine (AM) as well as *Viscum album L.* extracts, anthroposophic medications, art therapy and eurythmy therapy alone, have evidence of efficacy against cancer related fatigue.

Fatigue is recognized as one of the most common symptoms in patients receiving treatment for cancer, often persisting beyond the conclusion of active treatment and at the end of life (De Vita et al. 2011). It is defined as a multifaceted condition characterized by diminished energy and an increased need to rest, connected to mood and sleep disturbances, decrements in physical, mental, social, and vocational functioning and emotional and spiritual distress. It is often a component of a cluster of symptoms such as depression, pain, sleep disturbance, and menopausal symptoms. Prevalence estimates of fatigue vary from 25% to 90%. Causes are poorly understood and a multifactorial origin is supposed. Fatigue may also be a significant problem for cancer survivors, with many survivors reporting fatigue scores higher than that of an age-matched general population. Fatigue has been seen as a predictor for survival in patients with breast cancer (Groenvold et al. 2007).

Conventional pharmacological medications have poor success and aerobic training, followed by behavioral approaches, is the treatment with the best available evidence, even though it seems insufficient to improve cognitive fatigue. (Kröz et al. 2013a). Treatment plans need to be individualized and complementary therapies have potential in the treatment of fatigue in patients with cancer (Sood et al. 2007; De Vita et al. 2011). Fatigue has been described as main goal for integrative treatment with anthroposophic medicine and other CAM in oncology, more than pain or distress (Ben Arye et al. 2013). According to a few studies (Wode et al. 2009, Kienle et al. 2010), including 3 RCTs (Piao et al. 2004; Semiglasov et al. 2004, 2006,) concomitant therapy of mistletoe extracts with chemotherapy appears to control or reduce cancer related fatigue, particularly in patients with breast cancer, although none of these studies specifically had used cancer related fatigue as primary outcome issue (Gutenbrunner et al. 2010).

Mistletoe-prescribing physicians often observe a marked improvement in fatigue after some months of treatment with *Viscum album* extracts for cancer. This observation is also reported by individual patients and might explain the popularity of *Viscum album* extracts in cancer. Fatigue improvement is also considered in clinical practice as one of the indicators for optimisation of the individual treatment. (Wode et al. 2009).

Waiting for further specific investigations, evaluation of fatigue has been more often investigated as part of quality of life studies. Kienle et al. (2010) reviewed 26 randomized controlled trials (RCTs) and 10 non-RCTs concerning *Viscum album L.* extracts (VAE) influence on quality of life. Many of the reviewed VAE studies described improvement in fatigue, exhaustion, and sleep in the course of treatment, suggesting to draw a special attention to the influence of VAE on fatigue. The most positive results regarding quality of life were achieved in patients with breast cancer.

A case report had been previously published, that evaluated specifically the positive impact of the intermittent use of an anthroposophic *Viscum album L.* extract in a young patient with recurrent breast cancer (Wode et al. 2009). Discontinuations were due to life conditions of the patient, fatigue was her main complaint and the improvement of fatigue was correlated to mistletoe use and ceased during the interruptions of treatment. Mistletoe treatment showed a positive effect on the severity of her fatigue symptoms.

The case report enclosed a review of ten of the studies on quality of life that included evaluation of fatigue, listed in Table 1 (Wode et al. 2009; Kienle et al. 2010). Positive outcomes on fatigue have been described as a sub-dimension of quality of life assessment both with anthroposophic and phytotherapeutic *Viscum album* extracts alone and with the whole treatment of anthroposophic medicine in AM hospitals. Of the 4 RCT including evaluation of fatigue, 3 showed an advantage (Piao et al. 2004; Semiglasov et al. 2004, 2006). No advantage was reported by Steuer-Vogt et al. (2001) in head and neck cancer.

Three retrospective comparative epidemiological cohort studies on pancreatic (Matthes et al. 2007), breast (Bock et al. 2004), colorectal (Friedel et al. 2009) cancer, described an improvement and a significant advantage for the patients treated also with mistletoe in combination with conventional treatment. One

retrospective study described a positive effect of perioperative treatment with mistletoe (Schumacher et al. 2003).

A positive effect of the anthroposophic medicine as whole system on cancer related fatigue was described in two studies, concerning the quality of life of in-patients of 2 AM hospitals in Switzerland (Heusser et al. 2006) and in Sweden (Carlsson et al. 2004, 2006). Both studies evaluated patients with advanced cancer, treated with *Viscum album* extracts, and other anthroposophic medications and non-pharmacological interventions and fatigue was part of the quality of life assessment with EORTC QLQ C30. Fatigue appears as a global problem, interweaving with circadian rhythms, sleep, neurocognitive and mood alterations (Gutenbrunner et al. 2010; Kröz et al. 2013a) and a whole system approach might offer more hints for improvement. Single interventions have been rarely evaluated and little evidence exists in the treatment of cancer related fatigue. Some suggestions can come from the treatment of fatigue as a symptom of other conditions.

Among the medications used for fatigue in anthroposophic medicine, Levico water and Hepar Magnesium can be quoted. Levico water – an arsenical-ferruginous spa water, traditionally prescribed in Italy for exhaustion and anaemia, and mentioned by R. Steiner (1920) as valuable treatment - is prescribed in anthroposophic medicine, in thermal baths and in homeopathic low dilution (Levico D3, Levico comp), to strengthen vitality (Schmidt 2008; Ben Arye et al. 2013). *Hepar Magnesium*, a D10 potency of 60% hepar bovis and 40% magnesium hydroxydatum, administered weekly intravenously showed potential positive effect on seasonal fatigue syndrome (Baars et al. 2008), as well as in fatigue associated to fibromyalgia (Baars et al. 2010).

Among the non-pharmacological interventions, eurythmy therapy and art therapy, that are standard treatments in anthroposophic medicine, have also started being studied in relation to cancer patients' fatigue. *Eurythmy therapy* integrates individually specific movement sequences and meditative indications, is practised with regular active exercise for at least some weeks, and improves heart-rate variability (Seifert et al. 2012) and distress (Kanitz et al. 2011), also related to fatigue. Art therapy combined with chemotherapy influenced positively fatigue symptoms in a pilot study (Bar sela et al. 2007). Art therapy, eurythmy therapy and rhythmical massage were associated to improvement of fatigue in chronic disease (Hamre et al. 2007abc).

A possible positive effect of eurythmy therapy and art therapy has been evaluated in a pilot study, comparing to aerobic training (AT) a multimodal therapy concept (MM), consisting of psycho-, sleep-education and new approaches based on anthroposophic medicine such as eurythmy and painting therapy. 31 patients with breast cancer suffering from cancer related fatigue were divided, out of preference, in two groups (21 to MM and 10 to AT), for a ten-week intervention study. Most of the patients had recurrence-free breast cancer, after conventional treatment, with an average disease duration of 3 years in the AT group and of 3, 9 years in the MM group. They were assessed with questionnaires for cancer related fatigue (Cancer Fatigue Scale, CFS-D), sleep (Pittsburgh Sleep Quality Index, PSQI), autonomic regulation (aR scale), self regulation (Self-regulation scale, SRS) and patients' satisfaction. Significant improvements were found in the MM group with regards to CFS-D, global quality of sleep, sleep efficiency (PSQI), aR and rest/activity regulation compared to baseline (all  $p < 0.05$ ). In the AT group aR orthostatic-circulatory and rest/activity regulation improved significantly ( $p < 0.05$ ), too. No improvement in cognitive fatigue was seen in either group. Satisfaction was good or very good in the MM group and moderate in the AT group.

Fatigue is frequently observed in survivors, especially from lymphoma and breast cancer, and contributes to reduced working capacity. The persistence of fatigue, in cancer free intervals 1-8 years, is estimated 20-36% (Gutenbrunner et al. 2010). The relationship of fatigue and alteration of circadian rhythms/autonomic regulation with the risk of cancer and of cancer-recurrences and mortality starts finding evidences. Autonomic regulation seems to be a prognostic factor in breast cancer survivors, capable of reducing cancer-related fatigue. A prospective observational study comparing 90 women with breast cancer and 80 healthy women suggests that autonomic regulation is inversely related to fatigue, particularly cognitive-related fatigue, and distress. Autonomic regulation is significantly reduced in patients with breast cancer and a high autonomic regulation has been a predictor for less fatigue, cognitive fatigue and depression for the 6 years following the first evaluation. The effect of the single components could not be differentiated and further studies are needed to assess efficacy, but the results of this study already suggest a more comprehensive and durable therapeutic approach in the follow up of patients with cancer (Kröz et al. 2013b).

Finally, *Viscum album* L. extracts and the whole system of anthroposophic medicine showed evidence, in prospective RCT/NRCT and retrospective studies, of a positive effect on cancer-related fatigue, during the conventional treatments and in primary and advanced disease. The benefit of *Viscum album* extracts and of

the whole system on fatigue seems to represent a relevant item of the observed improvement in quality of life.

Mistletoe extracts, some anthroposophic medications and non-pharmacological therapies (art therapy, eurythmy therapy) can positively contribute alone to the treatment of fatigue. Multimodal approaches, that include the mentioned interventions, can improve cancer related fatigue, even after years of persistence, and are attended with high satisfaction and compliance, offering a promising alternative to aerobic training. A positive impact has been seen in global fatigue, global sleep quality and autonomic regulation. A better evaluation of patients after the end of cancer treatment and the introduction of multimodal long-term interventions, such as the described anthroposophic medicine multimodal concept or whole system, might be effective on cancer-related fatigue and in general on health-related quality of life of survivors.

**Table 1**

Clinical trials on mistletoe treatment of cancer that also evaluated influence on fatigue (secondary outcome measure).

Sample size	Study type	Primary study questions	Assessment of fatigue/fatigue score	Results and significance*
<b>Studies on mistletoe application</b>				
2011	RCT (mistletoe vs. local anal. RCT, double-blind)	QoL	TQM score	Improvement and advantage (total TQM score advantage)
2012	RCT, double-blind (mistletoe vs. placebo)	QoL (EORTC QLQ-C30)	EORTC QLQ-C30	Significant advantage (NS) difference of total score
2012	RCT, double-blind (mistletoe vs. placebo)	QoL (FACT-G)	U11.7-8	Significant advantage
2009	RCT, open (mistletoe vs. no mistletoe)	Response-free survival	EORTC QLQ-C30	No advantage
2009	Phase II trial (single-arm)	Tumor response	Statement	Improvement
2004	Retrospective comparative epidemiological cohort study (mistletoe vs. no mistletoe)	Adverse drug reactions from conventional cancer drugs, disease symptoms, functional capacity, hospitalization	Statement	Improvement and significant advantage
2004	Retrospective comparative epidemiological cohort study (mistletoe vs. no mistletoe)	Adverse drug reactions from conventional cancer drugs, disease symptoms, functional capacity, hospitalization	Statement	Improvement and significant advantage
1992	Retrospective comparative epidemiological cohort study (mistletoe vs. no mistletoe)	Adverse drug reactions from conventional cancer drugs	Statement	Improvement and significant advantage
1988	Retrospective comparative epidemiological cohort study (mistletoe vs. no mistletoe)	Adverse drug reactions from conventional cancer drugs	Statement	Significant advantage
<b>Studies on whole-system AM care including mistletoe application</b>				
2007 (1-3)	Matched pair study (AM versus conventional care)	QoL	EORTC QLQ-C30	Improvement and small advantage
2001	Single-arm observational study	QoL	EORTC QLQ-C30	Significant improvement

The references see Kienle et al. (2009)

\* Improvement refers to pre-post difference, advantage refers to difference of pre-post change between comparison groups

Abbreviations: RCT: randomized controlled trial; QoL: quality of life; AM: anthroposophic medicine; TQM: Traditional Chinese Medicine Index; U11.7-8: Global Quality of Life Scale; FACT-G: Functional Assessment of Cancer Therapy-General; EORTC QLQ-C30: European Organization for Research and Treatment

Care Quality of Life Questionnaire. Not considered were indirect measurement of fatigue (Mazzuca, et al. "Unanswered special time to find"). Not included are those studies that also used quality of life evaluation tools but did not use a fatigue tool, or that did not present any details on fatigue (overall comparative trials n=10; RCT n=15; open, observational which reported an advantage, the other one not, one single-arm trial used RCT and reported an improvement.

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## Constipation

### *Constipation and acupuncture/TCM*

No reviews about cancer patients treated with acupuncture or moxibustion for constipation were found, except a RCT in Chinese (Zhang et al. 2009) on 66 cancer patients with lung, pancreatic, liver, breast, oesophageal, and ovarian cancers who were chronically taking morphine sulphate controlled-release tablets for constipation. The authors evaluated the efficacy of electroacupuncture (EA) bilaterally on points ST36 and ST25 in comparison to a randomized group of patients treated with mosapride citrate. The symptoms in both groups improved after the treatment (90,7% EA e 87,9% control group) but the results for EA were significantly better ( $p < 0.01$ ). Conclusions were that EA has a positive effect in treating the constipation caused by the oral taking of morphine sulphate controlled-release tablet.

Constipation in non cancer patients is often treated with good results by acupuncture or moxibustion, above all in China.

Lin et al. (2009) reviewed the literature for the control of constipation in non oncological patients and reported 137 studies. Of these, 21 were high quality studies: 18 used Chinese herbal medicine and 3 acupuncture. One of the 3 acupuncture RCTs compared the acupuncture with a conventional medicine (lactulose); one trial with *Sennae folium*, and another with deeper acupuncture on Tianshu (ST 25). The therapeutic effect in the treatment group was greater than in the control group in all 3 studies ( $p < 0.01$ ,  $p < 0.05$ ,  $p < 0.001$ ). There was heterogeneity in diagnostic procedures and interventions among the studies, and also the outcome indicators were different. Therefore, the results should be interpreted cautiously. Two trials (articles in Chinese) are reported in this review (Zhang 2006, Liu 2004). Both of them have been published but not in PubMed journals.

Lee et al. (2010) conducted a systematic review about moxibustion for treating constipation. Twelve databases were searched from their inception to March 2010. Only randomized clinical trials (RCTs) were included if they compared moxibustion with placebo, sham treatment, drug therapy or no treatment. The methodological quality of these RCTs was assessed with the Cochrane risk of bias analysis. All 3 RCTs included in the study had a high risk of bias. Two of them found favourable effects ( $p < 0.001$ ) of moxibustion indirect versus glycerin enema (Du 2008 in 160 postpartum women of whom 80 treated with moxa on *Tongbian* acupoint; Li 2001 in 60 patients of whom 40 treated with acupoint CV8). The third RCT looked at indirect moxibustion versus no treatment (Kwon 2005) and included 36 patients who had suffered strokes; 17 of them were treated with indirect moxa at ST25. There were significant differences in frequency of bowel movements ( $p = 0.001$ ) and the Constipation Assessment Scale (CAS) ( $P = 0.001$ ) between the moxibustion group and 19 of the control group who were not treated. The author's conclusions are that, given the poor methodological quality of all RCTs, the results of the review are insufficient to suggest that moxibustion is an effective treatment for constipation and more rigorous studies are needed.

Du et al. (2012) published a review and a meta-analysis (in Chinese) including 15 studies involving 1,052 non cancer patients. It was demonstrated that acupuncture and moxibustion were more effective on constipation than conventional therapy ( $p < 0.0001$ ). In comparing abdominal pain, defecation duration and general symptom scores, statistical significance can be found between the acupuncture, the moxibustion group and the control group (abdominal pain:  $p < 0.0001$ ; defecation duration:  $p < 0.004$ ; general symptom scores:  $p = 0.03$ ). The authors affirm that acupuncture and moxibustion are effective in treating constipation but further high quality studies with large samples are necessary.

Cao et al. (2012) published a Cochrane Protocol about acupuncture for chronic constipation and reported that in China many clinical studies of acupuncture have been completed for treatment of this condition.

Lu et al. in a recent review (2013) report that acupuncture has been used for various types of constipation and describe a systematic review by Lin (2009) who researched the effectiveness of acupuncture versus conventional laxatives in 3 RCTs reporting positive results.

Zhang et al. (2013) published a review and meta-analysis of 15 RCTs involving 1,256 participants. All trials were conducted in China and published in Chinese journals. The outcomes show a change in the number of weekly spontaneous bowel movements, colonic transit activity, effective rate, Cleveland Clinic Score and health-related quality of life score. The meta-analysis indicated that acupuncture for chronic functional constipation was probably as effective as conventional medical therapy in the change of bowel movements. For the colonic transit activity, acupuncture might be the same as conventional medical therapy and could be better than sham acupuncture. For the Cleveland Clinic Score, acupuncture was unlikely inferior to conventional medical therapy and the deep acupuncture was better than normal depth acupuncture in abdominal region. No obvious adverse event was associated with acupuncture for constipation. In

conclusion, acupuncture for chronic functional constipation is safe and may improve weekly spontaneous bowel movements, quality of life, and relevant symptoms. However, the evidence was limited by the small sample size and the methodological quality.

Several studies on constipation in non oncological patients are reported below.

Liu et al. (2004), in a Chinese article, compared the short-term therapeutic effects of deep needling Tianshu (ST 25) and routine-depth needling Tianshu (ST 25) on senile constipation. The total effective rate and the short-term cured rate were 100.0% and 57.7% in the deep-needling group, and 38.0% and 0 in the routine depth needling group, respectively, with significant difference between the 2 groups, and deep-needling Tianshu (ST 25) was safe. The conclusions are that deep-needling Tianshu (ST 25) is better for the treatment of senile functional constipation.

Zhang (2006) evaluated the short-term and middle-term therapeutic effects and the safety of deep acupuncture at Tianshu (ST 25) for the treatment of slow transit constipation (STC) in 60 cases of STC randomly divided into an acupuncture group and a control group. The conclusions were that deep acupuncture at Tianshu (ST 25) has a definite short-term therapeutic effect in Cleveland constipation score (CCS) and therapeutic effect of CTT (colic transite time) (P0.01) and some middle-term therapeutic effect on STC, with no adverse reaction.

Wang et al. (2010 - article in Chinese) in a RCT randomised 95 cases of functional constipation into deep puncture at ST 25 group (48 cases), shallow puncture at ST 25 group (24 cases) and medication group (lactulose, 23 cases). In deep puncture at ST 25 group, Tianshu (ST 25) was punctured deeply to the peritoneum, with electric stimulation. In shallow puncture at ST 25 group, Tianshu (ST 25) was punctured shallowly, 5 mm beneath the skin, with electric stimulation. In the medication group, Duphalac was administered orally. These cases were treated continuously for 4 weeks in 3 groups and followed up for 6 months. In deep puncture at ST 25 group, the frequency of weekly defecation and the numbers of person who had defecation 4 times a week increased and Cleveland Clinic Score (CCS) decreased, which were similar to the efficacy in shallow puncture at ST 25 group (all  $p > 0.05$ ). The efficacy of both ST 25 groups was superior to that of the medication group (both  $p < 0.05$ ). In comparison, the deep puncture at ST 25 group acted more quickly than either shallow puncture at ST 25 group or medication group and its efficacy remained much longer.

A RCT by Park et al. (2011) treated 26 subjects bilaterally on the same points ST23 and ST27.

The subjects were identified with either Qi deficiency or Qi excess syndrome, and treated 3 times a week for 4 weeks with true moxibustion. Eleven with a moxa pillar (0.6 × 20 mm, Kihoang company, South Korea) and sham (n.13) adding insulation below the moxa pillar to prevent the transfer of heat from the moxa pillar to the patient. There was no statistical significance between the 2 groups ( $p = 0.1$ ),  $p = 0.44$  in defecation frequency, Bristol stool form scale BSS, constipation assessment scale CAS respectively. There was only a difference between the groups with excess syndrome compared to deficiency syndrome regarding defecation frequency (3.3 95% CI: 0.41, 6.19,  $p = 0.03$ ). The sham treatment looked similar to the real moxibustion treatment in its appearance and burning procedure and was given by adding insulation below the moxa pillar to prevent the transfer of heat from the moxa pillar to the patient.

Xiao et al. (2011) randomized 160 cases with acute cerebral infarction into 4 groups: acupuncture plus herbal medicine group, Chinese herbal medicine group, acupuncture group and glycerine enema group (40 cases in each one). Acupuncture was applied to Shaoshang (LU 11), Shangyang (LI 1), Fenglong (ST 40), Tianshu (ST 25), Zhigou (TE 6) and other points not specified. The results in the acupuncture plus herbal medicine group were superior apparently to the other groups. The differences in the interval time of defecation, stool quality and nerve function score after 7 days and 21 days treatment were significant statistically compared to the other groups ( $p < 0.05$ ,  $p < 0.01$ ).

Li et al. (2012) presented a protocol for a randomized controlled four-arm trial to conduct in China. The trial includes 700 patients treated with acupuncture (3 groups) and a control group treated with mosapride citrate. The acupuncture groups are: (1) Back-Shu and Front-Mu acupoints of Large Intestine meridians (Shu-Mu points group); (2) He-Sea and Lower He-Sea acupoints of Large Intestine meridians (He points group); (3) Combining used Back-Shu, Front-Mu, He-Sea, and Lower He-Sea acupoints of Large Intestine meridians (Shu-Mu-He points group) for 16 sessions.

The result of this trial (not yet available) will confirm whether acupuncture is effective in treating functional constipation and whether traditional acupuncture theories play an important role.

Liu et al. (2013) reported the study protocol for a multicenter RCT on 1,034 patients randomized in EA group (517) and sham EA (517). The EA group will receive needling at ST25, SP14 and ST37 and the sham

EA group will receive needling at sham locations points about 2 or 3 cm away from ST25, SP14 and ST37. This trial evaluates the efficacy and safety of EA for severe chronic functional constipation.

Anders et al. (2012) observed that in children acupuncture for the treatment of hospital induced constipation (HIC) is acceptable and effective. Ten cases were studied, the average age being 5.5 years. The acupuncture treatment was given on point L11 using fixed indwelling acupuncture needles (0.9 mm long) before considering starting conventional local constipation therapy with laxative suppositories. The results demonstrated that all children defecated within 2 hours after LI11 stimulation, after a median of 3 days of HIC. No patient required conventional local constipation therapy and no adverse events were reported.

### Conclusions of the literature and the authors

No reviews about cancer patients treated with acupuncture or moxibustion for constipation were found, except a RCT in Chinese.

The Guidelines of SIO (2009) do not attribute a grading for the treatment of constipation. On the basis of the same criteria the authors of T.N.I.M have evaluated that the adequate grading is 2B (weak recommendation, moderate quality evidence), because recently RCTs conclude that acupuncture is a promising option in the treatment of constipation.

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### *Constipation and Herbal Medicine*

Herbal drugs most commonly used in constipation are those characterized by anthraquinones such as *Aloe* spp. (aloe), *Cassia acutifolia* and *Cassia angustifolia* (Senna), and *Rhamnus frangula* (frangula), *Rhamnus purshiana* (cascara), *Rheum palmatum* and *Rheum officinale* (rhubarb) and bulking agents such as bran, *Plantago ovata* (psyllium), and plant agar containing sugars such as tamarind, cassia and plum.

Although laxatives have been used for centuries, clinical studies on their effectiveness are somewhat limited and very few studies in cancer patients were done.

It is known that a proactive approach to preventing constipation is recommended strongly in at-risk patients with cancer, particularly those receiving medications such as vinca alkaloids, or opioids that slow colonic transit times. Management of constipation can be complex and challenging because it often has more than one cause in patients with cancer.

Five common causes have been identified: the cancer itself, which can obstruct the bowel, affect the autonomic nervous system, or cause spinal cord compression; disease effects such as dehydration, spinal cord compression, immobility, or changes in normal bowel habits; previous laxative abuse; cancer therapies such as vinca alkaloids; and interventions for symptom management such as opioids or tricyclic antidepressants (Wilkes, Barton-Burke, 2006).

Is it known that in cancer patients it is important to use drugs that improve symptoms; therefore herbal medicines may be added to manage constipation. As the data in the literature are few and conflicting, it is not possible to identify a single protocol based on medicinal plants in constipation.

### **Anthraquinones laxatives**

Anthraquinones are produced by a variety of plants, such as *Aloe* spp. (aloe), *Cassia acutifolia* and *Cassia angustifolia* (senna), and *Rhamnus frangula* (frangula), *Rhamnus purshiana* (cascara), *Rheum palmatum* and *Rheum officinale* (rhubarb). The compounds are inactive glycosides that when ingested, and are hydrolyzed by colonic bacterial glycosidases to yield active molecules, these increase intestinal motility. The anthraquinones typically induce defecation 6 to 8 hours after oral dosing.

Anthraquinones cause apoptosis of colonic epithelial cells, which then are phagocytosed by macrophages and appear as a lipofuscin-like pigment that darkens the colonic mucosa, a condition termed pseudomelanosis coli. This data and some inconsistent evidence in the literature indicate that the use of anthraquinones drugs not only may induce side effects on colonic mucosa in healthy subjects but also may complicate the clinical state of cancer patients. For this reasons they are not studied and used in cancer-induced constipation (Willems M. 2003, Portalatin M. 2012).

The laxative effect of *Aloe* spp. (see also Radiodermatitis paragraph) comes from the juice, and is mediated by aloe-emodin-9-anthrone, the main active juice metabolite, which acts specifically on the colon.

The empirical data suggest the *Aloe* spp. dried juice is intended for short-term use in cases of occasional constipation. Today, there are no available studies on the effects of Aloe laxative neither in healthy and cancer human subjects.

The recommended dosage as a laxative for adults, elderly and adolescents over 12 years (10 – 30 mg hydroxyanthracene derivatives only once daily at night) is supported by experts' opinions and by clinical studies with other anthranoid-containing laxatives such as senna preparations. Generally, it is sufficient to take an anthranoid-containing laxative up to 2-3 times a week (EMEA. 2006).

Another herb widely used in the treatment of constipation is *Cassia acutifolia* (also known as Senna). Its main active constituents are sennosides A and B (ca. 4%), which are rheindianthrone diglycosides. The EMA suggests that the maximum daily dose of Senna is quantified in 30 mg of hydroxyanthracene glycosides and that the use for more than 1-2 weeks requires medical supervision.

Moreover, Senna leaves may cause abdominal pain, spasm, and passage of liquid stools, particularly in patients with irritable colon. However, these symptoms may also occur in case of individual overdose, when it is necessary to reduce the dosage.

The efficacy of Senna preparations has been evaluated in clinical trials in the treatment of constipation and for bowel cleansing before radiological investigations or colonoscopy. Some evidence show that chronic use may lead to disorders in water equilibrium and electrolyte metabolism and may result in albuminuria and haematuria.

The limitation of these studies is that the only evidence of the Senna efficacy is obtained by preparations of Senna in combination with fibres.

To date, there is no well-designed non-experimental descriptive study with a mono-preparation of Senna available which investigates the laxative effects both in occasional constipation and in cancer human subjects. Hence, evidence is obtained from expert reports, opinions and extensive clinical experiences.

In conclusion, the EMA documents refer of well-designed clinical studies that deal with combination products for occasional constipation and with high doses of Senna preparations for bowel cleansing and they clarify the pharmacodynamics (EMA. 2006). A systematic review of Morales MA (2009) shows that there is no scientific evidence about altered transit and the chronic use of Senna, as well as about Senna use and the induction of tumors.

### Bulk-forming laxatives

Bulk-forming laxatives are vegetable that increase in fecal mass: *Plantago ovata* (psyllium), *Triticum aestivum* (bran), guar gum, plant agar and dietary fiber. Only the psyllium has scientific evidence in cancer patients.

Woolery M et al. (2008) in a systematic review of evidence-based interventions for the prevention and management of constipation in cancer patients analyzes the literature about psyllium, often prescribed to these patients in spite very few research on the efficacy in this population. The authors show that the evidence for its use in chronic constipation is conflicting (Brandt LJ. 2005, Frizelle F. 2005, Ramkumar D. 2005). Of three systematic reviews, one concluded, that based on low-intermediate quality RCTs, psyllium appears to improve stool frequency and consistency (Brandt LJ. 2005); the second concludes that moderate evidence supports its use (Ramkumar D. 2005); and the third reports numerous RCTs of mixed quality (Frizelle F. 2005). Several publications have identified potential harms associated with psyllium, which may have implications for cancer patients. To prevent adverse events, patients must have good functional status, such as practicing physical activity and being able to consume adequate fluids. Adults should take psyllium with at least 200-300 ml of water as recommended by experts.

Psyllium should not be administered in large amounts because it has been associated with increased flatulence, abdominal distension, bloating, mechanical obstruction of the esophagus and colon, and anaphylactic reactions (Brandt LJ. 2005, Frizelle F. 2005). Therefore, it should be used with caution in patients with severe constipation and, according to expert opinion, in patients with advanced cancer because it may worsen symptoms (Woolery M. 2008).

Psyllium should be avoided in patients who do not have adequate physical activity or fluid intake and/ or who suffer severe constipation, as it may worsen the manifestations of the problem.

In an observational study, the response to treatment was poor among patients with slow colonic transit, whereas 85% of patients without abnormal physiology improved or became symptom-free. Side effects include delayed gastric emptying and loss of appetite in some patients. Also, there have been some reports of serious acute allergic reactions, cough, and asthma (Portalatin M. 2012).

According to Cherny et al. (2004), daily laxatives are indicated in any patient receiving opioid therapy. Today, no data to indicate superiority of any of these laxative approaches. Many expert clinicians suggest that the best relief with the lowest medication volume and incidence of adverse effects is obtained by the combination of a softening and stimulant agent (e.g. docusate and casanthranol, or docusate and senna). Purely bulk-forming agents, such as methylcellulose and psyllium, are not generally recommended because for a safe use that they should be taken with a large volume of fluid, otherwise they may form concretions and lead to impaction (Cherny NI. 2004).

Given the scarcity of studies and evidence, there are no specific indications for these medicinal plants, and more detailed studies are needed.

### Summary table

Plant	Clinical indications	Grading	Dosage
<i>Aloe spp.</i>	Constipation	2C	10-30 mg hydroxyanthracene derivatives only once daily at night
<i>Cassia acutifolia</i>	Acute constipation	2C	Infusion: 0.5-2g/day Fluid extract: 2ml Syrup: 8ml
<i>Plantago ovata</i>	Constipation	2B	Seed: 10-30gr/day

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## Diarrhea

### *Diarrhea and acupuncture/TCM*

In the literature, no systematic reviews or RTCs about the effect of acupuncture on diarrhea in patients with cancer were found. In China, acupuncture has been used to treat functional gastrointestinal (GI) symptoms in other diseases, for thousands of years.

Takasaki, in a review (2006), reports that acupuncture at ST-36 causes muscle contractions via the parasympathetic autonomic nervous system in the constipation-predominant irritable bowel syndrome (IBS-C) while at CV-12 it causes muscle relaxation via the parasympathetic autonomic nervous system. Acupuncture is thus useful in the diarrhea-predominant irritable bowel syndrome (IBS-D), because enhanced colonic motility and accelerated colonic transit are reported in such patients.

Yin et al. in a review (2010) of the literature, report that the effects of acupuncture or electro-acupuncture (EA) on gastrointestinal motility were fairly consistent and the major acupuncture points used in these studies were ST36 and PC6. A number of clinical studies have been published, investigating the therapeutic effects of EA on a number of functional gastrointestinal diseases, such as gastroesophageal reflux, functional dyspepsia and irritable bowel syndrome. However, the findings of these clinical studies were inconclusive. In summary, acupuncture or EA is able to alter gastrointestinal motility functions and improve gastrointestinal motility disorders. Anyway, more studies are needed to establish the therapeutic roles of EA in treating functional gastrointestinal diseases such as constipation and diarrhea.

With specific reference to diarrhea in non-oncological patients, there are some studies published in Chinese, which refer to adults with diarrhea in irritable bowel syndrome.

Sun et al. (2011) explored the effect of acupuncture treatment on the clinical symptoms and quality of life (QOL) in 63 patients with diarrhea-predominant irritable bowel syndrome, with a single-blinded randomized control study. Patients were assigned to two groups, 31 in the treatment group (ST25 ST36 ST37 SP6 LR3 GV20 Yintang-Ex-HN3) and 32 in the drug control group (oral pinaverium bromide) for 28 days. The conclusions were that acupuncture treatment in IBS-D patients could effectively alleviate the degree and frequency of attacks of abdominal pain, diarrhea, abdominal distension, and markedly relieve the tenesmic sensation, with better efficacy than that of pinaverium bromide ( $P < 0.01$ ).

A RCT (Li et al. 2012-article in Chinese) came to the same conclusions. This trial compared treatment with acupuncture (ST25, SP36, ST37, SP6, LR3 once a day, 3 or 4 treatments a week ) to treatment with a Western medication (pinaverium-Dicetel®).

The symptom score and IBS-QOL score all improved significantly after treatment in both groups (all  $p < 0.01$ ). The improvements in the acupuncture group were superior to those in the Western medication group (all  $p < 0.01$ ).

Chinese studies have also been published relating the use of acupuncture in children. These trials have demonstrated the efficacy, with statistically significant differences, of acupuncture on chronic diarrhea in comparison to a control group.

A RCT (Wang et al. 2005 - article in Chinese) on infantile diarrhea, compared the therapeutic effects of acupuncture plus massage therapy (80 cases) to a control group (40 cases - Diosmectite, Smecta) on infantile diarrhea. The cured rate of 55.0% in the treatment group was better than 35.0% in the control group ( $p < 0.05$ ). The conclusion was that acupuncture plus massage therapy has obvious therapeutic effects on infantile diarrhea.

Cui et al. (2008 - article in Chinese) and Chen et al. (Chinese article - 2013) published 2 RCTs that studied infantile diarrhea (136 cases of diarrhea in the autumn and 120 cases of pediatric chronic diarrhea). In the first group moxibustion and Chinese herbs were used and the control group was treated with diosmectite (Smecta®). In the second study, the control group was treated with bifidobacterium and lactobacillus tablets. Moxibustion was done on CV8 in the first study and on CV8 and CV4 in the second study. Both studies demonstrated the validity of treatment with moxibustion in comparison to the treatment received by the control group (respectively  $p < 0.01$ ,  $p < 0.05$ ).

### **Conclusions of the literature and of the authors**

In the literature, we found no systematic reviews or RTCs about the effect of acupuncture and TCM on diarrhea in patients with cancer.

It is instead promising the use of acupuncture, electroacupuncture and moxibustion in the non-cancer diarrhea in adults and children, as well as validated by the current clinical practice.

SIO Guidelines (2009) do not attribute a grading for the treatment of diarrhea. On the basis of the same criteria the authors of TNIM, considering the studies that were subsequently published after 2009 have evaluated that the adequate grading is 2B (weak recommendation, moderate quality evidence).

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### *Diarrhea and herbal medicine*

The medicinal plants used for the treatment of diarrhea are characterized by a high content of tannins or pectins. Unfortunately, there is no information about their use in cancer patients since these plants have very few studies on their astringent action in humans.

### **Tannins Plants**

The tannins form a temporary protective layer of coagulated proteins on the intestinal mucosa. The action of this protective layer is not yet well defined but probably acts by desensitizing the nerve endings and reducing peristaltic stimuli. Since the tannins are poorly absorbed in the intestinal tract, their action is essentially local inside the gastrointestinal lumen.

Although tannins are not absorbed systemically, their local accumulation can irritate, so they are not recommended in case of inflammation or ulceration of the intestinal tract, and chronic intake can interfere with digestion by inhibiting the action of digestive enzymes.

The main medicinal plants containing tannins are *Agrimonia eupatoria*, *Alchemilla vulgaris*, *Camellia sinensis*, *Potentilla spp.*, *Quercus robur* and *Rubus fruticosus*. Only *P. erecta* has scientific evidence.

### **Potentilla spp.**

The genus *Potentilla* (family Rosaceae, subfamily Rosoideae), has been known since ancient times for its curative properties. Extracts of the aerial and/or underground parts have been applied in traditional medicine for the treatment of inflammations, wounds, types of cancer, infections due to bacteria, fungi and viruses, diarrhoea, diabetes mellitus (Tomczyk M. 2009).

The EMA suggests a daily dosage of infusion (single dose 1.4-4 g, several times daily up to a maximum daily dose of 12 g), decoction (single dose 1.4-3 g, several times daily up to a maximum daily dose of 6 g), tincture 1:5, ethanol 70% (single dose: 1-2 ml in water, 3 times daily), tincture 1:5, ethanol 45% and liquid extract (single dose: 2-4 ml, 3 times daily) (EMA. 2010).

If administered with other drugs, EMA recommends taking it 1 hour or more before or after intake of other drugs to avoid a reduction of their.

Subbotina MD et al. (2003) have demonstrated that the effect of a *P. tormentilla* extract, 3 drops, 3 times a day up to 5 days was superior to placebo ( $p < 0.0001$ ) in the treatment of rotavirus diarrhea in children between 3 months to 6 years. However, the use in children and adolescents under 18 years has not been established due to lack of adequate data. (EMA. 2010).

Some recent in vitro studies show the *Potentilla* action on cancer cells. Radhika M et al. (2012) studied the effectiveness in antitumor activity of *P. fulgens* in Ehrlich ascites tumour (EA) and MCF-7 cancer cells. The *P. fulgens* extract resulted in increasing in vivo survivality of mice bearing EA cells and loss of cell viability in a dose-dependent manner in MCF-7 cells. This effect may be attributed to apoptotic cell death as confirmed by flow cytometric analysis and PARP1 proteolysis. More recently, Tomczyk M et al. (2013) analyzed the biological activity of aqueous extracts of *Potentilla* spp. (Rosaceae): *P. fruticosa*, *P. norvegica*, *P. pensylvanica*, *P. thuringiaca*, *P. crantzii* and *P. nepalensis*. The data show that all extracts especially those of *P. fruticosa*, tested at dose levels between 25 and 250 microg/mL, suppress the metabolism of myofibroblasts and show a radical scavenging (DPPH) effect in a concentration-dependent manner.

Even if the tannins are not recommended in presence of inflammation and ulcers, Huber R et al. (2007) have evaluated the safety, pharmacology, and clinical effects of different doses of PE extract in patients with active ulcerative colitis. In this study, 60 patients with active ulcerative received the extract in escalating doses of 1200, 1800, 2400 and 3000 mg/d for 3 weeks each. Each treatment phase was followed by a 4-week washout phase. The data suggest that PE is safe up to 3000 mg/d, but the efficacy in patients with ulcerative colitis and inflammatory gastrointestinal diseases should be further evaluated.

### **Pectin and herbal medicins**

To follow, a RCT on *Musa paradisiaca* (MP) antidiarrheal action is reported. MP, also known as green banana, has been a traditional remedy for many digestive disorders, including childhood diarrhea. Recently, in a prospective, in-hospital controlled trial, it was demonstrated that adding MP to the diets of diarrhoeal children significantly hastened their clinical recovery, corrected abnormal mucosal permeability and improved nutrient absorption. Rabbani et al. (2010) studied the effectiveness of green banana in the home management of acute (<7 days) or prolonged ( $\geq 7$  days) diarrhoea at the community level. A cluster randomized field trial was conducted among 2968 Bangladeshi rural children 6-36 months old. In the trial, whole fruits were cooked in boiling water for 10 min with the skin intact, then cooled and peeled off and the

pulp taken out. The amount to be given and the frequency of feeding varied by age of the child. For children aged 6–12 months, the recommended quantity ranged from one-half to one full fruit per day (1/2–1 cup); for 12–24 months, 1–2 fruits (1–2 cups) and for 24–36 months, three fruits (three cups) per day. The recovery rates of children with acute diarrhoea receiving MP (vs. control) were significantly more increase on day 3 ( $p < 0.001$ ) and day 7 ( $p < 0.001$ ), while children with prolonged diarrhoea had significantly higher recovery rates on day 10, ( $p < 0.001$ ) and 14 ( $p < 0.001$ ) (Rabbani GH. 2010).

These results indicate the possible use of MP in the treatment of diarrhea; however, more studies are needed to demonstrate the antidiarrheal action of this and other pectin medicinal plants.

#### Summary table

Plant	Clinical indications	Grading	Dosage
<i>Potentilla erecta</i>	Treatment of diarrhea, inflammations, wounds, diabetes mellitus, infections due to bacteria, fungi and viruses	2C	Infusion: single dose 1.4-4 g, up to a maximum 12 g/day Decoction: single dose 1.4-3 g, up to a maximum dose of 6 g/day Tincture: single dose 1-2 ml or 2-4 ml in water, 3 times daily
<i>Musa paradisiaca</i>	Treatment of pediatric diarrhea	1B	For children aged 6-12 months: from one-half to one full fruit per day (1/2–1 cup) for 12–24 months, 1–2 fruits (1–2 cups) for 24–36 months, 3 fruits (3 cups) per day

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### *Diarrhea and homeopathy*

Unfortunately there are not specific studies on the homeopathic treatment of diarrhea as a symptom of cancer disease nor as a side effects in cancer. However several studies have shown individualized homeopathic therapy to be effective in treating childhood diarrhea. This disease, despite the widespread availability of oral rehydration therapy, remains a major cause of morbidity and mortality in children around the world.

A randomized double-blind clinical trial (Jacobs, 1994) comparing homeopathic medicine with placebo in the treatment of acute childhood diarrhea was conducted in León, Nicaragua, in July 1991. Eighty-one children aged from 6 months to 5 years were included in the study. An individualized homeopathic medicine was prescribed for each child and daily follow-up was performed for 5 days. Standard treatment with oral rehydration treatment was also given. There was no significant difference in the likelihood of resolution of diarrheal symptoms between the treatment and placebo groups (hazard ratio = 1.02, 95% confidence interval: 0.79-1.32), with a median time until resolution of 3 days for both groups. Children in the treatment group had an average of 2.6 unformed stools per day compared to 2.8 among those in the placebo group; this difference was not significant ( $p = 0.43$ ). The median number of unformed stools was 7 among children in the treatment group and 8 among those in the placebo group ( $p = 0.41$ ).

Another study was conducted by J. Jacobs in Nepal (Jacobs J 2000) with a individualized remedy. The study underlines that individualized homeopathic treatment decreases the duration of acute childhood diarrhea and suggests that larger sample sizes be used in future homeopathic research to ensure adequate statistical power. Homeopathy should be considered for use as an adjunct to oral rehydration for this illness.

A meta-analysis (Jacobs J. 2003) based on the 3 studies mentioned below shows that the studies have shown a positive treatment effect of individualized homeopathic treatment for acute childhood diarrhea, but sample sizes were small and results were just at or near the level of statistical significance. Because all three studies followed the same basic study design, the combined data from these studies were analyzed to obtain greater statistical power and a meta-analysis of the effect-size difference of the three studies was also conducted. Combined analysis shows a duration of diarrhea of 3.3 days in the homeopathy group compared with 4.1 in the placebo group ( $P = 0.008$ ). The meta-analysis shows a consistent effect-size difference of approximately 0.66 day ( $P = 0.008$ ). The authors conclude that the results from these studies confirm that individualized homeopathic treatment decreases the duration of acute childhood diarrhea.

Instead in another study (Jacobs J. 2006) 292 children with acute diarrhea were recruited; 145 were randomized to the experimental group and 147 to the placebo group. Tablets containing a combined preparation of the 5 most common single homeopathic remedies used to treat diarrhea or a placebo were administered by a parent after each unformed stool. Children were followed up daily for 7 days or until symptoms resolved, whichever occurred first. Children in the treatment group had an average of 2.6 unformed stools per day compared to 2.8 among those in the placebo group; this difference was not significant ( $p = 0.43$ ). The median number of unformed stools was 7 among children in the treatment group and 8 among those in the placebo group ( $p = 0.41$ ). There was no significant difference in the likelihood of resolution of diarrheal symptoms between the treatment and placebo groups (hazard ratio = 1.02, 95% confidence interval: 0.79–1.32), with a median time until resolution of 3 days for both groups.

<b>Type of study</b>	<b>Therapeutic protocol</b>	<b>N. patients and disease</b>	<b>End points criteria</b>	<b>Results</b>	<b>Author, year</b>
A double-blind randomized controlled trial	Tablets containing a combined preparation of the five most common single homeopathic remedies used to treat diarrhea or placebo were administered by a parent after each unformed stool	292 children with acute diarrhea was recruited; 145 were randomized to the experimental group and 147 to the placebo group	Children were followed up daily for 7 days or until symptoms resolved, whichever occurred first. Time until resolution of symptoms, daily rate of unformed stools, and total number of unformed stools were compared between the two groups	There was no significant difference in the likelihood of resolution of diarrheal symptoms between the treatment and placebo groups (hazard ratio = 1.02, 95% confidence interval: 0.79-1.32), with a median time until resolution of 3 days for both groups	Jacobs, 2006
Combined results and meta-analysis from 3 randomized, controlled clinical trials	Children were randomized to receive either an individualized homeopathic medicine or placebo to be taken as a single dose after each unformed stool for 5 days	Three double blind clinical trials of diarrhea in 242 children aged from 6 months to 5 years were analyzed as 1 group	Combined analysis shows a duration of diarrhea of 3.3 days in the homeopathy group compared with 4.1 in the placebo group (P0.008). The meta-analysis shows a consistent effect-size difference of 0.66 day (P0.008)	The results from the studies confirm that individualized homeopathic treatment decreases the duration of acute childhood diarrhea and suggests that larger sample sizes be used in future research to ensure adequate statistical power	Jacobs, 2003
Randomized, double-blind, placebo-controlled trial	Individualized homeopathic medicine or placebo, to be taken one dose after each unformed stool for 5 days	Of the 126 children initially enrolled, 116 completed treatment	Predefined measures were based on the previous study: (1) duration of diarrhea, defined as the time until there were fewer than three unformed stools per day, for two consecutive days, and (2) Average number of stools per day for each group	The mean number of stools per day over the entire 5-day treatment period was 3.2 for the treatment group and 4.5 for the placebo group (P = 0.023). A Kaplan-Meier survival analysis of the duration of diarrhea, which included data from all patient visits, showed an 18.4% greater probability that a child would be free of diarrhea by day 5 under homeopathic treatment (P = 0.036)	Jacobs, 2000
Double-blind randomized controlled trial	Individualized homeopathic treatment	81 children (6 months to 5 years)	This study was performed to determine whether homeopathy is useful in the treatment of acute childhood diarrhea	The treatment group had a statistically significant (P < .05) decrease in duration of diarrhea, defined as the number of days until there were less than three unformed stools daily for 2 consecutive days. There was also a significant difference (P < .05) in the number of stools per day between the 2 groups after 72 hours of treatment	Jacobs, 1994

Tab. 1. RCTs on homeopathic treatment of diarrhea.

## Conclusions of the literature and authors

The studies conducted in Honduras, Nicaragua and Nepal by Jacobs show that the results are consistent with the finding that individualized homeopathic treatment decreases the duration of diarrhea and the number of stools in children with acute childhood diarrhea. The meta-analysis confirms that individualized homeopathic treatment decreases the duration of acute childhood diarrhea and suggests that larger sample sizes be used in future homeopathic research to ensure adequate statistical power.

On the contrary, the homeopathic combination therapy (not individualized) tested in 2006 did not significantly reduce the duration or severity of acute diarrhea in children. Homeopathy should be considered for use as an adjunct to oral rehydration for this illness.

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## Edema and lymphedema

### *Edema, Lymphedema and acupuncture/TCM*

Kanakura et al. (2002 Japan) successfully treated edema occurring in the lower extremities after intrapelvic lymphonode dissection for malignant gynecologic tumors or prevented this postoperative complication with moxibustion and acupuncture. This treatment was initiated after the occurrence of lymphedema in 12 patients and as soon as possible after surgery in 12 others. All cases showed improvement or marked improvement after the treatment on acupuncture points. An increase in deep body temperature with acupuncture or moxibustion was found to be essential for a successful treatment.

Filshie and Hester (2006) in the chapter “Contraindications and cautions” of their Guidelines, indicate that needling should be avoided in lymphoedematous limbs or limbs prone to lymphedema in the ipsilateral arm in patients who have undergone axillary dissection. This is due to the risk of the development of swelling and lymphedema after insertion of any needle.

The review of Chao et al. (2009), for the management of adverse events due to treatments of breast cancer, examines 26 publications and one clinical study (Alem et al. 2008) in managing post-mastectomy edema. The object of the study (n.29) was to evaluate the effect of acupuncture (controlateral to the mastectomy side) in rehabilitation of motor function, reduction in lymphoedema and improvement in perceived heaviness and tightness in the arms of women who had undergone breast cancer surgery. Although the study showed the improvement in movement amplitude of the shoulder, heaviness and tightening and degree of lymphedema, Chao et al. concluded that the small sample size, lack of control group and lack of long term observation, increased doubts about the conclusions.

Generally, the literature states that the current treatments for lymphedema are expensive and require ongoing intervention; the use of needles and even the lifting of objects using the affected arm have been prohibited.

Cassileth et al. (2011) conducted a pilot study (n.9) on the safety and effectiveness of acupuncture in women diagnosed with chronic lymphedema after breast cancer surgery. The needles were inserted in both affected and unaffected limbs. No serious adverse events occurred during or after 73 treatment sessions. Conclusions are that acupuncture appears to be safe and may reduce lymphedema associated with breast cancer surgery.

The same authors (2013) evaluated the safety and potential efficacy of acupuncture on upper-limb circumference in women (n.37) with lymphedema. The needles were inserted in both affected and unaffected limbs. There were no serious adverse events and no infections or severe exacerbations after 255 treatment sessions and 6 months of follow-up interviews. The conclusions are that acupuncture for lymphedema appears safe and may reduce arm circumference. Although these results await confirmation in a randomized trial, acupuncture can be considered for women with no other options for sustained arm circumference reduction.

Acupuncture and moxibustion have been shown to be effective in treating upper body lymphedema, (De Valois et al. 2012). They conducted an exploratory single-arm observational clinical study (n.35) in patients with breast, head or neck cancer undergoing routine lymphedema maintenance. Lymphedema was mild-to-moderate uncomplicated for  $\geq 3$  months,  $\geq 3$  months post active cancer treatment, in addition to usual care. This study has demonstrated statistically significant improvement after 4 weeks and no serious adverse effects.

### Single clinical studies on lymphedema in adults

Type of Study	Therapeutic Protocol	N. of patients and disease	Endpoint criteria	Results	Author, year
observational study	BL67 (in moxa) ST36 Sp6 BL23 KI1 SP2 CSP3 SP12 (in Kyuto-skin) both moxibustion and acupuncture  5 times a week	n.24  (12 after the occurrence of lymphedema; 12 as soon as possible after surgery) malignant gynaecologic tumours	subjective valuation edema  measurement temperature surface and deep body	6 improvement, 6 marked improvement  increased temperature deep body more than surface  none of 12 patients have developed edema (preventive effect)	Kanakura, 2002
observational study no control group	CV2 CV3 CV12 LI15 TE14 LU5 TE5 LI4 ST36 SP6 SP9 SJ5 SJ14 REN2 REN3 REN12 Controlateral to the mastectomy side  24 acupuncture sessions	n.29 after mastectomy	1) range of motion 2) sensation VAS  3) citrometry (circumferential measurement) difference 4) degree (0-3 score)	improvement in range of movement of shoulder flexion and abduction (P<0.001); degree of lymphoedema (P=0.016); sense of heaviness and tightening (P<0.001); arm circumference no significant (p=0.057).	Alem, 2008
pilot study	acupuncture bilateral  TE14 LI15 LU5 LI4 ST36 SP6 CV3 CV12 twice a week for 4 weeks	n. 9 breast cancer	circumferential measurement	reduction in 4 women  no serious adverse events	Cassileth, 2011
exploratory single arm observational clinical study	1) acupuncture and moxibustion + usual care flexible protocol 7 individualised treatments 2) 6 optional additional treatments	n. 33 breast, head, neck cancer	MYMOP scores  SF36  PANAS	Group 1, group 2: mean MYMOP Improvement between groups(p < 0.0001)  SF36 scores for breast cancer participants were significant 4 weeks after treatment.  no serious adverse events	De Valois, 2012

### **Conclusions of the literature and the authors**

SIO Guidelines (2009) do not attribute a grading for the treatment of lymphedema. On the basis of the same criteria, the authors of T.N.I.M have evaluated that the adequate grading is 2C (weak recommendation, low or very low quality evidence).

However most recent studies suggest that acupuncture can be a promising option in the treatment of lymphedema, especially for the women operated for breast cancer.

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### Edema and herbal medicine

To date, there are few studies on medicinal plants used in the treatment of cancer-related edema. There are evidences for *Boswellia serrata* that must be validated in larger studies to evaluate efficacy, safety and also drug interactions.

#### **Boswellia serrata**

The genus *Boswellia* identified a medicinal plant native to Arabia and India. Recently, the pharmacological properties and clinical effectiveness of *Boswellia serrata* (BS) have been studied systematically.

Some evidences show that BS products act as inhibitors of inflammation processes, with efficacy against perifocal edema in brain tumors or brain metastases. They are recommended for the treatment of brain edema as an alternative to glucocorticoids and are claimed to improve accompanying clinical conditions like headache, pareses, dysphasia/aphasia and the overall well being (Dennert G. 2009).

BS resin is a mixture containing more than 200 different substances, for instance: resin, long-chain sugar compounds, essential oils, proteins, and inorganic compounds. Boswellic acids (BAs) have been identified as the putative active principle of the gum resin. BAs are pentacyclic triterpenes with different functional groups in position 3 and 11 of their carbon rings; they selectively inhibit the key enzyme of leukotriene synthesis 5-LO and reduce leukotrienes biosynthesis in a concentration-dependent manner.

In a systematic review, Ernst E (2008) found 7 controlled clinical trials investigating the anti-inflammatory effects of BS. This study and others subsequent link the BS use to the treatment of chronic asthma, Crohn's disease or osteoarthritis (Sengupta K. 2008-2010, Clark CE. 2010, Vishal AA. 2011).

There are very few published data about the effects of BS in brain edema and brain tumors. The most promising study came from Kirste S. et al. (2011) who conducted a randomized, placebo-controlled, double-blind pilot study to investigate the efficacy of BS on cerebral edema in patients irradiated for brain tumors. The author reports that as early as 2001, Streffer et al. had investigated the use of the BS preparation H15 in 12 patients with cerebral edema demonstrating a clinical or radiological response in 8 of them. Moreover, Kirste et al. (2011) enlist 44 patients with primary or secondary malignant cerebral tumors who were randomly assigned to radiotherapy plus either BS 4200 mg/day or placebo. The data suggest that if measured immediately after the end of radiotherapy and compared with baseline, there is a reduction of cerebral edema of >75% in 60% of patients receiving BS and in 26% of patients receiving placebo (p=0.023).

**Dosage:** 400 mg of *Boswellia* extracts are administered orally as capsules or tablets. Providers recommend a dosage of 4 to 6 g daily for adults in the treatment of perifocal brain edema. (Dennert G. 2009).

**Side effects:** Krister et al. (2011) detected that the common adverse effects of radiotherapy were the same in all the groups (dermatitis, alopecia). Moreover, some patients from the BS group have shown diarrhea grade 1-2.

**Drug interactions:** There are no known drug interactions between BS and other synthetic drugs. The only interaction studied is the synergistic effect between BS and essential oil of myrrh in bactericidal action (de Rapper S. 2012).

#### **Summary table**

<b>Plant</b>	<b>Clinical indications</b>	<b>Grading</b>	<b>Dosage</b>
<i>Boswellia serrata</i>	Treatment of inflammatory states, perifocal edema in brain tumours or metastases	2B	400 mg of capsules or tablets (or 4-6 gr/day in perifocal brain edema)

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### *Edema and homeopathy*

Even if there are not researches related to edema in cancer patients, there are some interesting studies relating to edema in post-operative treatment.

Totonchi A and Guyuron B (2007) conducted a research to compare the efficacy of *Arnica montana* to corticosteroids in reducing the postoperative edema and bruising associated with rhinoplasty. The study compared the efficacy of these products following rhinoplasty.

Forty-eight primary rhinoplasty patients were randomized into 3 groups: group P received 10 mg of dexamethasone (intravenously) intraoperatively followed by a 6-day oral tapering dose of methylprednisone; group A received Arnica 3 times a day for 4 days; and group C received neither agent and served as the control. Three blinded panelists rated the extent of ecchymosis, the intensity of the ecchymosis, and the severity of the edema.

The results underline that on postoperative day 2, there were no significant differences in the ratings of extent and intensity of ecchymosis among the groups. There was a significant difference for the edema rating ( $p < 0.0001$ ), with group C demonstrating more swelling compared with groups A and P. In addition, on postoperative day 8, group P demonstrated a significantly larger extent of ecchymosis ( $p < 0.05$ ) and higher intensity of ecchymosis ( $p < 0.01$ ) compared with groups A and C. There were no differences in the magnitude of edema by postoperative day 8 among the 3 groups. When the differences between day 2 and day 8 ratings were considered, groups A and C exhibited significantly more resolution of ecchymosis by day 8 compared with group P ( $p < 0.05$ ).

Karow JH et al. (2008) proposed a study to answer the question: "Is Arnica D4 as efficacious as diclofenac in relation to symptoms and wound healing after foot surgery?" In the randomized double-blinded, parallel-group study (GCP-standard), the efficacy of Arnica D4 10 pillules (taken orally, 3 times per day) and diclofenac sodium, 50 mg (taken orally, 3 times per day) were investigated for equivalence in 88 patients 4 days after hallux valgus surgery.

Outcome parameters were: postoperative irritation, patient mobility, rated pain, and use of analgesics. The hierarchic equivalence test based on one-sided Wilcoxon-Mann-Whitney-U confidence intervals (CIs) was used. Equivalence was perceived, when the lower margin of the 95% CI was  $> 0.36$  corresponding to a range of equivalence of 1/2 standard deviation.

Arnica D4 and diclofenac were equivalent for wound irritation (lower margin of the 95% CI on day 4: 0.4729 for rubor; 0.3674 for swelling; 0.4106 for calor) and patient mobility (0.4726). A descriptive analysis showed the superiority of Arnica D4 with respect to patient mobility ( $p = 0.045$ ). With respect to pain, Arnica D4 was inferior to diclofenac (lower margin of the 95% CI 0.026). No significant differences were found regarding the use of additional analgesics during the 4 postoperative days Arnica D4 was significantly better tolerated than diclofenac ( $p = 0.049$ ). Nine (9) patients (20.45%) of the diclofenac group and 2 (4.5%) of the Arnica D4 group reported intolerance. There was no disturbance in wound healing in any of the patients.

### **Conclusions of the literature and authors**

Even if there are no researches in the oncological field, the study suggests that both Arnica and corticosteroids may be effective in reducing edema during the early postoperative period. Arnica does not appear to provide any benefit with regard to extent and intensity of ecchymosis. The delay in resolution of ecchymosis for patients receiving corticosteroids may outweigh the benefit of reducing edema during the early postoperative period.

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## Hot flashes

### *Hot flashes and acupuncture/TCM*

Filshie and Hester's guidelines indicate that acupuncture should be taken into consideration for treating the vasomotor symptoms of breast, prostate and other tumours. A review of Lu et al. (2008) which examined a clinical study (16 women treated with ear acupuncture in breast cancer) and 2 RCT (1 RCT included 72 women treated with sham or true acupuncture; 1 RCT included 38 treated with electro-acupuncture or relaxation) suggests that acupuncture can improve the vasomotor symptoms in women with breast cancer. The effects can last up to 6 months even though there is little difference between the true and sham acupuncture.

Another review (Sagar 2008) considered 3 prospective uncontrolled cohort studies (1 in men with hot flashes in prostate cancer and 2 others in women taking tamoxifen for breast cancer), demonstrating that acupuncture can stimulate the reduction of the vasomotor symptoms associated with anti-cancer hormone therapy. Needles and semi-permanent seeds seem to be linked in the reduction of long term symptoms. A pilot study in men experiencing hot flashes due to secondary hormone therapy for prostate cancer showed a marked decrease in the frequency without any adverse events or change in serum testosterone levels. The same review reports 2 RCTs with opposite conclusions: a RCT with 103 women in physiological menopause and one RCT with 72 women with breast cancer. In both studies false acupuncture was used in the control group (in the second study, the sham acupuncture group was crossed over to true acupuncture): the conclusion was that hot flash frequency was reduced; however acupuncture was not any more effective than sham acupuncture.

A systematic review (Lee et al. 2009) in patients with breast cancer included 6 RCTs, of which 3 compared the effects of manual acupuncture with sham acupuncture (non or minimal penetrating, non acupuncture point). One RCT (59 women with breast cancer undergoing adjuvant estrogen-antagonist treatment) showed favourable results regarding the frequency of hot flashes ( $p > 0,001$ ), while other two RCTs failed to do so. The meta-analysis show significant effects of acupuncture compared with sham acupuncture ( $n = 189$   $P = 0.05$ ) but marked heterogeneity was observed in this model. The review also included other 3 RCTs: 1 RCT compared the effects of electro-acupuncture (EA) with hormone therapy; hormone therapy was more effective than the EA; 1 RCT compared acupuncture with venlafaxine (antidepressants), and 1 RCT compared acupuncture with relaxation: these failed to show significant intergroup differences. In conclusion the evidence is not convincing to suggest acupuncture is an effective treatment of hot flashes in patients with breast cancer.

The same authors (Lee et al. 2009) realized another review which took into consideration 6 RCTs on menopause, 4 of which included surgical menopause. Acupuncture versus sham acupuncture was compared (penetrating/minimal/superficial non acupuncture point or not specific point). 5 RCTs did not encounter specific effects regarding the frequency and intensity of hot flashes. The sixth RCT (acupuncture versus non penetrating acupuncture on non-acupuncture point) demonstrated favorable effects of acupuncture on the intensity of menopausal vasomotor symptoms but not on their frequency; only a small number of subjects were treated. The authors conclude that RCT with sham acupuncture did not demonstrate favorable results in treating hot flashes. In a systematic review (Lee et al. 2009) of vasomotor disturbances of patients with prostate cancer, 6 trials are reviewed. Five of these were observational studies and one was a RCT (manual acupuncture versus acupuncture plus electro-acupuncture). Four studies, among which the RCT, showed positive effects for reducing hot flashes (HF) frequency; 2 studies among which the RCT, reported favourable effects for HF severity. The authors conclude that all included trials suggest beneficial effects of acupuncture for reducing HF frequency and intensity. However, the evidence is not convincing due to the quality of the studies.

According to the guidelines of the Society for Integrative Oncology (SIO 2009 - Deng et al.), acupuncture does not seem to be more effective than sham acupuncture for the treatment of hot flashes. In patients with severe symptoms who do not respond to medication, treatment with acupuncture can be considered. The degree of recommendation is 1B (strong recommendation, moderate quality evidence).

A systematic review (Frisk 2010) of the treatment of hot flashes in men with prostate cancer considered 32 studies of which 1 pilot study with acupuncture, 1 RCT with acupuncture versus electro-acupuncture, 1 retrospective audit of electronic records, 1 observational study with treatment using auricular acupuncture together with hormone therapy. The authors conclude that estrogen produces greater improvement but with many side effects while acupuncture can have a moderate effect on the hot flashes even though this has not been proved.

A Cochrane review (Rada et al. 2010) which evaluates the efficacy of non-hormonal therapies in reducing hot flashes in women with a history of breast cancer, included only one study on acupuncture and one study on magnetic-therapy (of the 16 RCTs considered) concluding that they may not lead to any differences in the number and severity of hot flashes.

Recently a Cochrane review (Dodin et al. 2013) evaluated the effect of acupuncture on hot flashes in women in physiological and iatrogenic menopause. The authors included 16 RCTs, with 1,155 women, comparing any type of acupuncture to no treatment/control or other treatments for reducing menopausal hot flushes and improving the quality of life of symptomatic perimenopausal/postmenopausal women.

Eight studies compared acupuncture versus sham acupuncture. No significant difference was found between the groups for hot flash frequency (414 women, low quality evidence) but flashes were significantly less severe in the acupuncture group, with a small effect size (6 RCTs 297 women, very low quality evidence). There was substantial heterogeneity for both these outcomes. In a post hoc sensitivity analysis excluding studies of women with breast cancer, heterogeneity was reduced to 0% for hot flash frequency and 34% for hot flush severity and there was no significant difference between the groups for either outcome. Three studies compared acupuncture versus Hormone Therapy (HT). Acupuncture was associated with significantly more frequent hot flashes than HT (114 women, low quality evidence). There was no significant difference between the groups for hot flash severity (2 RCTs, 84 women, low-quality evidence). One RCT compared electro-acupuncture versus relaxation. There was no significant difference between the groups for either hot flash frequency (38 women, very low quality evidence) or hot flash severity (38 women, very low-quality evidence).

Four studies compared acupuncture versus waiting list or no intervention. Traditional acupuncture was significantly more effective in reducing hot flash frequency from baseline (3 RCTs, 463 women, low-quality evidence), and was also significantly more effective in reducing hot flash severity. The effect size was moderate in both cases. The authors concluded that they found insufficient evidence to determine whether acupuncture is effective for controlling menopausal vasomotor symptoms. When they compared acupuncture with sham acupuncture, there was no evidence of a significant difference in their effect on menopausal vasomotor symptoms. When they compared acupuncture with no treatment there appeared to be a benefit from acupuncture, but acupuncture appeared to be less effective than HT. These findings should be treated with great caution as the evidence was low or very low quality and the studies comparing acupuncture versus no treatment or HT were not controlled with sham acupuncture or placebo HT.

### Single clinical studies on hot flashes in men (adults)

Type of study	Therapeutic protocol	N. patients and disease	Endpoints criteria	Results	Author, year
Trial randomized • manual acupuncture (TA) • electro acupuncture (EA)	1) TA bilaterally: BL15 BL23 BL32 unilaterally: GV20 HE7 PC6 LR3 SP6 SP9 2) EA same points, with BL 23 BL 32 bilaterally electrostimulated  weekly for 12 weeks	n.36 randomized n.29 studied prostate cancer	number of and distress from hot flashes in 24 h and change in “hot flash score”	EA and Ta lowered number of and distress from hot flashes. The hot flash score decreased 78% and 73%, respectively. after 12 weeks hot flashes per 24 h decreased significantly in the EA group ( p = 0.012) and in the TA group ( p = 0.001) after 12 weeks distress by flashes decrease in the EA group ( p = 0.003), and in the TA group ( p = 0.001),	Frisk, 2009
pilot study	auricular acupuncture (5 points autonomic, shen men kidney liver lung) weekly for 10 weeks	n.60 prostate cancer with LHRH agonist treatment	Measure Yourself Concerns and Well-being questionnaire (MYCAW)	95% of patients reported a decrease in the severity of symptoms (p <0.01).	Harding, 2009
pilot study	acupuncture and EA twice each week for the first 4 weeks and once per week for an additional 6 weeks  GB34 BL15 BL23(EA) BL32(EA) GV20 HE7 PC6 LR2 SP6	n. 25 enrolled n. 22 evaluable prostate cancer	Hot Flash Score (HFS)	after 4 weeks 9 of 22 patients had a > 50% reduction in HFS 12 of 22 patients met this response definition at any time during the course of therapy	Beer, 2010
observational study	acupuncture GB34 KI3 Tayang HT7 PC6 LI11 and EA SP6 ST36 BL15 BL23 twice weekly for 4 weeks	n.17 enrolled n. 14 evaluable prostate cancer	HFS	the improvement at 8 months was 80.3%, (HFS decrease p = 0.002).	Ashamalla, 2011

### Single clinical studies on hot flashes in women (adults)

Type of study	Therapeutic protocol	N. patients and disease	Endpoints criteria	Results	Author, year
observational study	Acupuncture: BL62 LR 14 KI3 HT7 TE6 SP6 LI 11 ST36 GV 20 LI4 6-14 sessions	n.22 consecutive  breast cancer with chemotherapy and tamoxifen	HF day and night Diary card	significantly difference (p<0.001) in HF frequency (day and night) and intensity	Tukmachi, 2000
RCT 1) psychological well-being 2) electro-acupuncture (EA)	1) applied relaxation 2)EA BL15 BL23 BL32 bilaterally HT7 SP6 SP9 LR3 PC6 GV20  12 sessions follow up 6 months	n. 38 randomized (19 group 1, 19 group 2) n.31 evaluable  breast cancer	Number flashes/24h Kupperman Index (KI)	in both groups at 6 months decrease of number of hot flashes/24h (p< 0.0001) and decrease of the KI (p<0.001)	Nedstrand, 2005
RCT 1)acupuncture  2) sham acupuncture (SA)  Sham group where crossed over to true acupuncture starting at week 7	1) acupuncture DU14 GB20 BL13 PC7 HT7 KI7 ST36 SP6 Ear shenmen sympathetic point twice weekly for 4 weeks 2) Streitberger sham needle few cm away from the points follow up 6 months	n.72 randomized (42 group 1, 30 group 2) breast cancer	HF per day	HF frequency was reduced and persisted for up to 6 months no statistical significance between groups	Deng, 2007
RCT 1)acupuncture (TA) 2) sham acupuncture (SA)	1)LV3 GB20 LU7 KI3 SP6 REN4 PC7 LV8 on the opposite side of the body to the operation side 2)minimal acupuncture, points well away from acupuncture points 10 weeks follow up 12 weeks	n.59 randomized (30 group 1, 29 group 2) breast cancer with tamoxifene	Number flashes/24h Kupperman Index (KI)	decrease in the TA group (P \ 0.001) during treatment, a further reduction (P \ 0.017) following 12 weeks no significant changes were seen in the SA group (P = 0.382 and P = 0.86, both versus baseline) the difference in acupuncture versus sham response was significant both during treatment and during the following 12 weeks (both P \ 0.001)	Hervik, 2009
RCT 1) acupuncture  2) venlafaxine	1) acupuncture  KI3 BL23 SP6 GB20 DU14 DU20 ST36 LV3 HT7 PC7 Ren6 LU9 for 12 weeks twice for 4 weeks weekly for 8 weeks	n.50 randomized (25 group 1, 25 group 2) breast cancer		both groups exhibited significant decreases in hot flashes, depressive symptoms, and other quality-of-life symptoms from pre- to post-treatment by 2 weeks post-treatment, the venlafaxine group experienced significant increases in hot flashes, whereas hot flashes in the acupuncture group remained at low levels venlafaxine group experienced 18 incidences of adverse effects (e.g., nausea, dry mouth, dizziness, anxiety); acupuncture no negative adverse effects	Walker, 2010
RCT 1) true acupuncture (TA) 2) sham (minimal) acupuncture (SA)	Questionnaire in the post 2 years after acupuncture (true or sham) treatment Not specified treatment	n.82 randomized (41 group 1, 41 group 2) n.61 completed	Kupperman Menopausal Index	patients previously treated with acupuncture complained less of hot flashes, and had a more positive outlook on life, than women treated with SA	Hervik, 2010

		treatments (33 group 1, 28 group 2) breast cancer			
single-arm observational study	acupuncture BL13 BL14 BL15 BL18 BL20 BL23 LU7 KI6 Ren4 SP6 He6 (Yanglao) KI7 LI11  8 sessions	n. 54 recruited n.50 completed treatments  breast cancer	Women's Health Questionnaire (WHQ)  Hot Flashes and Night (HFNSQ)	significant statistical and clinical improvements (p < 0.0001) in hot flashes frequency, including anxiety/fears, sleep problems	De Valois, 2010
Single group, non randomized, quasi-experimental	acupuncture points used during treatment were dependent on the individual subjects' TCM diagnoses as determined by the licensed acupuncturists 3 sessions within a 2 week period 8 week study	n. 10 breast cancer	Hot flash Related Daily Interference Scale (HFRDIS)	decrease in number of hot flashes from baseline to follow up 5 weeks (p=0.02).	Otte, 2011
RTC 1) true acupuncture (TA) 2) sham acupuncture (SA) 3) no treatment control group	1) (TA) PC6 KI3 SP6 LV3 2) (SA) non acupuncture points in the same region as TA, needles inserted superficially one a week for 5 weeks	n.94 randomized (31 group 1, 29 group 2, 34 group 3) breast cancer	VAS	in the TA group a significant effect on hot flashes compared with SA group (p < 0.05) the effect lasted for at least 12 weeks after last treatment	Bokmand, 2012
RCT subject-blinded trial 1) true acupuncture (TA)  2) control acupuncture (CTRL)	twice a week for 5 weeks 1) acupuncture Li4 Ht6 LR3 St36 unilaterally and Sp6 and Ki7 bilaterally 2) park sham needles applied 1 cm away from the points used in true acupuncture group Follow up at week 6	n.84 randomized n.74 completed treatments breast cancer with tamoxifen	Hot flashes and sweating frequency using a validated scale (Larson) Circulating Levels of hormones	In the TA group reported improvements in hot flashes after 6 weeks compared to the CTRL group both groups reported improvement regarding severity and frequencies in hot flashes and sweating but no statistical difference was found between them severity of sweating at night a statistically significant difference (P = 0.03) in the TA group	Liljegren, 2012
Multicentre randomized prospective study 1) electroacupuncture (EA) 2) hormone therapy (HT)	1) (EA) bilaterally BL15 BL23 BL32 – unilaterally GV20 Ht7 PC6 LR3 SP6 SP9 For 12 weeks 2) combined estrogen/progestagen for 24 months	n.45 randomized n.44 evaluable (27 group 1, 18 group 2) breast cancer	hot flashes score (HFS)	At 12 weeks HFS decreased in the EA by 80% compared to 100% in the HT group	Frisk, 2012
prospective single-arm observational study	acupuncture GV20 M-HN-3 extrapoints HT8 KI10 LV2 3 times weekly for 4 weeks	n.10 breast cancer undergoing antiestrogen therapy with tamoxifen or anastrozole	visual analogue scale (VAS) and total hot flash score	acupuncture significantly alleviated severity of hot flashes (p < 0.001) and total hot flash score (p = 0.006) during treatment and 4 weeks after the treatment	Jeong, 2013

## Conclusions of the literature and the authors

The guidelines of Filshie et al. (2006) indicate that specific conditions which should be taken into consideration are vasomotor symptoms stemming from breast cancer, prostate cancer or other tumours that do not respond to conventional treatment or for patients who choose acupuncture instead of conventional therapy due to the potential side effects.

According to the guidelines of the Society for Integrative Oncology (SIO 2009) acupuncture does not seem to be more effective than sham acupuncture in the treatment of vasomotor symptoms (hot flashes). Treatment with acupuncture can be considered for patients who present severe symptoms and who do not respond to drug therapy. The degree of recommendation is 1B (strong recommendation, moderate quality evidence).

Lee et al. (2009) in the three reviews mentioned, conclude that the evidence of efficacy of acupuncture on the frequency and intensity of hot flashes is not convincing because there is not a statistically significant difference between manual acupuncture or electro-acupuncture or sham acupuncture. Of 12 studies, 3 compare sham acupuncture (in various forms-minimally penetrating, superficial, etc.) with acupuncture. The Cochrane review 2013 (Dodin et al.) clarifies the situation because it analyzes the studies separately, based on the chosen control group and compares the results versus sham acupuncture, hormone therapy, relaxation, waiting list and no intervention. The authors concluded that they found insufficient evidence to determine whether acupuncture is effective for controlling menopausal vasomotor symptoms, because when they compared acupuncture with sham acupuncture, there was no evidence of a significant difference. The greatest problem in acupuncture research is how to define the appropriate control group: sham acupuncture is not like a placebo and comparing the effects of acupuncture and sham acupuncture can underestimate the actual benefits of acupuncture, as stated by various authors.

In conclusion acupuncture treatment can be a promising therapeutic technique to deal with the symptoms of menopause. It is recommended for women who can not to be treated with HT due to oncological risks or because of an ongoing or past oncological pathology. It is also advisable when the patient refuses HT or having already been treated with HT, she continues to suffer from hot flashes, psychological problems, insomnia and other symptoms studied. On the basis of these criteria the authors of TNIM, considering the recent studies evaluated that the adequate grading is 1A (strong recommendation, high-quality evidence).

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### *Hot flashes and herbal medicine*

The herbal medicines traditionally used in treatment of hot flashes are: *Cimicifuga racemosa*, *Glicine max*, *Trifolium pratense* and *Vitex agnus-castus*.

The studies that analyze the action on the hot flashes treatment of *Vitex agnus-castus* (VA) are still few and none of them concern cancer patients. Only a randomized, controlled clinical trial performed on 93 women over 16 weeks analyzed the action of VA in combination with *Hypericum perforatum* in the management of menopausal symptoms. The data show that this herbal combination was not superior to placebo for the treatment of menopausal symptoms (van Die MD. 2009).

### **Cimicifuga racemosa**

*Cimicifuga racemosa* (CR), also known as *Actaea racemosa* or black cohosh, is a perennial plant member of the Ranunculaceae (buttercup) family that is native to North America. Native Americans used it in the treatment of many conditions, including gynaecologic disorders and musculoskeletal complaints. The principal modern use of CR is based on its purported efficacy in the treatment of menopausal symptoms, primarily hot flashes, sleep disturbances, depression, dysmenorrhoea and climacteric symptoms.

Clinical trials referring to the hot flashes treatment with *Cimicifuga racemosa* show conflicting data; this is probably due to the sample size, the non-homogeneity of the samples and the different experimental design. (see Tab. 1)

A Cochrane Database systematic review (Leach MJ. 2012) to evaluate the clinical effectiveness and safety of CR for menopausal symptoms in perimenopausal and postmenopausal women concludes that there is currently insufficient evidence to support its use. This systematic review evaluated 16 randomised controlled trials, and enrolled 2027 perimenopausal or postmenopausal women. All the studies used oral mono-preparations of black cohosh at a median daily dose of 40 mg, for a mean duration of 23 weeks. Comparator interventions included placebo, hormone therapy, red clover and fluoxetine. Reported outcomes included vasomotor symptoms, vulvovaginal symptoms, menopausal symptom scores and adverse effects. There was no significant difference between black cohosh and placebo in the frequency of hot flashes (mean difference 0.07 flashes per day; 95% confidence interval -0.43 to 0.56 flashes per day; P=0.79; 393 women; three trials; moderate heterogeneity: I (2) = 47%) or in menopausal symptom scores (standardised mean difference -0.10; 95% confidence interval -0.32 to 0.11; P = 0.34; 357 women; four trials; low heterogeneity: I(2) = 21%). Furthermore, compared to black cohosh, hormone therapy significantly reduced daily hot flash frequency (three trials; data not pooled) and menopausal symptom scores (SMD 0.32; 95% CI 0.13 to 0.51; P=0.0009; 468 women; five trials; substantial heterogeneity: I (2) = 69%). These findings should be interpreted with caution given the heterogeneity of the studies.

Similarly Laakman E. et al. (2012) show that CR treatment is not better than placebo, and suggest that the association of CR and *Hypericum perforatum* demonstrated a positive effect on climacteric complaints.

Finally, a systematic review (Walji R. 2007) about the safety of CR in cancer patients concludes that the use of black cohosh appears to be safe in breast cancer patients without risk for liver disease, although further research is needed in this and other populations. In this review the authors analysed 5 clinical and 21 preclinical studies of CR and cancer (breast and prostate) to treat hot flashes and other related symptoms. Furthermore, clinical studies, case reports, animal studies, and *in vitro* assessments of the safety of black cohosh for patients with hormonally sensitive cancers were summarized and interpreted. The data showed that efficacy of black cohosh for the treatment of hot flashes in women with breast cancer is inconclusive. There is laboratory evidence of antiproliferative properties but RCTs don't confirm a protective role in cancer prevention. Black cohosh seems to have a relatively good safety profile, with relevance to cancer patients, does not exhibit phytoestrogenic activity and is, in fact, possibly an inhibitor of tumor growth; although further research is needed to confirm this data.

**Dosage:** The EMA suggests the use of CR for the relief of menopausal complaints such as hot flashes and profuse sweating, at a daily dose of 40 mg of dry extracts divided into 1 or 2 single doses substance. The dried extracts advised are: dry extract (DER 5-10:1) extraction solvent ethanol 58% (V/V), Dry extract (DER 4.5-8.5:1) extraction solvent ethanol 60% (V/V), Dry extract (DER 6-11:1) extraction solvent propan-2-ol 40% (V/V).

**Side effects:** Liver toxicity and skin reaction have been reported. Patients with a history of liver disorder should take CR preparations with caution. CR must be stopped if signs and symptoms suggestive of liver injury like tiredness, loss of appetite, yellowing of skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine are developed (EMA. 2010).

In a recent meta-analysis of randomized, double-blind, and controlled clinical trials (Naser B. 2011), the authors analyzed 5 studies involving 1,117 women to evaluate the efficacy and safety of the isopropanolic black cohosh extract (iCR) in perimenopausal and postmenopausal women. In this paper the overall fixed effect  $\pm$  SEM was  $0.055 \pm 0.062$  ( $P=0.37$ ) for aspartate aminotransferase and  $0.063 \pm 0.062$  ( $P=0.31$ ) for alanine aminotransferase. There is no evidence of adverse effect on liver function.

Similarly, to evaluate the risk of hepatotoxicity of CR Firenzuoli F. et al. (2011) contacted patients consuming the extract continuously for at least 12 months and selected 107 women treated with isoflavones at the dose of 500 or 1000mg daily as dry extract, standardized and titrated in 2.5% of actein, a triterpene glycoside (Figure 2), for treatment of menopause related disorders like anxiety, depression, flashes and myalgia. The data show that CR rhizome extract should not be considered a potential hepatotoxic substance. However, in another systematic review aimed at studying the adverse effects induced by the use of CR, the authors conclude that it has been associated with serious safety concerns that urgently require further investigation (Borrelli F. 2008).

Therefore, pending further information we suggest caution in the use.

**Drug interactions:** *in vitro* studies show synergistic interactions between CR and tamoxifen and other chemotherapy agents for the inhibition of cancerous cell growth (Einbond LS. 2006, Al-Akoum M. 2007).

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Open-label, randomized study	CR: Menofem/Klimadyn on corresponding of 20 mg  Period: 1 year	136 breast cancer survivors aged 35-52 years	To examine the effect of CR on hot flashes caused by tamoxifen adjuvant therapy in young premenopausal breast cancer survivors	The number and severity of hot flashes were reduced after intervention. Almost half of the patients of the intervention group were free of hot flashes, while severe hot flashes were reported by 24.4% of patients of intervention group and 73.9% of the usual-care group ( $P<0.01$ )	Hernández Muñoz G. 2003
Pilot study	CR commercial product (Remifemin) g Remifemin, 1 tablet orally twice a day.  Period: 4 weeks	21 women with hot flashes, 13 had a history of breast cancer	Estimate the effectiveness of black cohosh to reduce hot flashes  Criteria: daily questionnaires during baseline and treatment weeks	Black cohosh appeared to reduce hot flashes and had a low toxicity. The efficacy found in this trial seems to be more than would be expected by a placebo effect (20%-30% hot flash reduction in previous trials)	Pockaj BA 2004
Double-blind, randomized, cross-over clinical trial	CR: 1 capsule of 20 mg	132 patients randomly assigned	Evaluate the efficacy of CR for the treatment of hot flashes in women Criteria: daily hot flash diary	Patients receiving CR reported a mean decrease in hot flash score of 20% compared with 27% decrease for patients on placebo ( $p = 0.53$ ). Mean hot flash frequency was reduced 17% on black cohosh and 26% on placebo ( $p = 0.36$ )	Pockaj BA. 2006
Prospective observational study	CR: 1-4 tablets, (2.5 mg) of isopropanolic extract of black  Period: 6 months	50 breast cancer patients in treatment with tamoxifen	Criteria: MRS II	Hot flashes, sweating, sleep problems, and anxiety improved, urogenital and musculoskeletal complaints did not change. 90% of patients reported the tolerability of the black cohosh extract as very good or good	Rostock M. 2011

Tab.1. Single clinical studies on *Cimicifuga racemosa* use in hot flashes. Legend: CR (*Cimicifuga racemosa*), MRS II (Menopause rating scale).

### **Isoflavone herbal medicines**

Isoflavones, which have been known to exist in plants for more than 100 years, have a relatively limited distribution in nature. Among the commonly consumed foods by humans, they are found in physiologically relevant amounts only in soybeans and foods derived from this legume, although a variety of plants such as red clover are also rich sources.

The effectiveness of isoflavones in the treatment of hot flashes was analysed by Howes LG et al. (2007) in a systematic review. The data suggest that isoflavone supplementation was associated with a significant reduction in flashes (effect size  $-0.28$ , 95% confidence intervals  $-0.39$  to  $-0.18$ ,  $p < 0.0001$ ). Marked heterogeneity was found between the studies, but the effect remained significant when analyzed using a random effects model (delta  $= -0.49$ , 95% confidence interval  $-0.81$  to  $-0.17$ ,  $P = 0.001$ ). The percentage reduction in hot flashes was significantly related to the number of baseline flashes per day and the dose of isoflavone studied ( $\beta = -0.49$  and  $-0.26$ , respectively, both  $p < 0.0001$ ).

These data are not always consistent with those obtained from systematic reviews relating to the activities of individual medicinal plants (*Glycine max* and *Trifolium pratense*) on hot flashes.

**Drug interactions:** No serious side effects associated with the use of isoflavones are reported. In vitro studies show that isoflavones inhibit oxidative metabolism and influence drugs-transporter proteins such as P-glycoprotein and the multispecific organic anion transporter. Therefore, there is the possibility of drug interactions and in general these compounds are not recommended for use in cancer patients taking tamoxifen. Finally, they are not recommended in pregnant women as may interfere with the normal development of the male reproductive tract (Capasso F. 2006).

### ***Glicine max***

Soy is obtained from the seeds of *Glycine max*, an annual herbaceous plant. The soybean is one of the richest foods in isoflavones and consists mainly of: genistein and daidzein, and other isoflavones. To date many studies on its role in the treatment of hot flashes have been produced and the data do not support the effectiveness of the hot flashes treatment based on soy. Tab. 2

From 2003 to 2013, only two systematic reviews have been selected. Briefly, Cassidy A. et al. (2006) conclude that there is a suggestion, but no conclusive evidence, that isoflavones from the sources studied so far have a beneficial effect on bone health. The consumption of whole-soybean foods and soybean-protein isolates has some beneficial effects on lipid markers of cardiovascular risk. The consumption of isolated isoflavones does not affect blood lipid levels or blood pressure, although it may improve endothelial function. For menopausal symptoms, there is currently limited evidence that soyabean-protein isolates, soyabean foods or red clover (*Trifolium pratense* L.) extract are effective but soyabean isoflavone extracts may be effective in reducing hot flashes. There are too few RCTs to reach conclusions on the effects of isoflavones on breast cancer, colon cancer, diabetes or cognitive function. The health benefits of soyabean phytoestrogens in healthy post-menopausal women are subtle and even some well-designed studies do not show protective effects. Bolaños R et al. (2010) analyzed whether intervention with soy (dietary, extract, or concentrate), as compared with placebo, reduces the incidence of hot flashes in climacteric women. Nineteen studies were analysed and heterogeneity in examined groups was detected. The authors conclude that although the overall combined results and the results by subgroups (according to the type of supplement used) showed a significant tendency in favour of soy, it is still difficult to establish conclusive results given the high heterogeneity of the studies. Therefore, further investigation is needed to assess the effectiveness, side effects, safety and toxicity of short and long-term use.

**Dosage:** The traditional use indicates a daily dose of GM equivalent to 35-135 mg of isoflavones (Capasso F. 2006).

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Double-blind, multicenter, randomized trial performed according to a 2 x 2 factorial design	I Group: 80 mg soy isoflavones+ 3 mg melatonin; II Group: 80 mg soy isoflavones alone; III Group: 3 mg melatonin alone; IV Group: placebo Period: 3 months	262 women	Evaluate the effect of soy isoflavones and melatonin in relieving menopausal symptoms.  Criteria: GCS	Present data do not show any advantage of isoflavones or melatonin over placebo for the relief of menopausal symptoms (p=0.537)	Secreto G. 2004
Randomised double-blind controlled trial vs placebo	Capsules:235 mg of soy extract with 17.5 mg of isoflavines – the total dose of isoflavines was 70 mg/ day. Period: 12 week	62 patients with histologically confirmed pre-existing diagnosis of breast cancer	Evaluate the effectiveness in menopausal of the GM treatment symptoms in patients with early breast cancer Criteria: EORTC QLQ-C30, MRS, BR23	The data suggest that there are no statistical difference in menopausal symptom scores or quality of life between the two arms of the study. (P = 0.844)	MacGregor CA. 2005

Tab.2. Single clinical studies on *Glicine max* use in hot flashes. Legend: BR23 (Breast Cancer Module), EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life-Care30), GCS (Greene Climateric Scale), MRS (Menopausal Rating Scale), GCS (Greene Climacteric Scale).

### ***Trifolium pratense***

*Trifolium pratense* (TP) is cultivated in many countries of the world. Several RTCs have been done to evaluate its effectiveness in hot flashes treatment in healthy and cancer patients. (see Tab. 3)

From an analysis of these studies, it is possible to note that the efficacy data are inconsistent and that more studies are needed to assess the herbal medicines action on hot flashes.

Similarly, Coon JT (2007) in a systematic review selected 17 potentially relevant papers and only 5 were suitable for inclusion in the meta-analysis. The data show that there is evidence of a marginally significant effect of TP isoflavones for treating hot flashes in menopausal women. Whether the size of this effect can be considered clinically relevant it is unclear.

**Dosage:** The traditional use indicates a daily dose of TP equivalent to 40-80 mg of isoflavones. (Capasso F. 2006).

**Side effects:** There is no apparent evidence of adverse events during short-term use; there are no available data on the safety of long-term administration (Coon JT. 2007).

**Drug interactions:** to date no drug interactions have been reported with synthetic drugs during human therapies; but, an *in vitro* study conducted on breast cancer cells, MCF7, shows that biochanin A (an isoflavone isolated from TP) inhibited CYP19 activity and gene expression (Wang Y. 2008).

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Double-blind, randomized, placebo-controlled trial	TP: Isoflavon tablets of 26 mg biochanin A, 16 mg formononetin, 1 mg genistein and 0.5 mg daidzein	177 women (age range 49-65 years) with Wolfe P2 or DY mammographic breast patterns	Determine the effects of red clover-derived isoflavone supplement daily for 1 year on mammographic breast density Criteria: Change in mammographic breast density, serum oestradiol, FSH, LH, menopausal symptoms and lymphocyte tyrosine kinase activity from baseline to 12 months	In contrast to studies showing that conventional HRT increase mammographic breast density, the isoflavone supplement did not increase it in this population of women. Furthermore, there were no effects on oestradiol, gonadotrophins, lymphocyte tyrosine kinase activity, or menopausal symptoms	Atkinson C. 2004
Randomized, double-blind, placebo-controlled pilot trial	Standardized 40 mg red clover isoflavone dietary supplement in women with a family history of breast cancer  Period: 3 years	401 healthy women aged 35-70 years with at least one first-degree relative with breast cancer	Evaluate the safety, tolerability and feasibility of the supplement for prevention of breast cancer in healthy women Criteria: Biochemical analysis every 6 months and mammography, bone density and transvaginal ultrasound (postmenopausal women only) once per year	There were no significant results to support a longer term breast cancer prevention study in healthy women. The data show that red clover isoflavones are safe and well tolerated in healthy women. Supplements containing red clover isoflavones did not adversely affect breast density, skeletal strength or cardiovascular status. In postmenopausal women, endometrial status was not adversely affected	Powles TJ. 2008
Randomized, four-arm, double-blind clinical trial	TP: 398 mg/d standardized to 120 mg isoflavones CR: 128 mg/d standardized to 7.27 mg triterpene glycosides  Period: 12 months	89 women randomized to the study	Evaluate the safety and efficacy of black cohosh and red clover compared with placebo for the relief of menopausal vasomotor symptoms.  Criteria: Diary	Compared with placebo, black cohosh and red clover did not reduce the number of vasomotor symptoms. Chemically and biologically standardized extracts of black cohosh and red clover were safe during daily administration for 12 months. (black cohosh, 34% reduction; red clover, 57%; placebo, 63%; and, CEE/MPA, 94%)	Geller SE. 2009
Prospective, randomized, double-blind, placebo-controlled study	Group TG: 1 cps/day (40 mg TP) Group PG: 1 cps/day (placebo capsules containing lactose control) Period: 12 months	120 women (45-65 years) with menopausal symptoms, more than 12-month amenorrhea and no treatment in the past 6 months were selected	Evaluate the effects of treatment with <i>Trifolium pratense</i> on climacteric symptoms and sexual satisfaction in postmenopausal women Criteria: KMI GRISS	12-month treatment with a daily dose of 40 mg of <i>Trifolium pratense</i> did not yield a significant improvement in menopausal symptoms and sexual satisfaction	del Giorno C. 2010
Randomized clinical trial	TP: 2 daily capsules of the active compound containing 80 mg red clover isoflavones  Period: 90 days	1009 postmenopausal women aged 40 or more	Evaluate the effect of red clover isoflavone supplementation on vasomotor and overall menopausal symptoms in postmenopausal women  Criteria: KMI	The data show a significant decrease in group A of KMI symptoms at 90, 97 and 187 days (Group A 73.5%, 72.2% and 75.4% vs Group B 8.2%, 0.9% and 6.7%). Red clover isoflavone supplementation was more effective than placebo in reducing daily vasomotor frequency and overall menopausal intensity in postmenopausal women	Lipovac M. 2012

Tab.3. Single clinical studies on *Trifolium pratense* use in hot flashes. Legend: TP (*Trifolium pratense*), CR (*Cimicifuga racemosa*), CEE/MPA (0.625 mg conjugated equine estrogens plus 2.5 mg medroxy progesterone acetate), KMI (Kupperman Menopausal Index), GRISS (Golombok Rust Inventory of Sexual Satisfaction)

## Summary table

Plant	Clinical indications	Grading	Dosage
<i>Cimicifuga racemosa</i>	Treatment of menopausal symptoms, primarily hot flashes, sleep disturbances, depression, dysmenorrhea and other symptoms	2B	40 mg of dry extracts divided into 1 or 2 single doses substance
<i>Glicine max</i>	Menopausal symptoms	1B	Dose of GM equivalent to 35-135 mg/day of isoflavones
<i>Trifolium pratense</i>	Menopausal symptoms	2B	Dose of TP equivalent to 40-80 mg/day of isoflavones

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### *Hot Flashes and homeopathy*

In a review (Thompson, 2009) 2 randomized studies evaluated the use of homeopathy for menopausal symptoms in the climacteric. Five patients participated in a placebo controlled semi-crossover survey in general practice and no statistically significant differences were found.

Two clinical trials of homeopathy for breast cancer survivors have been conducted, regarded as high-quality trials and included in a systematic review of homeopathic trials in the cancer setting. Both trials (Thompson, 2005) and (Jacob, 2005) used the same inclusion criteria: more than 3 hot flashes daily and similar exclusion criteria. Both trials do not demonstrate significant difference for the primary outcome measure between groups, although they may have been underpowered to detect a difference.

Clover Ratsey and A. D. (2002) conducted a study on 31 women of whom 20 had a previous diagnosis of breast cancer and reported noticeable improvements with regard to the frequency and intensity of hot flashes. Two double-blind randomized clinical trials were also conducted. The inclusion criteria of the patients were: breast cancer and at least three episodes of hot flashes per day. In the first study (Thompson et al., 2005) the intervention was individualized classical homeopathy, lasted 16 weeks and involved 53 women, mean age 52 years and 80% of patients used tamoxifen. In this case the results were not significant.

In the study conducted by Jacobs et al. (2005) there were 83 patients, average age of 55 years; the treatment lasted 6-12 months and a homeopathic complex consisting of Sanguinaria, Glonoinum and Lachesis was also used. Even in this case the results were not significant, but a positive trend was demonstrated in the reduction of the frequency of hot flashes in the first 3 months of treatment ( $p = 0.1$ ), and a reduction in the Kupperman Menopausal Index ( $p = 0.1$ ) after a year.

An open, multicenter, prospective, observational study was carried out to evaluate the usefulness of homeopathic treatment in distress during climacteric years. Homeopathic therapy was found to be useful in relieving menopausal distressing symptoms such as hot flashes, night sweats, anxiety, palpitation, depression, insomnia, and so on. The medicines found to be most frequently indicated and useful were Sepia, Lachesis, Calcarea carb., Lycopodium, and Sulphur (Nayak C. et al. 2011).

An observational longitudinal study was carried out on 1,067 women consecutively examined from 2002 to 2011 to study the socio-demographic features of the women treated at the Homeopathic Clinic for woman's disorders Hospital of Lucca (Italy), the observed diseases, the most commonly used remedies, outcome and follow-up (Panozzo MA et al. 2013). The outcome was assessed using the Glasgow Homeopathic Hospital Outcome Score (GHHOS). The mean age of the patients was 41 years, 747 (70%) coming from the Province of Lucca, mainly clerks (290) and students (115). 35.3% had already used conventional therapy and 15.3% homeopathic treatment. The most frequently observed diseases were gynecological problems in 620 (63.3%), 23.3% patients with menopausal disorders, 12% with menstrual irregularities, and 13.5% with psychological disorders. 81 cases (32.5%) with menopausal disorders were followed up. Patients with a major improvement or resolution (GHHOS = +3 +4) were 152 (43.6%) and in menopausal complaints 35 (43.1%), 71.4% if we considered also GHHOS +2.

A double-blind randomized clinical trial (Desiderio F., in press) on the use of homeopathy in the treatment of menopausal symptoms for patients operated for breast cancer was recently completed; the data have not yet been published. The study seems to provide interesting results.

During the pilot phase of the study 10 patients whose symptoms were measured at time 0 (before treatment) and 1 (after 3 months of treatment) were treated. The symptoms evaluated according to NCI-CTC were: hot flashes, night sweats, vaginal discharge, abnormal vaginal bleeding, dryness/vaginal itching, dyspareunia, gastric disorders, dermatological disorders, headaches, fluid retention, anxiety/depression, other. There was a reduction in symptoms in all patients with a statistically significant difference ( $p < 0,001$ ).

At the conclusion of the study 35 women were enrolled; only 31 of them completed a 6 month therapy (16/19 placebo, 15/16 active drug). Four women abandoned the therapy before 3 months.

The comparison of symptoms at time 0 and at time 1 (after 6 months), showed a statistically significant reduction ( $p < 0.05$ ) in favor of the active drug about the total score ( $p = 0.0185$ ), night sweats ( $p = 0,0097$ ) and gastro-intestinal disorders ( $p = 0.0395$ ).

The other differences were not significant ( $p > 0.05$ ), but symptoms such as hot flashes, insomnia and water retention were found to be of borderline significance.

<b>Type of study</b>	<b>Therapeutic protocol</b>	<b>N. patients and disease</b>	<b>End points criteria</b>	<b>Results</b>	<b>Author, year</b>
Uncontrolled, pilot outcome study	The six most frequently prescribed medicines taken by patients rating their overall benefit as +3 or +2 at the final consultation were: Amyl nitrosum, Calc carb., Lachesis, Natrum mur, Pulsatilla, Sepia	31 patients divided into 3 groups: menopausal symptoms with no history of breast carcinoma (No cancer), menopausal, carcinoma of the breast but no recent Tamoxifen (Ca, no TMX), menopausal, carcinoma of the breast, taking Tamoxifen (Ca, TMX)	Amelioration of hot flashes with homeopathic treatment	Most of the patients reported clinically relevant improvement	Clover, 2002
Prospective randomised subject, care provider, statistician blind placebo controlled trial with 3 parallel arms	Subjects were randomized to receive either an individualized homeopathic single remedy, a homeopathic combination medicine, or placebo	83 women with a history of carcinoma in situ or Stage I to III breast cancer who had completed all surgery, chemotherapy and radiotherapy (women taking Tamoxifen were also included), who had hot flushes for at least 1 month, with an average of at least 3 hot flushes per day in the week prior to beginning treatment Age: mean 55.5 years	Hot flash severity score (frequency times severity of hot flushes from symptom diary) at entry to the study and at 1, 2, 3, 6, 9 and 12 months after randomisation Secondary outcome measures: total number of hot flushes Kupperman Menopausal Index (KMI) SF-36 (Short Form 36) quality of life score FSH (Follicle Stimulating Hormone) level before and after treatment	There was no significant difference in the primary outcome measure, the hot flash severity score, although there was a positive trend in the single remedy group. A statistically significant improvement in general health score in both homeopathy groups ( $p < 0.05$ ) on the SF-36 after 1 year was found. There were no statistically significant differences between the three groups in the KMI score or in individual symptoms of the KMI score except for an increase in headaches in the group taking the homeopathic combination at 6 and 12 months. The general health score of the SF36 was significantly increased in both homeopathy groups compared with placebo. There was an increase in the number and severity of hot flashes in the subgroup not taking Tamoxifen and receiving the proprietary combination (post hoc)	Jacobs, 2005
Prospective randomised placebo controlled trial with 2 parallel arms	a) individualized homeopathy: 5 consultations and prescriptions in various forms  b) placebo	53 women treated for breast cancer, who had more than 3 hot flashes/day, did not have metastatic disease, were not on any other treatment for hot flashes, did not have any severe concurrent illnesses, and were	Primary outcome measure MYMOP - a change of 0.8 was considered to be a clinically relevant change Secondary outcome measures Menopausal Symptom	85% of women completed the study. There was no evidence of a difference between groups for either MYMOP activity (adjusted difference = -0.4, 95% confidence interval CI -1.0 to 0.2, $p = 0.17$ ) or profile scores (adjusted difference = -0.4, 95% CI -0.9 to 0.1, $P =$	Thompson, 2005

	For the individualised homeopathy, there was unrestricted remedy choice and unrestricted ability to change remedy. Outcome assessments were appropriate from a homeopathic perspective	not undergoing, or about to receive, any adjuvant chemotherapy	Questionnaire Patient diaries of frequency and severity of hot flashes EORTC QLQ C30 (European Organisation for Research and treatment of Cancer Quality of Life Questionnaire C30) HADS (Hospital Anxiety and Depression Scale) FAQ (Final assessment Questionnaire) GHHOS (Glasgow Homeopathic Hospital Outcome Scale)	0.13). Clinically relevant improvements in symptoms and mood disturbance were seen for both groups over the study period. Adverse effects were reported by approximately one quarter of women in both groups	
Open, multicenter, prospective, observational study	The selected homeopathic medicine was prescribed in a single dose	150 patients enrolled from general outpatient department of the 6 Institutes/Units of Central Council for Research in Homoeopathy (CCRH). Evaluation at T0 and T1: after 1 year of treatment	Uniform questionnaire assessing 15 predefined symptoms of menopause with assessment of each symptom at every visit	Homeopathic therapy relieved menopausal symptoms such as hot flashes, night sweats, anxiety, palpitation, depression, insomnia	Nayak C, 2011

### Conclusions of the literature and the authors

From the analysis of the review, homeopathy appears to do little harm but clinical effect remains unclear for women with menopausal symptoms who do not want to or cannot take HRT (e.g breast cancer survivors). The studies appear to show that homeopathic therapy may be useful in treating secondary symptoms of iatrogenic menopause even though the significance of the results is controversial.

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## Insomnia

### *Insomnia and acupuncture/TCM*

The Guidelines of Filshie and Hester (2006) indicate insomnia that does not respond to standard treatments is a specific condition to be taken into account for the treatment of acupuncture.

A review and a Cochrane meta-analysis (Cheuk et al. 2012, update of Cochrane 2007) included 33 RCTs and 2,293 participants suffering from insomnia (age 15 - 98 years) with medical conditions including cancer. The studies considered compared acupuncture therapy in various forms (somatopuncture, electroacupuncture, acupressure and magnetic acupressure) alone or associated to other treatment versus no treatment, placebo or sham treatment or versus other treatment. Acupoints chosen and acupuncture methods and duration of therapy were highly variable. The most frequently used acupoints were: Shenmen on hands HT7 (in 17 studies), Neiguan PC6 (9 studies), Baihui GV20 (9 studies) Shenmen on ears (8 studies).

Improvements in sleep quality were found in acupressure treatment versus no treatment (2 studies, 280 participants OR 13,8 95% confidence interval (CI 1.79 to 95.59), acupressure versus sham/placebo (2 studies, 112 participants, OR 6.62, 95% CI 1.78 to 24.55) and acupuncture with other treatment compared to the treatment alone (13 studies, n.883 patients 3:08-OR 95% CI 1.93 to 4.90). On subgroup analysis only needle acupuncture but not electroacupuncture showed benefits. All studies, however, had a high risk of bias (low methodology), poor methodological quality and high levels of heterogeneity; therefore, according to the authors the evidence is not sufficiently rigorous to support or reject acupuncture in the treatment of insomnia. High-quality clinical studies with higher sample are required.

Garcia et al. in the review of 2013 on a variety of symptoms, including insomnia (3 studies: Cui 2003, Feng 2011, Frisk 2012) report that poor sleep quality is common among patients undergoing cancer treatment but few studies have evaluated the use of acupuncture to improve sleep, and only 3 studies met the inclusion criteria. All three reported positive outcomes, but they were unblinded studies with high risk of bias (ROB).

Below a few and relevant articles which are reported also in the Table.

Cerrone et al. (2008) evaluated the efficacy of acupressure in insomnia in 25 patients affected by sleep disorders, 14 of whom had a neoplastic disease. The results demonstrated an improvement in the quality of sleep in 15/25 (60%) patients, and a stronger efficacy in 11/14 cancer patients (79%). This study confirms previous clinical data about the efficacy of acupressure in the treatment of sleep disorders, particularly in cancer-related insomnia.

Ruan et al. (2009) published a study conducted in China on 67 volunteer patients suffering from chronic insomnia (more than 6 months) treated with electroacupuncture. Forty-seven patients completed the treatment with significant improvement in sleep quality before and after treatment ( $p < 0.05$ ).

De Valois et al. (see Chapter on Anxiety) in an observational study carried out in England (2010) treated 50 patients with breast cancer with 8 weekly treatments of acupuncture finding significant improvements ( $p < 0.0001$ ) in the frequency of hot flashes and psychological symptoms including sleep disorders.

In a non-randomized study conducted by Otte et al. (2011) 10 breast cancer survivors treated with acupuncture (3 sessions) showed statistically significant improvements in both vasomotor disturbances of sleep. However, it is necessary a large randomized controlled trial (see Chapter on Hot flashes).

In China Feng et al. (2011) conducted a study on 80 cancer patients suffering from depression and sleep disorders randomized into 2 groups: acupuncture versus fluoxetine. The study demonstrated a statistically significant difference in the improvement of depression, quality of sleep and helped in improving the quality of life of patients with cancer (see Chapter on Anxiety).

Frisk et al. (2012) evaluated the effects of electroacupuncture (EA) in 45 women randomized into 2 groups (EA compared versus hormone therapy). After 12 weeks of treatment and 12 months, both therapies had improved the quality of life and sleep disorders with statistical significance.

**Single clinical studies on insomnia in cancer patients (adults)**

Type of study	Therapeutic protocol	N. patients and disease	Endpoints criteria	Results	Author, year
RCT 1. acupuncture + estazolam 2. estazolam	7. GV 20 GV 24 EX HN1 HT7 PC6 CV12 ST40 SP4 once daily for 30 days 8. 1-2mg for the same period	120 cases : 60 group 1, 60 group 2	Sleep efficiency	Therapeutic effects in acupuncture group was 96,7% vs. 86,7% (control group)	Cui, 2003
single-arm observational study	HT 7 acupression for at least two consecutive weeks (using a medical device named H7 Insomnia Control)	n.25 (14 of whom had a neoplastic disease)	Not reported	improvement in the quality of sleep in cancer patients (11/14 [79%]).	Cerrone, 2008
single-arm observational study	Electroacupuncture Main acupoints PC6, HT7, SP6, KI3, KI6, BL62 and other acupoints added in different syndromes: BL20,BL15,PC7,DU24,RN 6, RN7,RN12,ST40,ST45, SP1,LI11,ST41,LR3,LI4 4 courses of treatment (1 continuous 10 days)	67 volunteers (8 without neoplastic diseases); 47 concluded treatment	Pittsburgh sleep quality index (PSQI) PARAD ISE P&D9600 Type (USA) polysomnogram test	Changes in sleep quality between pre- treatment and post-treatment were significant (p <0.05) EA prolonged slow wave sleep (SWS) time and relatively rapid eye movement sleep (REM sleep)P <0.01 vs. pre-treatment	Ruan, 2009
single-arm observational study	acupuncture BL13 BL14 BL15 BL18 BL20 BL23 LU7 KI6 Ren4 SP6 He6 (Yanglao) KI7 LI11 8 treatments	n.50 ≥ 6 months post active breast cancer taking tamoxifen	Women's Health Questionnaire (WHQ) Hot Flashes and Night Sweats Questionnaire (HFNSQ)	significant statistical and clinical improvements. Anxiety/Fears Sleep Problems (p=0.0001) and Vasomotor Symptoms	De Valois, 2010

Single group, non-randomized, quasi-experimental	Acupuncture: a mean of 10 needles per session, points (38) dependent on the individual subject (with the most common points located in the Lung meridian)  Duration: 8 weeks	10 breast cancer patients	Pittsburgh Sleep Quality Index (PSQI)  Sleep Diary	increase on average sleep latency after treatment (from week 5 to 8, (p=.04); a decrease in the percentage of time awake after sleep onset from baseline to follow-up 2 (week 8) (p=0.05)	Otte, 2011
RCT 1) treatment group acupuncture 2) control group Fluoxetine	acupuncture ST40 SP9 SP10 SP6 Yintang (EX-HN3) DU20 Sishencong (EX-HN1) PC6 ear Shenmen (TF4) 1 time per day, for 20-30 min for 30 days	n.80 randomized (n.40 group 1, 40 group 2) Different types of cancer	Pittsburgh Sleep Quality Index (PSQI)	after treatment the PSQI score significantly lower than those of the control group (11.44 +/- 1.89, P < 0.01)	Feng, 2011
Multicentre randomized prospective study 1) electroacupuncture (EA) 2) hormone therapy (HT)	1)(EA) bilaterally BL15 BL23 BL32 – unilaterally GV20 Ht7 PC6 LR3 SP6 SP9 For 12 weeks 2) combined estrogen/ progestagen for 24 months	n.45 randomized n.44 evaluable (27 group 1, 18 group 2) breast cancer 30 completed treatment (19,11)	Women's Health Questionnaire (WHQ) Subscale sleep problems Sleep data in Log-books	At 12 weeks and 12 months all sleep parameters improved in both EA and HT groups	Frisk, 2012

### Conclusion of the literature and authors

The Guidelines of Filshie and Hester (2006) indicate specific conditions to take into consideration for the treatment of insomnia which does not respond to standard treatments with acupuncture.

There are studies with positive and promising results related to acupuncture and acupressure in the treatment of insomnia; however, the low number and especially the heterogeneity of the same studies do not permit to give conclusions. Further studies and especially high quality RCTs are needed.

SIO Guidelines (2009) do not attribute a grading for the treatment of insomnia. On the basis of the same criteria, the authors of T.N.I.M have evaluated that the adequate grading is 2C (weak recommendation, low or very low quality evidence)

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### *Insomnia and herbal medicine*

Among all the herbal medicines both studied and used in the treatment of insomnia are *Humulus lupulus*, *Hypericum perforatum*, *Lavandula angustifolia*, *Matricaria recutita*, *Passiflora incarnata* and *Valeriana officinalis*. The only one studied in cancer clinical trials is *Valeriana officinalis*.

#### **Valeriana officinalis**

*Valeriana officinalis* (VO) is a popular European herb used since the 17th century for its mild sedative and tranquilizing properties. The genus *Valeriana* comprises about 150 species, but only VO has been included in official Pharmacopoeias (Block KI. 2004).

VO was the most studied soporific herbal medicine, reflecting its rich folkloric tradition of use in restlessness, anxiety (see anxiety and depression paragraph), hysteria, nervous headache and mental depression via its active constituents valeranal, iso/valerianic acid and valerenic acid. The evidence concerning valerian is quite varied, and currently does not support its use in treating insomnia. Moreover, there are few studies on its efficacy in the treatment of insomnia-related cancer (See. Tab.1). These results are supported by systematic reviews and meta-analyses (Bent S. 2006, Taibi DM. 2007), Fernández-San-Martín MI. 2010). The Bent et al. review, which included 16 eligible RCTs on valerian and valerian in combination with other herbal medicines, found that 9 out of 16 studies did not have positive outcomes in regard to improvement of sleep quality; Taibi et al. review, which included 29 controlled studies, concluded that most studies found no significant difference between valerian and placebo. Valerian in combination with hops or kava appears also to not be firmly supported by the available data. Finally, Fernández-San-Martín et al. meta-analysis, which includes 8 eligible RCTs on valerian preparation compared with placebo, found that the mean differences in Latency Time and Sleep Quality Scale between the Valerian and placebo treatment groups was respectively 0.70 min (95% CI, -3.44 to 4.83) and -0.02 (95% CI, -0.35 to 0.31) concluding that VO would be effective for a subjective improvement of insomnia.

**Dosage:** The EMA suggests a single dose of 20 ml of liquid extract (1:6.3) or 40-75 drops of liquid extract (1:1) in a half glass of water or 500 mg dry extracts. Suggested dosages of fixed combination of VO/*Humulus lupulus* dry extracts are: 80 mg/20 mg - 160 mg/40 mg for 3 x 3 or 3 x 2 doses, 187 mg/45 mg up to 3 x 1 doses, 100 mg/30 mg for 2-3 doses, 250 mg/65 mg up to 3 x 1 doses, 125 mg/25 mg up to 3 x 2 doses, 175 mg/35 mg up to 6 doses, 100 mg (24 mg – 3 mg dry extracts) for 3 x 2 doses, 68 mg/16 mg for 3 x 3 doses, 225 mg/30 mg 3 x 3 doses and 77 mg/18.8 mg for 3 x 2 doses. For the insomnia treatment the doses was administrated 1h before bedtime. The use of these fixed combinations is not recommended in adolescents and children below the age of 18 years, due to lack of adequate data (EMA 2009).

**Side effects:** Gastrointestinal symptoms (e.g. nausea, abdominal cramps) may occur after ingestion of valerian root preparations. Safety during pregnancy and lactation has not been established. Pakseresht S (2011) in a randomized double-blinding clinical study on the effect of *Valeriana officinalis* vs. placebo in treatment of obsessive-compulsive disorder concludes that many patients cannot tolerate the side effects of VO.

**Drug interactions:** Clinically relevant interactions with drugs metabolized by the CYP 2D6, CYP 3A4/5, CYP 1A2 or CYP 2E1 pathways have not been observed. Combination with synthetic sedatives is not recommended. A study of Carrasco MC (2009) showed that the active principles of VO and *Passiflora incarnata* might increase the inhibitory activity of benzodiazepines binding to the GABA receptors, causing severe secondary effects.

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Multicenter, randomized, placebo-controlled, parallel-group study	I Group: VO+HL (respectively 187 and 41.9 mg) II Group: diphenhydramine (50 mg) for 14 days + placebo for 14 days III Group: Placebo Period: 28 days	184 adults with mild insomnia	Evaluate the efficacy and safety of a VO-HL combination and diphenhydramine for the treatment of mild insomnia Criteria: Sleep diary, ISI, CGI, SF-36 scale	The findings show a modest hypnotic effect for a valerian-hops combination and diphenhydramine relative to placebo. Sleep improvements with a VO-HL combination are associated with improved quality of life	Morin CM, 2005
Televised, Web-Based Randomised Trial	VO: 3 tablets containing 200 mg, 1 hour before bedtime Period: 14 days	405 participants from 18 to 75 years old who have suffered from insomnia for more than 1 month	Primary end point: minimally important improvement in self-reported sleep quality Criteria: PSQI, sleep diary	VO appears to be safe, but with modest beneficial effects at most on insomnia compared to placebo (p>0.05)	Oxman AD, 2007
Phase II randomized, double-blind, cross-over controlled trial	VO: 300 mg 30 minutes before bedtime Period: 2 weeks	16 old women with insomnia	Evaluate the effects of nightly VO extract to improve sleep of old women with insomnia Criteria: PSG	VO did not improve sleep in this sample of old women with insomnia. (p>0.05)	Oxman AD, 2007
Randomized, double blind, placebo-controlled, prospective clinical study	VO+HL: respectively 500 and 120 mg  Period: 4 weeks	43 patients	Demonstrate clinical efficacy of a fixed valerian hops extract combination (Ze 91019) in patients suffering from non-organic sleep disorder Criteria: Registration of the sleep parameter by a transportable home monitor system	VO and HL combination was significantly superior to the placebo in reducing the sleep latency whilst the single valerian extract failed to be superior to the placebo	Koetter U, 2007
Double blind, randomized, placebo-controlled sleep-EEG study in a parallel design using electrohypnograms	VO+HL: combination of 460 mg each extract 15 minutes before EEG recording during the medication night Period: 2 nights	42 healthy volunteers (30 to 70 years old, mean age of males 48.2 years, of females 50.2 years) with insomnia	Evaluate if a single administration can be an effective sleep aid Criteria: sleep questionnaire, electrohypnogram	The EEG derived parameter "sleep quantity" as calculated from the electrohypnogram proved superiority of the VO-HL combination over placebo. (p<0.0001)	Dimpfel W, 2008
Phase III randomized, placebo-controlled, double-blind study	VO: 450 mg of valerian 0.8% valerenic acid, 1 hour before bedtime Period: 8 weeks	227 patients diagnosed with cancer and receiving therapy	Evaluate the efficacy of a VO supplement for sleep in people with cancer undergoing cancer treatment Criteria: PSQI, FOSQ, BFI, POMS, CTCAE	Data did not show that VO, 450 mg, at bedtime could improve sleep as measured by the PSQI (p=0.696). Exploratory analyses revealed improvement in secondary outcomes,	Barton DL, 2011

Randomized, triple-blind, controlled trial	VO: 530 mg Period: 4 weeks	100 postmenopausal women aged 50 to 60 years with insomnia	Evaluate the effects of valerian extract taken nightly on the improvement of sleep quality in postmenopausal women experiencing insomnia Criteria: PSQI	such as fatigue (p=0.008) VO improves the quality of sleep in women with menopause with insomnia (p < 0.001)	Taavoni S. 2011
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Tab. 1. Single clinical studies on insomnia in adults. Legend: VO (*Valeriana officinalis* extract), BFI (Brief Fatigue Inventory), CTCAE (Common Criteria Terminology Criteria), CGI (Clinical Global Impression), FOSQ (Functional Outcomes of Sleep Questionnaire), HL (*Humulus lupulus extract*), ISI (Insomnia Severity Index), POMS (Profile of Mood States), PSG (Polysomnography), PSQI (Pittsburgh Sleep Quality Index), SF-36 scale (The Short Form-36 Health Survey).

### **Other herbal medicines**

Relatively few clinical trials have explored, but not in cancer patients, the sleep enhancing properties of other herbal agents with putative potential to relieve or prevent insomnia and improve overall sleep quality. These herbs include *Humulus lupulus*, *Hypericum perforatum* (see anxiety and depression paragraph), *Lavandula angustifolia*, *Matricaria recutita* and *Passiflora incarnata* (see anxiety and depression paragraph).

#### ***Humulus lupulus***

*Humulus lupulus* (HL) is a traditional herb used to relief mild symptoms of mental stress and aid sleep in combination with *Valeriana officinalis* (VO).

The current literature on the combined use of HL+VO suggests that there are inconsistent data of the combined treatment to identify specific protocols.

This is supported by some reviews and one RCT (Tab.1) that analyzed the use of VO-HL combination in the treatment of insomnia. Salter et al. (2010) review stresses that, in general, both valerian and hops are considered safe when consumed within the recommended dosage range (see *Valeriana officinalis*: suggested dosage of *Valeriana officinalis*-*Humulus lupulus* combination) and that adverse reactions to these herbs are rare. The authors included 4 eligible RCTs (Fussel A. 2000, Morin CM. 2005, Koetter U. 2007, Dimpfel W. 2008 see Tab.1) on VO-HL combination. Three of these studies found the combination to be effective in improving at least one of the sleep parameters measured, while the Morin's study does not report a significantly improved sleep for any of the parameters measured.

The EMA recommended dosages of HL are: 0.5-1.0 g dried inflorescences of comminuted herbal substance, 0.5-2.0 ml of liquid extract (1:1) prepared with ethanol/water 45% v/v, 1.25 g of herbal substance corresponding to liquid extract (1:10) prepared with sweet wine and 2.0-4.0 ml tincture (1:5) prepared with ethanol/water 60% v/v. To aid sleep, 1 to 2 single doses half to one hour before bedtime with an earlier dose during the evening, if necessary. The use is not recommended in children under 12 years of age and safety during pregnancy and lactation has not been established (EMEA 2008). To date no side effects to the use of HL is known. However, Wesolowska O. (2010) presented the first *in vitro* interaction of an HL extract constituent (8-prenylnaringenin) with a clinically important multidrug resistance-associated ABC transporters of cancer cells. More studies are needed to confirm this interaction.

#### ***Lavandula officinalis***

*Lavandula officinalis* essential oil (LEO) is used in aromatherapy as relaxant and, when inhaled, has been reported to have sedative effects in humans. (see anxiety and depression paragraph).

Some RCTs show the effectiveness of LEO in the treatment of insomnia. In a recent randomized study Chien LW et al. (2012) analyzed the effects of 12 weeks of lavender aromatherapy on self-reported sleep and heart rate variability (HRV) in 66 midlife women with insomnia. The experimental group (n = 34) received LEO inhalation, 20 min each time, twice per week, with a total of 24 times, while the control group (n = 33) received health education program for sleep hygiene with no intervention. The data shows that the LEO treatment is significant in the experimental group (P < 0.001), and that LEO inhalation may have a persistent short-term effect on HRV with an increase in parasympathetic modulation.

Similarly, Lewith GT et al. (2005) studied the effect of LEO, administered through aromastream, in patients with insomnia. This single-blinded, randomized pilot study, in agreement with the previous study, shows a statistically positive effect on the LEO group. But, given the low sample size and the different experimental designs, larger trials are required to draw definitive conclusions.

#### ***Matricaria recutita***

*Matricaria recutita* (MR), also known as Chamomile, is commonly used as infusions, tablets, or essential oils to promote relaxation and as a sleep aid. Despite the common use of MR to improve sleep, there is limited evidence of the sedative effect of this popular herb as only a few studies were found during the literature search. The very mild sedative effects of MR have been attributed to the flavonoid apigenin, which binds to benzodiazepine receptors.

Furthermore, an in-vitro study shows anti-cancer properties of methanolic extracts of chamomile against various human cancer cell lines through a significant decrease in cell viability (Srivastava JK. 2007).

MR extract is generally well-tolerated; however, there are several reports of some skin reactivity. This activity manifests primarily as contact dermatitis or positive results on patch tests, possibly due to the sesquiterpene lactone component, common in the daisy plant family (Compositae or Asteraceae). Allergic conjunctivitis can result from eye washing with chamomile tea. Allergic reactions on ingestion of chamomile

do not appear to be a significant problem. However, individuals with hay fever or hypersensitivity to pollens from other members of Asteraceae may cross-react to chamomile tea ingested internally.

### Summary table

Plant	Clinical indications	Grading	Dosage	Note
<i>Hypericum perforatum</i>	Mild to moderate depression and insomnia	1A	Dry extract: From 600 to 1800 mg of extract, titrated to 0.3-0.5% in hypericin	Be careful due to interactions with drugs
<i>Humulus lupulus</i>	mild symptoms of mental stress and insomnia	2B	In combination with <i>Valeriana officinalis</i> dry extract (see text)	
<i>Lavandula angustifolia</i>	Generalized anxiety disorder and insomnia	2B	cps: 80 mg/day Inhalation: final solution 1-2% Massage: final solution 1% (1:2) Essential lavender oil in water into an ultrasonic ionizer aromatherapy diffuser	
<i>Matricaria recutita</i>	Insomnia	T		
<i>Passiflora incarnata</i>	Depression, anxiety and insomnia	T	Dry extract: 1-2 g (1-3 times daily)	
<i>Valeriana officinalis</i>	Anxiety, hysteria, nervous headache, mental depression and insomnia	2B	20 ml of liquid extract, 40-75 drops of liquid extract, 500 mg dry extracts	

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### *Insomnia and homeopathy*

There are not specific studies on insomnia related to cancer treated with homeopathy, but some interesting researches on insomnia and homeopathy have been conducted.

Bell Ir. et al. (2010) used polysomnography as a modern methodology for evaluating the objective effects of taking homeopathic remedies that clinicians claim exert effects on sleep quality in susceptible individuals. Animal studies have previously shown changes in non rapid eye movement sleep with certain homeopathic remedies.

In the study young adults of both sexes (age 18-31) with above-average scores on standardized personality scales for either cynical hostility or anxiety sensitivity (but not both) and a history of coffee-induced insomnia participated in the month-long study. At-home polysomnographic recordings were obtained on successive pairs of nights once per week for a total of eight recordings. Subjects (N=54) received placebo pellets on night 8 (single-blind) and verum pellets on night 22 (double-blind) in 30 CH doses of one of two homeopathic remedies, Nux vomica or Coffea cruda. Subjects completed daily morning sleep diaries and weekly Pittsburgh sleep quality index scales, as well as profile of mood states scales at bedtime on polysomnography nights.

Verum remedies significantly increased PSG total sleep time and NREM, as well as awakenings and stage changes. Changes in actigraphic and self-rated scale effects were not significant.

Brooks AJ et al. (2012) used 2 different homeopathic remedies, Nux vomica (NV) and Coffea cruda (CC), studying the effects on subjective mood ratings in healthy adults with a history of coffee-induced insomnia. The impact of individual personality traits, anxiety sensitivity or Type A cynical hostility, and homeopathic constitutional type (HTYPE-NV, HTYPE-CC), on remedy effects was examined to evaluate differential responsiveness, in accord with clinical claims.

Young adults of both sexes (ages 18-31) with above-average scores on standardized personality scales for either cynical hostility or anxiety sensitivity, and a history of coffee-induced insomnia, participated in the month-long study. At-home polysomnographic recordings were obtained on successive pairs of nights once per week for a total of 8 recordings. Subjects (N = 59) received placebo pellets on night 8 (single-blind) and verum pellets in 30c doses of one of two homeopathic remedies, NV or CC, on night 22 (double blind). Subjects completed the Profile of Mood States Scales at bedtime.

Naudé DF and al. (2010) treated chronic primary insomnia defined as difficulty in initiating or maintaining sleep or of non-restorative sleep that lasts for at least 1 month and causes significant distress or impairment in social, occupational or other important areas of functioning. They used the homeopathic simillimum that is that remedy which most closely corresponds to the totality of symptoms; remedy selection is based on a full evaluation of the patient's physical, emotional and mental characteristics. The purpose of this randomised, double-blind, placebo-controlled study was to evaluate the efficacy of homeopathic simillimum in the treatment of chronic primary insomnia.

Thirty participants affected by primary insomnia were selected in accordance with DSM-IV TR (2000) and then randomly divided between treatment and placebo groups. The measurement tools used were a Sleep Diary (SD) and the Sleep Impairment Index (SII). (2) After an initial consultation, 2 follow-up consultations at 2-week intervals took place. Homeopathic medication was prescribed at the first and second consultations. The SII was completed at each consultation and participants were instructed at the first consultation to start the SD.

Type of study	Therapeutic protocol	N. patients and disease	End points criteria	Results	Author, year
Randomised, double-blind, placebo-controlled study	Nux vomica (NV) and Coffea cruda (CC)	Healthy adults with a history of coffee-induced insomnia	The impact of individual personality traits, anxiety sensitivity or Type A cynical hostility, and homeopathic constitutional type (HTYPE-NV, HTYPE-CC), on remedy effects was examined to evaluate differential responsivity, in accord with clinical claims	The remedies produced differential effects on anger and overall mood, with improved mood following CC administration. A similar trend for depression was observed. Anxiety sensitive subjects experienced less tension following CC, whereas hostile subjects receiving CC became tenser. The high HTYPE-CC receiving CC experienced less vigor. The high HTYPE-CC receiving NV experienced more vigor	Brooks AJ, 2010
Randomised, double-blind, placebo-controlled study	54 subjects received placebo pellets on night 8 (single-blind) and verum pellets on night 22 (double-blind) in 30CH doses of one of two homeopathic remedies, Nux vomica or Coffea cruda	54 patients, young adults with histories of coffee-related insomnia	At-home polysomnographic recordings were obtained on successive pairs of nights once per week for a total of eight recordings	Verum remedies significantly increased PSG total sleep time and NREM, as well as awakenings and stage changes. Changes in actigraphic and self-rated scale effects were not significant	Bell IR, 2010
Randomised, double-blind, placebo-controlled study	Homeopathic simillimum	Chronic primary insomnia	Measurement tools: a Sleep Diary (SD) and the Sleep Impairment Index (SII).	The homeopathic simillimum treatment of primary insomnia was effective, compared to placebo.	Naudé DF, 2010

### **Conclusions of the literature and authors**

The studies demonstrated the feasibility of using in-home, all-night sleep recordings to study homeopathic remedy effects. Findings are similar though not identical to those reported in animals with the same remedies. Possible mechanisms include initial disruption of the nonlinear dynamics of sleep patterns by the verum remedies.

SD data revealed that verum treatment resulted in a significant increase in duration of sleep throughout the study, compared to the placebo treatment which resulted in no significant increase in duration of sleep. A significant improvement in SII summary scores and number of improved individual questions were found in the verum group, responses to all the eleven questions having improved significantly upon completion of the study. An initial improvement occurred in the placebo group, but was not sustained. Comparison of results between the groups revealed a statistically significant difference.

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## Leukopenia

### *Leukopenia, Neutropenia and acupuncture/TCM*

Lu et al. (2007) reviewed published RCTs of acupuncture's effect and explored the acupuncture parameters applied in these trials, searching biomedical databases in English and Chinese from 1979 to 2004. The populations of the studies were cancer patients who were undergoing or had just completed chemotherapy or chemo-radiotherapy, randomized to either acupuncture therapy or usual care. The methodological quality of trials was assessed. From 33 reviewed articles, 682 patients (421 in the study arms and 261 in the control arms) from 11 eligible trials were included in the analysis.

All trials were published in non-PubMed journals from China. The methodological quality of these trials was considerably poor (they were randomized but none of them used blinding or sham acupuncture as control). The median sample size of each comparison group was 45, and the median trial duration was 21 days. Various methods were used in these trials: manual acupuncture (n 5), EA (n. 1), warming needle (n. 2), acupuncture point injection with saline (in 1). Frequency of acupuncture treatment was once a day, with a median of 16 sessions in each trial and points used (from 1 to 10 and more). In 7 trials in which white blood cell (WBC) counts were available, acupuncture was associated with an increase in leukocytes in patients during chemotherapy or chemo-radiotherapy, with a weighted mean difference of 1,221 WBC/microL on average (95% confidence interval 636-1,807;  $p < .0001$ ).

In a RCT Zhao et al. (2007 – article in Chinese) randomized patients with post chemotherapy leucopenia: 113 subjects were treated with indirect moxibustion (ginger-partitioned) and 108 with oral Chinese patent medicine. After 10 and 25 days, the leukopenia had significantly improved more in the moxibustion group compared to the control group ( $P < 0.01$ ) but there was an improvement in both groups. There were no side effects resulting from either of the two therapies.

Lu et al. (2009) carried out a pilot randomized controlled study on 21 patients with post chemotherapy leukopenia, in treatment for ovarian cancer. Acupuncture seems to have had a myeloprotective effect (there was an increase in the white blood cell count) in comparison to sham acupuncture ( $p = 0.046$ ).

Han et al. (2010 - article in Chinese) carried out a randomized control study on 86 patients with leukopenia from chemotherapy. All the patients were treated with a granulocyte colony-stimulating factor (G-CSF) and one group was also treated with acupuncture. After 10, 17 e 24 days, the leukocyte count was higher in the acupuncture group than in the control group ( $P < 0.05$ ). The conclusion of the authors is that acupuncture can improve leukopenia caused by chemotherapy.

### Single clinical studies on leukopenia in adults

Type of Study	Therapeutic Protocol	N. patients and disease	Endpoints criteria	Results	Author, year
RCT 1) moxibustion 2) oral administration of Chinese patent medicine	1) ginger-partitioned moxibustion at GV14 BL17 BL20 and other points not specified  2) oral administration of Chinese patent medicine  10, 15 days	n.221 (n.113 group 1, 108 group 2)  After chemotherapy treatment	white blood cell (WBC) count absolute neutrophil count (ANC)	significant differences between the two groups (both $P < 0.01$ )  (84.1% and 66.4% in the group 1 and 35.2% and 33.3% in the group 2).	Zhao, 2007
Pilot, RCT  1) active acupuncture 2) sham acupuncture	1) active acupuncture LR3 K3 SP6 ST36 SP10 LI4 PC6 LI11 GV20 depth needle 10 mm. 2) sham acupuncture In 7 pre-defined sham needling sites away from regular acupuncture points. depth needle 0.2mm 10 sessions of acupuncture, 2–3 times per week beginning 1 week prior to cycle 2 of chemotherapy and ending at the beginning of cycle 3 of chemotherapy	n.21 randomized (11 group 1, 10 group 2)  ovarian cancer	white blood cell (WBC) count, absolute neutrophil count (ANC)  plasma granulocyte colony-stimulating factor (G-CSF) weekly	median leukocyte value in the acupuncture significantly higher than in the group 2 ( $p=0.046$ ).  ANC higher but not statistically significantly different ( $p=0.116-0.16$ )  no statistically significant differences in plasma G-CSF between the 2 groups	Lu, 2009
RCT  1) granulocyte colony-stimulating factor (G-CSF) + acupuncture  2) granulocyte colony-stimulating factor (G-CSF)	1) acupuncture TE6, LI11 LI4 and other points not specified + G-CSF 2) G-CSF	n.86 randomized (43 group 1, 43 group 2) after chemotherapy treatment	WBC counts  ratios of mature neutrophilic granulocyte	WBC counts in group 1 were higher on the 10 <sup>th</sup> , 17 <sup>th</sup> and 24 <sup>th</sup> day after treatment (all $P < 0.05$ ).  the ratios of mature neutrophilic granulocyte in group 1 were all higher than those in the group 2 at the same time (all $P < 0.01$ )	Han, 2009

### **Conclusions of the literature and the authors**

In the literature there were few studies in PubMed and not of high quality about the effect of acupuncture on leukopenia. Nevertheless, all the studies reported in our research demonstrate an increase in leucocytes in patients who had been treated with chemo or radiotherapy, as confirmed in the present clinical practice.

SIO Guidelines (2009) do not attribute a grading for the treatment of leukopenia.

On the basis of the same criteria the authors of T.N.I.M have evaluated that the adequate grading is 2C (weak recommendation, low or very low quality evidence).

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### *Neutropenia and anthroposophic medicine*

The first paper describing the use of mistletoe extracts to improve the neutrophil count in hemato-oncological patients and in chemotherapy-induced neutropenia was published by Mathé et al. in 1963. A pure stimulation of neutrophils was observed administering intravenously a polysaccharide extract from the mistletoe plant. Since then, *Viscum album* L. extracts have shown *in vitro*, in animals and in humans relevant properties to stimulate the number and activity of neutrophils and the repair of bone marrow after damage. That makes them an interesting tool for myeloprotection during conventional anti-cancer treatments. The literature gives evidence that *Viscum album* extracts can reduce the side effects of chemo- and radiotherapy and that a reduction of neutropenia can contribute to reduce toxicity and to enhance the tolerability of conventional treatments.

A prospective randomized open label pilot study was conducted on 95 patients with early breast cancer, with the objective to determine the clinical response (quality of life including fatigue) and, specifically, neutropenia. The pilot study showed that mistletoe extracts may prevent neutropenia induced by polichemotherapy (CAF) (Tröger et al. 2009). The patients were allocated in 3 groups, receiving 6 cycles of CAF (cyclofosfamide, 5FU, adriamycin). Two of the groups received an additional treatment with *Viscum album* extracts. Neutropenia was defined as neutrophil counts  $<1,000/\mu\text{l}$  and assessed at baseline and one day before each CAF cycle. The study compared one of the groups, that received a combination of chemotherapy and a *Viscum album* extract (Iscador® M special, sc. 0.01 – 5 mg, 3 times weekly), and the control group, that received chemotherapy alone. Neutropenia occurred in 3/30 of the mistletoe treated patients and in 8/31 of control patients ( $p = 0.182$ ). Odds ratio for the proportion of patients with neutropenia in the mistletoe group versus the control group was 0.32 (95% confidence interval 0.08–1.35). The patients received mistletoe therapy only during chemotherapy. No negative influence of the additional mistletoe therapy on the effectiveness of chemotherapy of the patients in the study was detected, referring to the frequency of relapse or metastasis within 5 years (Tröger et al. 2013).

A similar protective effect against chemo-induced neutropenia is suggested by another study (Mansky et al. 2013). The two stage, dose escalation phase I clinical trial was designed to observe the safety of the combination of gemcitabine and a subcutaneously injected mistletoe extract in a 44 patients with advanced solid cancers and limited treatment options, many of whom were heavily pretreated. Twenty patients were treated in stage I (mistletoe dose escalation phase, Helixor® A 1-20, 1-50, 1-100, 1-200, and 1-250 mg s.c. daily, respectively) and 24 in stage II (gemcitabine dose escalation phase, 900-1680 mg/m<sup>2</sup>).

The combination of mistletoe and gemcitabine was well tolerated and treatment compliance was high. The MTD (maximal tolerated dose) was gemcitabine 1380 mg/m<sup>2</sup> weekly on day one and eight of a 3-week cycle combined with mistletoe 250 mg daily. The administration of mistletoe up to high dosages was safe, compliance was good and gemcitabine pharmacokinetics were not affected by the combination.

A mistletoe dose-dependent trend towards increased absolute neutrophil count nadir during cycle 1 and a maximum absolute neutrophil count during cycle 2 were observed. No episode of febrile neutropenia was observed in any of the 44 patients, even at the highest gemcitabine dose of 1650 mg/m<sup>2</sup>. A remarkable absence of episodes of febrile neutropenia even at high gemcitabine dosage deserves to be confirmed in a larger, more homogenous cancer population. Nevertheless, the lack of febrile neutropenia in a set of heavily pretreated patients, of whom almost 50% received gemcitabine doses of 1100 mg/m<sup>2</sup> or higher, is noteworthy.

In a randomised phase II study investigating the combination of a *Viscum album* extracts (Iscador®) with carboplatin-containing regimens (Bar Sela et al. 2013) in chemotherapy-naive patients with non small cell lung carcinoma, the rate of grade 3-4 haematological toxicities was 42% in the mistletoe arm, compared to 49% in the control arm, without statistical significance ( $p = 0.07$ ), and patients in the mistletoe arm needed less chemotherapy dose reductions ( $p = 0,005$ ) and less hospitalisation ( $p = 0,02$ ).

A reduction of leucopenia during conventional treatments was shown also in retrospective comparative epidemiological cohort studies on pancreatic cancer (Stauder et al. 2009; Matthes et al. 2010). In a multicenter, controlled, retrospective, observational cohort study (Matthes et al. 2010) with parallel groups conducted in Germany on 396 patients with histologically verified pancreatic tumor, treated with adjuvant gemcitabine after complete macroscopical resection, 201 received additional mistletoe therapy (Iscador® Qu) and 195 represented the control group. Within the gemcitabine/viscum group significantly fewer patients than in the overall control group experienced tumor-associated symptoms or cytotoxic drug related adverse reactions (incidence 13.7% versus 48.9%); particularly, among other common adverse drug reactions, leucopenia and fever/infections were remarkably lower. The results were confirmed in a subgroup analysis (Stauder et al. 2009) that evaluated a sub-total of 270 patients, of whom 75 had received additional mistletoe

therapy with Iscador® Qu. Among the patients treated with chemotherapy (gemcitabine, 5FU, combinations) and/or radio-therapy, the patients who had received additional Iscador showed significantly fewer adjuvant therapy induced adverse drug reactions, especially leucopenia and infections, than the control group: 8,3% versus 46,7%,  $p < 0,001$ .

Stimulatory effects of mistletoe on neutrophils and lymphocytes have been reported *in vitro*, in animal experiments as well as in patients (review in Büssing Ed. 2000 and Kienle et al. 2003). Neutrophils count is not only relevant to reduce aggressive treatments' damages. Convincing evidence has accumulated showing that they can play a role in the resistance to tumor growth and metastasis (Hajto 1986).

A single intravenous infusion of a *Viscum album* extract (Iscador® M 2%) in patients with breast cancer increased number and activity of neutrophils in the following 48 hours (Hajto 1986), among other immunomodulating activities.

According to several studies *Viscum album* extracts and their components can positively stimulate neutrophils (e.g. Hajto 1986ab; Hajto et al. 1986, 1989, 1996; Kovacs et al. 1991; Henn 1995; Kühn et al. 1996; Büssing et al. 2004, 2008, 2009; Burkhardt et al. 2010). Mistletoe extracts have been shown to provide DNA-stabilizing effects in human peripheral blood mononuclear cells (PBMC) *in vitro*. The stimulating and protective effects on PBMC of healthy blood donors were shown *in vitro ex vivo*, assessing mitochondrial activity and replication in healthy PBMC and malignant cell lines.

Mistletoe extract strongly stimulated healthy PBMC but not malignant Jurkat cells. In addition, mistletoe extract seemed to partially protect selectively healthy PBMC, but not the malignant cells, from the cytostatic effect of 4-hydroperoxycyclophosphamide. Mistletoe extracts may exert a DNA-protective effect in normal PBMC. This effect could be due to DNA stabilization, to enhancement of DNA repair, or to other so far undefined mechanisms. The mistletoe effects on PBMC cannot be attributed to single components, as it has been seen in experiments both with isolated lectins and with non-lectin components or lectin-poor VAE (Stein et al. 1994,1998; Hajto et al. 2006; Lyu et al. 2006; Burkhardt et al. 2010).

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## Mucositis

### *Mucositis and herbal medicine*

In the mucositis treatment several herbal medicines are traditionally used: *Aloe barbadensis*, *Rhodiola algida*, *Rosa damascena* and *Krameria triandra*. Among the medicinal plants listed, only *Aloe barbadensis* and *Rhodiola algida* have been studied in mucositis with human clinical trials while *Rosa damascena* has been studied in recurrent aphthous stomatitis. *Krameria triandra* has been studied before 2003 and reported in the treatment of mouth and pharynx inflammation.

### **Aloe barbadensis**

*Aloe barbadensis* (AB), also known as *Aloe vera*, has been used for many centuries for its therapeutic properties. Although over 75 active ingredients from the inner gel have been identified, therapeutic effects have not been correlated well with each individual component. Many of the medicinal effects of aloe leaf extracts have been attributed to the polysaccharides found in the inner leaf parenchymatous tissue, but it is believed that these biological activities should be assigned to a synergistic action of the compounds rather than a single chemical substance.

There are two forms of extracts with different composition and pharmacological properties: the dry juice, rich in anthraquinones obtained from external tubules beneath the epidermis of the leaf and the gel obtained from the central parenchyma, free of anthraquinones and rich in water, lecithin, polysaccharides, amino acids, vitamins, enzymes, growth factors, organic acids, and vitamins (Firenzuoli F. 2009).

Many compounds with diverse structures have been isolated from both the central parenchyma tissue of AB leaves and the exudate. The dry juice contains 1,8-dihydroxyanthraquinone derivatives and their glycosides which are mainly used for their cathartic effects, while, many researchers, have identified partially acetylated mannan (or acemannan) as the primary polysaccharide of the gel. This is used for its anti-diabetic, immunomodulatory, anti-inflammatory, anti-oxidant, wound healing, anti-cancer, skin hydration and antimicrobial effects (Hamman JH. 2008).

The dry juice of the leaves of AB contains not less than 28% of these derivatives, expressed as barbaloin (aloin A and B) and calculated with reference to the dried herbal substance (EMEA 2006).

Several studies revealed the anti-inflammatory, analgesic, liver protection, antiproliferative, anticarcinogenic and antiaging properties of AB; some of them attribute these effects to antioxidant properties, cyclooxygenase-2 suppression and immunomodulatory mechanisms (Hamman JH. 2008).

A last study of Cochrane Oral Health Group (Worthington HV. 2011) about the prevention of oral mucositis in patients with cancer receiving treatment identified 10 interventions that seem to have some benefit in preventing or reducing the severity of mucositis associated with cancer treatment. However, the strength of the evidence is variable and the benefits may be specific for certain cancer types and treatment. The authors conclude that there is a need for further well designed, and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent. Similarly, a review (Amirossein A. 2012) shows that the results about the efficacy of AB used in mucositis are inconsistent (See Tab.1).

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Phase II double-blind randomized trial	AB group: 20mL of AB solution (94.5% aloe juice, 5.0% pear juice concentrate, 0.4% lemon-lime flavor, and 0.1% citric acid) 4 times a day	58 head-and-neck cancer patients	Evaluation of oral AB in preventing radiation-related mucositis in patients with head-and-neck neoplasms	Oral AB did not improve tolerance to head-and-neck radiotherapy, decrease mucositis, reduce soreness, nor improve patient well-being	Su CK, 2004
Randomized double-blind trial	AB: 1.2 ml (70% concentration)  Period: a) 6 weeks b) 12 weeks	64 patients with oral lichen planus	Efficacy of topical AB in patients with or. Lichen planus  Criteria: OHIP-49 HAD	In the AB group, complete pain remission was achieved in 31.2% of cases after 6 weeks, and in 61% after 12 weeks;in	Salazar-Sánchez N. 2010

				the placebo group were 17.2% and 41.6%, respectively	
Double-blind (case control) clinical trial	AB: 2% oral gel  Period: 10 days	40 patients with oral minor aphthous lesions	Evaluation of therapeutic effects of AB gel on minor recurrent aphthous stomatitis  Criteria: VAS	AB 2% oral gel is not only effective in decreasing the recurrent aphthous stomatitis patients' pain score and wound size but also decreases the aphthous wound healing period ( $p \leq 0.05$ )	Babae N. 2012

Tab.1. Single clinical studies on *Aloe barbadensis* in adults. Legend: AB (*Aloe barbadensis*), OHIP-49 (Oral Health Impact Profile 49), HAD (Hospital Anxiety-Depression scale), VAS (Visual Analogue Scale).

In a preclinical study on the effectiveness of AB versus dexpanthenol, Dörr W et al. (2005) show that with single irradiation dose in mouse, neither dexpanthenol nor AB extract significantly changed the oral mucosal radiation response. However, with fractionated irradiation, drug administration significantly increased the isoeffective radiation doses, independent of dexpanthenol or AB content.

The authors have induced a tongue mucosal ulceration through graded single or fractionated irradiation dose and have treated the lesions with topical administration of dexpanthenol or a base, with or without AB extract for 14 or 24 days.

In a single dose irradiation none of the formulations yields a significant change in incidence or time course of ulceration, while in base treatment the latent time to ulceration is prolonged, compared to the control (6.3 days) without AB (8.0-8.2 days,  $p < 0.001$ ) and with dexpanthenol and AB (7.3 days,  $p = 0.0239$ ) (Dörr W. 2005).

Hamman JH (2008) in a review claims that differences in plant composition have contributed to discrepancies in the results obtained from many studies. This difference is due to geographic location as well as differences in gel extraction methods and sample preparation techniques.

**Dosage:** The use of Aloe gel free of aloin, titrated in polysaccharides, or pure polysaccharides (acemannan) 200-400 mg per dose is recommended (Firenzuoli F. 2009). AB gel is often used liberally on the skin. There are no available reports of systemic absorption leading to clinically relevant evidence; the topical use in children is common well tolerated. Avoid if known allergy to plant of the Liliaceae family (Ulbricht C. 2007).

**Side effects:** No specific toxicity was observed in mice when aloe extract was orally administered up to 50 mg/kg daily for 12 weeks and aloin was orally administered up to 60 mg/kg daily for 20 weeks. (EMEA 2006). In humans, recently, some cases of aloe-induced hepatotoxicity have been reported. Yang NH et al. (2010) report 3 cases of aloe-induced toxic hepatitis. Three women (57, 62, and 55 years-old) were hospitalized for acute hepatitis.

The patients have taken respectively aloe tablets containing 250 mg of an extract of *Aloe arborescens* and 28.5 mg of an extract of *Aloe vera* for about 6 months, aloe powder containing 420 mg of an extract of AB for about 3 months and aloe extracts for about 5 months before hospitalization. Upon discontinuation of the oral aloe preparations, liver enzymes returned to normal level.

Also, after prolonged use of topical aloe gel, urticaria, contact dermatitis and widespread dermatitis have been reported (EMEA 2006).

**Drug interactions:** The data on drug interactions of AB with other medications are inconsistent, although, it is not recommended to combine oral AB with oral hypoglycemic agents, laxatives, non-potassium sparing diuretics, oral corticosteroids and oral hydrocortisone, sevoflurane, thyroid hormones, azidothymidine. (Ulbricht C. 2007).

### **Rhodiola algida**

*Rhodiola algida* (RA) is widely used in traditional Chinese medicine to stimulate the immune system. In-depth studies about the dosage, safety and drug interactions have not been conducted. This medicinal plant is poorly researched, only two articles have been published in the last 10 years; a preclinical study on its immune system stimulant property (Li HX. 2009) and a clinical trial on its action in mucositis treatment (Loo WT. 2010).

Between 2006 and 2007, Loo WT et al. enlisted 130 breast cancer patients who received 4 cycles of 5-fluorouracil, epirubicin and cyclophosphamide after modified total mastectomy. These patients were randomly assigned to test and control groups. RA mixture was consumed by the test group for 14 consecutive days after each cycle of chemotherapy. All patients were given 0.2% chlorohexidine mouth wash to be used every day. Complete blood counts, liver and renal function tests together with the number and size of oral ulcerations were analyzed after each cycle. Weight loss, complaints of nausea or vomiting and degree of pain were noted.

The data show that RA increases immunity of patients receiving chemotherapy post mastectomy thus favoring the proliferation of lymphocytes and decreasing the quantity of oral ulcers ( $p < 0.05$ ) (Loo WT. 2010).

### **Rosa damascena**

*Rosa damascena* mill L (RD) is one of the most important species of Rosaceae family. The therapeutic effects of RD in ancient medicine include abdominal and chest pain, strengthening the heart, menstrual bleeding, digestive problems, and reduction of inflammation, especially of the neck. North American Indian tribes used a decoction of the root of *R. damascena* to ease children's cough. This plant is also used as a gentle laxative. Some data suggest that RD oil is active in depression, grief, nervous stress and tension. Vapour therapy of rose oil is helpful for some allergies, headaches, and migraine (Hongratanaworakit T. 2009). The major products are Rose water, Rose oil and dried flowers.

The medicinal functions of Rosaceae in general and of RD in particular, are partly attributed to their abundance of phenolic compounds. Phenolics possess a wide range of pharmacological activities, such as antioxidant, free-radical scavengers, anticancer, anti-inflammatory, antimutagenic, and antidepressant (Boskabady MH. 2011).

So far, there are no information about dose and timing of administration and adverse effects or drug interactions.

In a randomized, double-blind, placebo-controlled trial, Hoseinpour H. et al. (2011) studied the effect of *Rosa damascena*, in the treatment of recurrent aphthous stomatitis. Fifty patients were enrolled in this 2-week study; the clinical efficacy of the mouthwash on pain, size, and number of ulcers in the test group was compared with that of the placebo group on days 4, 7, 11, and 14. The data suggest a significant difference on days 4 and 7 between the placebo and test groups in the treatment of recurrent aphthous stomatitis.

Finally, mucositis-related inflammation may have complications such as oral microbial infections. Oral fungal infections, caused predominantly by *Candida* species, are common in cancer patients at all stages of the disease, especially those receiving palliative care.

*Candida albicans* is known to form complex biofilms form on the oral epithelium or on the surfaces of intra-oral prostheses, and can result in pseudomembranous or erythematous candidosis.

*Melaleuca alternifolia* is a shrub that grows in New South Wales, Australia. From the distillation of its leaves the essential oil known as Tea Tree Oil (TTO) is extracted. TTO has recently reported to have minimal impact on developing resistance (Hammer 2012).

Moreover, it is best known for its antimicrobial activity against a wide spectrum of microorganisms, such as bacteria, fungi. TTO also has potent activity against many fungi, including some azole-resistant yeasts (Mondello et al., 2003; Bagg et al., 2006); there is some evidence of efficacy in treating fluconazole refractory oral candidosis in AIDS patients (Ramage G. 2012).

To date, despite numerous TTO-based products marketed and the traditional use, the TTO has not been studied in the treatment of mucositis in cancer patients. However an interesting study (Bagg J. 2006), has investigated 301 yeasts isolated from the mouths of 199 patients suffering from advanced cancer. The samples were examined by *in vitro* agar dilution assay for susceptibility to TTO. All of the isolates tested were susceptible, including 41 that were known to be resistant to both fluconazole and itraconazole. Clinical studies of TTO as an agent for the prevention and treatment of oral fungal infections in immune-compromised patients merit consideration.

## Krameria triandra

*Krameria triandra* (KT), also known as Rhatany, is traditionally used in the treatment of mucosal affections but no recent studies have been conducted since 2003 to support the use in this area. The medicinal part is the air-dried root, separated from the rhizome. The major active components are tannins, phlophaphenes and neolignans. In vitro the drug is antimicrobial, fungitoxic and astringent. Because of the tannin and lignan content, local treatment of oral and pharyngeal mucous membrane inflammation seems reasonable. The herbal drug is administered as comminuted herb for decoctions and other galenic preparations for topical application, especially in oral and pharyngeal areas. The usual daily dosage is about 1 gr of comminuted drug in 1 cup of water as decoction or 5 to 10 drops of KT tincture in 1 glass of water, 2 to 3 times daily.

No side effects are known in conjunction with the proper administration of designated therapeutic dosages. Internal administration can lead to digestive complaints because of the secretion-inhibiting efficacy. Rare cases of allergic mucous membrane reactions have been observed (Gruenwald J, 2004).

A non-randomized clinical study, single-arm, on the administration of natural products based KT in the treatment of the oral cavity (P. Tiemann 2006) has evaluated 32 female patients with breast cancer starting on chemotherapy. Plaque index, gingival index, degree of mucositis and 10 single symptoms were monitored once weekly for 4 consecutive weeks. Afterwards, plaque and gingival indexes were slightly decreased compared to baseline values. The degree of mucositis was increased by 1 grade in 15.6% while over 70% remained without symptoms. Overall, the individual symptoms are decreased from the seventh day of chemotherapy until the day 28. These data need to be confirmed by well-designed RCTs.

### Summary table

Plant	Clinical indications	Grading	Dosage
<i>Aloe barbadensis</i>	Treatment and prevention of chemotherapy side effects	1B	Aloin-free aloe gel, titrated in polysaccharides, or pure polysaccharides (acemannan) 200-400 mg per dose
<i>Rhodiola algida</i>	Stimulation of the immune-system	1B	Dosage and timing of administration are not standardized
<i>Rosa damascena</i>	Abdominal and chest pain, strengthening the heart, treatment of menstrual bleeding and digestive problems, and reduction of inflammation, especially of the neck	2B	Dosage and timing of administration are not standardized
<i>Krameria triandra</i>	Treatment of mucosal affections especially in oral and pharyngeal areas	2B	1 gr of comminuted drug in 1 cup of water as decoction or 5 to 10 drops of KT tincture in 1 glass of water, 2 to 3 times daily

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### *Mucositis and homotoxicology*

In a study (Oberbaum M. 2001) the authors assessed the efficacy of a homeopathic remedy (Traumeel) in the management of chemotherapy-induced stomatitis in children undergoing bone marrow transplantation.

A randomized, placebo-controlled, double-blind clinical trial was conducted in 32 patients (age 3-25 years) who had undergone allogeneic (16 patients) or autologous (16 patients) stem cell transplantation. Of the 30 evaluable patients, 15 were assigned placebo, and 15 were assigned Traumeel both as a mouth rinse, administered five times daily from 2 days after transplantation for a minimum of 14 days, or until at least 2 days after all signs of stomatitis were absent. Stomatitis scores were evaluated according to the World Health Organization grading system for mucositis. A total of five patients (33%) in the Traumeel treatment group did not develop stomatitis compared with only one patient (7%) in the placebo group. Stomatitis worsened in only 7 patients (47%) in the Traumeel treatment group compared with 14 patients (93%) in the placebo group. The mean area under the curve stomatitis scores were 10.4 in the Traumeel treatment group and 24.3 in the placebo group. This difference was statistically significant ( $p < 0.01$ ).

Type of study	Therapeutic protocol	N. patients and disease	End points criteria	Results	Author (Year)
Randomized, placebo-controlled, double-blind trial	Mouth rinse 5 times a day.  2 days after transplantation for a minimum of 14 days	32 patients (3-25 years) who had undergone allogeneic (16 patients) or autologous (16 patients) stem cell transplantation	Stomatitis scores evaluated according to the WHO on grading system for mucositis	Traumeel may reduce significantly severity and duration of chemotherapy-induced stomatitis in children undergoing bone marrow transplantation ( $p < 0.01$ ).	Oberbaum M, 2001

**\*Traumeel: Oral drops:** contains: medicinal ingredients: Arnica montana D2 5 g; Calendula officinalis D2 5 g; Hamamelis virginiana D2 5 g; Bellis perennis D2 2 g; Echinacea D2 2 g; Echinacea purpurea D2 2 g; Aconitum napellus D3 10 g; Hypericum perforatum D2 1 g; Chamomilla D3 8 g; Millefolium D3 5 g; Belladonna D4 25 g; Mercurius solubilis Hahnemanni D8 10 g; Hepar sulfuris calcareum D8 10 g; Symphytum officinale D8 8 g. Non-medicinal ingredients: ethanol, purified water

### **Conclusions of the literature and authors**

The study indicates that Traumeel may reduce significantly the severity and duration of chemotherapy-induced stomatitis in children undergoing bone marrow transplantation.

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### *Mucositis and anthroposophic medicine*

Mucositis can be a relevant adverse effect of chemotherapy, radiotherapy and targeted therapies, such as mTOR inhibitors and tyrosine kinase inhibitors. However often self-limiting, mucositis can cause pain, distress, impaired nutrition and debilitation. It can become a severe problem for the patient population receiving high-dose head and neck radiation therapy (85%-100%), stem cell transplantation (75%-100%), and myelosuppressive chemotherapy for solid tumors (5%-40%) and calls constantly for new management strategies (Peterson 2006). There is some evidence that e.g. oral hygiene (Quinn 2013) and the administration of K-CSF / GM-CSF can result in prevention and/or clinical improvement but not without toxicities (Chiapelli et al. 2005; Raber-Durlacher et al. 2013).

Among the studies investigating the influence on quality of life of the *Viscum album* L. extracts during conventional treatment (Kienle et al. 2010), Beuth et al. (2008) showed a reduction of mucositis symptoms. A multicenter comparative epidemiological cohort study was designed to investigate the impact of complementary treatment with a mistletoe extract (Helixor® M, A, P) on the quality of life of breast cancer patients during a defined aftercare period of approximately 5 years. 761 case reports from 53 German centres were examined. Mucositis was less frequent in the mistletoe treated patients (Beuth et al. 2008).

A reduced incidence of mucositis during conventional oncological treatment has been shown in a retrospective comparative epidemiological cohort studies on colorectal cancer (Friedel et al. 2009; Stauder et al. 2009).

One study specifically investigated the protective effect on chemotherapy related mucositis of an anthroposophic medicine composition for local use. Tielmann et al. (2007) documented prospectively the preventive and therapeutic effects of dental treatment and regular use of Weleda Ratanhia Mundwasser (herbal mouthwash) and Weleda Pflanzen-Zahngel (herbal tooth gel) in 32 female patients with breast cancer starting on chemotherapy. The medications are well known and frequently used in the clinical practice of anthroposophic physicians for their preventive and reparative efficacy in mucositis. A positive effect on oral mucositis during chemotherapy was shown in the patients in the study.

The principal active ingredients are extracts from ratanhia root and myrrh, indicated as phytotherapeutics for local treatment of slight inflammations of the mucous membrane in mouth and larynx. The primary effect of ratanhia (*Krameria triandra*) root extracts is tissue astringency. Myrrh tincture, an alcoholic solution of commiphora resins, shows additional antibacterial properties. Further ingredients of the ratanhia mouthwash are horse chestnut extract, volatile oils to stimulate the mouth mucosa and homeopathic components used in anthroposophic medicine to strengthen dental structure and to promote tooth enamel production (Fluoride of Calcium D10, Argentum vitr. D15, Magnesium sulfate D20, horse chestnut bark D20).

The herbal tooth gel contains extracts from ratanhia roots, myrrh and chamomile, delivering a broad range of effects with primarily anti-inflammatory, antibacterial and lesion healing properties. Volatile oils (from peppermint, spearmint and fennel seeds) are supposed to stimulate the mucosa. The test preparations were to be used 3 times daily. Plaque index, gingival index, degree of mucositis and 10 single symptoms were monitored once weekly by the same dentist for 4 consecutive weeks. After 4 weeks, plaque and gingival indexes were slightly decreased compared to baseline values. More than 70% of the patients remained without symptoms of mucositis even after 4 weeks. In only 15.6 % of the patients the degree of mucositis was increased in severity by 1 grade. On the whole, single symptoms decreased from day 7 since beginning of chemotherapy to day 28. During the observation period, no patient developed grade 3 oral mucositis. The local application was well tolerated. Mucositis symptoms were moderate in severity, and the results indicated a positive influence of the composition on the mucosal side effects of chemotherapy, suggesting further investigations.

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## Nausea and vomiting

### *Nausea and vomiting and acupuncture/TCM*

A systematic review published by the National Cancer Institute, revised in January 2013, analyzes the efficacy of various forms of acupuncture on chemotherapy and radiotherapy-induced nausea and vomiting. The techniques analyzed are acupuncture, electroacupuncture, (EA) and acupressure. Randomized clinical trials (RCTs), non randomized trials, prospective consecutive case series and retrospective studies were considered. The conclusion reached, based on the results of the studies, is that the greatest efficacy of acupuncture in the field of oncology is its use for treating chemotherapy-induced nausea and vomiting. This evaluation is shared by the majority of authors that report the effectiveness of acupuncture in postoperative nausea and vomiting and morning sickness. The Cochrane review with meta-analysis (Ezzo et al. 2006), taken up in 2010 by Konno, examined 11 RCTs involving 1,247 patients (Dibble 2000; Dundee 1987, Dundee 1988, Mc Millian 1991, Noga 2002; Pearl 1999; Roscoe 2002; Roscoe 2003; Shen 2000; Streitberger 2003; Treish 2003) (some of which can be seen in our chart). The patients were treated with acupuncture, EA, non-invasive electrostimulation, acupressure on PC6 and concurrent antiemetic therapy in chemotherapy. The use of all the techniques of stimulation (meta-analysis of 9 studies) demonstrated a significant reduction in the occurrence of acute vomiting (RR 0.82 95% confidence interval 0.69 to 0.99;  $P = 0.04$ ) in comparison to the control group; however, there was no reduction of acute or delayed nausea severity. Instead the pressure on acupuncture points (meta-analysis of 2 studies) reduced acute nausea ( $P = 0.04$ ), but not the acute vomiting nor the delayed symptoms. By modality of treatment, stimulation with needles reduced proportion of acute vomiting (RR = 0.74; 95% confidence interval 0.58 to 0.94;  $P = 0.01$ ), but not acute nausea severity. Electroacupuncture reduced the proportion of acute vomiting (RR = 0.76; 95% confidence interval 0.60 to 0.97;  $P = 0.02$ ), but manual acupuncture did not. The authors conclude that stronger types of stimulation such as electroacupuncture are more effective than weaker types such as pressure on acupuncture points.

Since the trials that were considered did not utilize recent antiemetics, the authors state that other studies are necessary. Self-administered acupressure can be a safe and economic means of controlling acute nausea. Nevertheless, these studies lack a control placebo. The authors' conclusions are that this review complements data on post-operative nausea and vomiting suggesting a biologic effect of acupuncture-point stimulation. Electroacupuncture has demonstrated benefit for chemotherapy-induced acute vomiting, but studies combining electroacupuncture with state-of-the-art antiemetics and in patients with refractory symptoms are needed to determine clinical relevance. Non-invasive electrostimulation appears unlikely to have a clinically relevant impact when patients are given state-of-the-art pharmacologic antiemetic therapy. In addition the stimulation of acupuncture points with any method is risk free and any side effects are rare, minimal and transitory.

There are few guidelines on this topic. Those of Filshie and Hester (2006) indicate that specific conditions which should be considered are resistant nausea and vomiting, either postoperative or chemotherapy - induced.

According to the Guidelines for the Practice of Integrative Oncology (Deng et al. USA 2009) of the Society for Integrative Oncology (SIO), acupuncture is recommended when nausea and vomiting associated with chemotherapy are difficult to treat or when the side effects of other treatments are clinically significant. (degree of recommendation 1 A: strong recommendation, high quality evidence).

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology™ Palliative Care 2010 on nausea and vomiting state that "Nausea and vomiting alternative therapies (e.g., acupuncture) or palliative sedation can also be considered".

A systematic review by Holmér Pettersson et al. (2012) on postoperative nausea and vomiting, included 21 papers from November 1996 until August 2009. The results indicate that the application of acupuncture reduced the incidence of nausea but not vomiting when compared to the use of antiemetic prophylaxis alone.

Garcia et al. in a systematic review (2013) evaluated 11 RCTs on nausea and vomiting, concluding that acupuncture is an appropriate additional treatment for post-chemotherapy nausea and vomiting. Only one of the studies had a low bias risk (ROB) or systematic errors. Other studies are necessary.

A systematic meta-analysis review (Lee et al. 2010) evaluated the efficacy of moxibustion as a support in conventional therapy. Eleven databases without language restrictions were used and a minor frequency of nausea and vomiting, due to chemotherapy, was demonstrated in the moxibustion group ( $n = 80$ , RR, 0.38, 95% CIs 0.22 to 0.65,  $P = 0.0005$ ) in comparison to the group that was only given conventional therapy.

### Single clinical studies on nausea and vomiting in adults

Type of Study	Therapeutic Protocol	N. patients and disease	Endpoints and criteria	Results	Author, year
RCT 1) antiemetic therapy 2) antiemetic therapy + EA 3) antiemetic therapy + false EA	1) prochlorperazine, lorazepam, diphenahydramine 2) prochlorperazine, lorazepam, diphenahydramine+ EA on PC6+ ST36 3) prochlorperazine, lorazepam, diphenahydramine + false EA near LU7+GB34  Duration: 5 days	n.104 randomized (34 group 1, 33 group 2, 37 group 3)  breast cancer In chemotherapy	number of emesis episodes	< n. episodes of vomiting in the EA group with pharmacological treatment (p<0.001)	Shen, 2000
			follow-up on 9 <sup>th</sup> day	no significant difference	
RCT 1) acupressure bands + pharmacological therapy 2) acustimulation bands + pharmacological therapy 3) pharmacological therapy	1) pressure on point PC6 (sea band) + (5-HT3 receptor antagonist) 2) stimulation of PC6 + (5-HT3 receptor antagonist) 3) (5-HT3 receptor antagonist)	n.739 randomized in chemotherapy	report diary severity of nausea 7 point scale number of vomiting episodes	in group 1 efficacy on nausea on day of treatment (P < 0.05)  no significant difference on delayed nausea and vomiting	Roscoe, 2003
RCT 1) antiemetic therapy acupressure 2) antiemetic therapy and acupressure placebo 3) only antiemetic therapy	1) dexamethasone (80%), ondansetron (49%), granisetron (24%), and dolasetron (17%) acupressure on PC6 2) dexamethasone (80%), ondansetron (49%), granisetron (24%), and dolasetron (17%) acupressure placebo on SI3 3) dexamethasone (80%), ondansetron (49%), granisetron (24%), and dolasetron	n. 160 randomized (53 group 1, 53 group 2, 54 group 3) (47,49, 51 completed treatment)  in chemotherapy	Rhodes index of nausea and vomiting	In group 1 reduction of delayed nausea significance (P<0.006)	Dibble, 2007
RCT 1) acupressure and	1) acupressure PC6 and pharmacological therapy (5-	n. 36 randomized (19 group 1,17 group 2)	Eight item 5 point Likert – type self reported	in group 1 reduction of nausea, vomiting, stress	Molassiotis, 2007

pharmacological therapy 2) pharmacological therapy	HT3 receptor antagonist + dexamethasone) 2) pharmacological therapy (5-HT3 receptor antagonist + dexamethasone)	In chemotherapy		statistical significance (P<0.05)	
RCT 1) EA + granisetron 2) granisetron	1) EA on ST36 + granisetron intravenous drip 2) granisetron intravenous drip	n. 246 randomized (127 group 1, 119 group 2) In chemotherapy	emesis questionnaire	total rate of 90.5% in observation group superior to that of 84.0% in control group (P < 0.01); nausea and vomiting scores of 2 groups decreased after treatment (both P < 0.001) degree of group 1 superior to that of control group (P < 0.001)	Yang, 2009
RTC 1) true acupuncture 2) sham acupuncture 3) standard care	1) PC6 true (needle penetration) 2) sham acupuncture 2 cun outside PC6 (needle not penetrating) 3) Serotonin-receptor – antagonists + Dopamine-receptor antagonists + Corticosteroids + Antihistamines or neuroleptics	n.277 randomized (109 group 1, 106 group 2, 62 group 3)  In radiotherapy	emesis questionnaire	nausea and vomiting in group 1 e 2 (37% versus 63%, RR 0.6) versus group 3 intensity of nausea in group 1 versus group 3 (p = 0.002)	Enblom, 2011
RTC 1) true acupuncture 2) sham acupuncture 3) standard care	1) PC6 true (needle penetration) 2) sham acupuncture 2 cun outside PC6 (needle not penetrating) 3) Serotonin-receptor – antagonists + Dopamine-receptor antagonists + Corticosteroids + others	n.277 randomized (109 group 1, 106 group 2, 62 group 3) In radiotherapy	nausea questionnaire	efficacy on nausea: group 1 = 95% group 2=96%  efficacy on relaxation, mood, reduced pain: group 1 e 2 = 67%  request for further treatment group 1 and 2 = 89%	Enblom, 2012
RTC 1) true transcutaneous electrostimulation + a standard antiemetic therapy 2) therapy standard antiemetic	1) PC6 transcutaneous electrostimulation in addition to antiemetic therapy (4 mg ondansetron, 10 mg dexamethasone intraoperatively; 10 mg metoclopramide intramuscularly post	n. 130 randomized (65 group, 65 group 2) (60, 59 evaluated)  post craniotomy	number episodes of nausea and vomiting over 24 hours	efficacy of group 1 versus control group statistical significance: vomiting (P=0.025) nausea (P=0.019)	Xu, 2012

	operative) 2) antiemetic therapy (4 mg ondansetron, 10mg dexamethasone intraoperatively; 10 mg metoclopramide intramuscularly post operative)				
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**Single clinical studies on nausea and vomiting in children**

Type of Study	Therapeutic Protocol	N. patients and disease	End points and criteria	Results	Author, year
Pilot Study 1) acupuncture 2) first cycle of chemotherapy without acupuncture	1) acupuncture during 2 <sup>nd</sup> or 3 <sup>rd</sup> cycle of chemotherapy 2) chemotherapy	n.23 solid malignant tumours high doses of chemotherapy	number of episodes of nausea and vomiting	antiemetics in group 1 (p=0.001) acupuncture effective in preventing nausea (P=0.001) and vomiting (P=0.01)	Gottschling, 2008
Pilot Study 1) true auricular acupression + standard care 2) sham auricular acupression + standard care	1) auricular acupression true shenmen, sympathetic, stomach, cardia, digestive subcortex + standard care (granisetron or ondansetron) 2) sham auricular acupression vision, eye, shoulder joint, ex. Knee + standard care (granisetron or ondansetron)	n. 10 in chemotherapy	Morrow assessment of nausea and emetics	significant reduction of nausea and vomiting (P<0.05) in comparison to children only treated with standard care	Yeh, 2012

## Conclusions of the literature and the authors

The literature agrees that acupuncture can be considered a treatment to be used for the nausea and vomiting associated with chemotherapy, radiotherapy or anaesthesia as it is effective, not costly and has reduced side effects. Furthermore, the treatment is simple and easily used by trained health care professionals and by the patients themselves. Therefore, it is necessary to encourage the widespread use of this technique, before and after treatment, in both oncological and surgical wards. However, it should be kept in mind (Bao 2009) that the clinical relevance of these results was limited by the fact that they predated the use of antiemetics of the most recent generation.

To conclude, in accordance with the 2009 SIO Guidelines, the grading is 1A (strong recommendation, evidence of high quality).

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### *Nausea and vomiting and herbal medicine*

The medicinal plants studied and used in human cancer treatment for nausea and vomiting symptoms are *Zingiber officinalis* and *Cannabis sativa*.

#### **Zingiber officinalis**

Ginger, scientifically known as *Zingiber officinalis* Rosce (ZO), has a long history of medicinal use, and the literature suggests that it has been used as a medicinal agent for nearly 2500 years (Haniadka R. 2012).

The rhizome of ZO, is one of the most widely used species of the ginger family (Zingiberaceae), contains a number of pungent constituents and active ingredients, while, the steam distillation of powdered ginger produces ginger oil, which contains a high proportion of sesquiterpene hydrocarbons, predominantly zingiberene.

Several authors analyze different aspects of the ZO action. Grzanna (2005) presents the use of ginger as an anti-inflammatory agent, Shukla and Singh (2007) dealt with the cancer prevention properties of the crude drug. The actions of ginger as a post-operative anti-emetic substance were the subject of a review by Chaiyakunapruk et al. (2006).

The exact mechanism responsible for the anti-emetic effects of ginger is unknown. However, aromatic, spasmolytic, carminative, and absorbent properties of ginger suggest that the ZO phytochemicals 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol may function as a 5-HT<sub>3</sub> antagonist, NK1 antagonist, and have antihistaminic and prokinetic effects.

*In vitro* studies suggest that these phytochemicals exert their anti-emetic effect at least in part by acting on the 5-HT<sub>3</sub> receptor ion-channel complex, probably by binding to a modulatory site distinct from the serotonin-binding site. In addition, this may include the indirect effects via receptors, in the signal cascade behind the 5-HT<sub>3</sub> receptor channel complex such as substance P receptors and muscarinic receptors. (Abdel-Aziz H. 2006, Haniadka R. 2012).

The compounds 6-gingerol and 6-shogaol have been shown to have a number of pharmacological activities, including antipyretic, analgesic, antitussive, and hypotensive effects. ZO extracts exhibit inhibition of platelet aggregation and thromboxane synthesis *in vitro*, which has led to concerns that ginger extracts may prolong bleeding; however, several European studies using ginger orally did not find any significant anticoagulant effects *in vivo*. (Monograph 2003, Badreldin HA. 2008, Marx WM. 2013)

In a systematic review, the authors analyzed the earliest clinical studies on the efficacy of ginger in preventing the Chemotherapy-Induced Nausea and Vomiting (CINV). Haniadka begins from the first three papers that described the effectiveness of ginger in reducing CINV in oncologic patients. However, despite the widespread use of ginger in the treatment of nausea in other contexts such as gestational nausea, the more recent literature provides inconsistent data for the use of ginger as treatment of anti-CINV (see Tab. 1) for patients undergoing chemotherapy. Hence, standard recommendations for such use are premature.

**Doses:** For most purposes a traditional dose of ginger is 1-4 g daily, taken in divided doses, while the timing of doses did not vary greatly between studies, with the initial dose generally given +/-1 hour from the first chemotherapy session (Monograph 2003, Marx WM. 2013).

**Side effects:** Few adverse effects from the ingestion of ginger are reported in literature. Oral ZO is generally well tolerated, with mild gastrointestinal adverse effects including abdominal discomfort, heartburn, and diarrhea being the most commonly reported. Some minor adverse effects have been associated with the use of ZO in humans. Ginger may cause heartburn, and in doses higher than 6 g may act as a gastric irritant. Inhalation of dust from ZO may produce IGE-mediated allergy (Badreldin HA. 2008).

Theoretically, ginger inhibits platelet aggregation, which could result in excessive bleeding, however this has not been reported in practice. When added to conventional anti-emetics used in the prophylaxis and treatment of chemotherapy-induced nausea and vomiting, ZO does not appear to increase adverse effects (Marx WM. 2013). It may be prudent to avoid using either ginger or compounds extracted there from during pregnancy in women, pending more studies.

**Drug interactions:** Zick SM et al. reported that when subjects received a combination of 2g ZO plus aprepitant (an NK1 inhibitor), the severity of delayed nausea increased when compared to control (p=0.01). This led the authors to hypothesize that ginger reduces absorption of medication by increasing gastric emptying and intestinal motility, or that it competitively interacts with the same receptors of the conventional drugs reducing the binding rate of medications when used in combination. More studies are needed to clarify the mechanism of action (Zick SM. 2009, Marx WM. 2013).

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Randomized, double-blind multicenter trial	ZO: 3 different doses/day (0.5 g, 1.0 g, or 1.5 g) Period: 6 days starting 3 days before chemotherapy	576 cancer patients	Determine the dose and efficacy of ginger in reducing the severity of chemotherapy-induced nausea on day 1 of chemotherapy Criteria: 7-point rating scale	All doses of ZO significantly reduced acute nausea severity compared to placebo on day 1 of chemotherapy (p = 0.003). The largest reduction in nausea intensity occurred with 0.5 g (p = 0.017) and 1.0 g (p = 0.036)	Ryan JL. 2012
Randomized, double-blind trial	All patients: ondansetron and dexamethasone i.v. 4-8 mg/day  I Group (w. 20-40 kg): ZO 1g/day II Group (W. 40-60 kg): ZO 2g/day  Period: Initial 3 days of chemotherapy	60 children and young adults aged 8-21 years and between 20 and 60 kg, newly diagnosed with bone sarcoma	Effect of ZO capsules vs placebo capsules as an additional antiemetic to ondansetron and dexamethasone Criteria: ESAS and NCI	Delayed moderate to severe nausea (p < 0.001) and vomiting (p = 0.022) are statistically decreased in experimental group	Pillai AK. 2011
Randomized, double-blind, placebo-controlled trial	ZO: 2 different doses/day (1.0 g ginger, 2.0 g) Period: 3 days	162 patients with cancer and CINV receiving chemotherapy	Primary end-point: Compare the effect of a low (1.0 g) and a high-dose (2.0 g) of powdered ZO vs. placebo Criteria: MANE	2.0-g dose of ZO did not increase the severity of delayed nausea (p=0.03). ZO provides no additional benefit for reduction of the prevalence or severity of acute or delayed CINV when associated with 5-HT3 receptor antagonists and/or aprepitant (p=0.07)	Zick SM. 2009
Randomized, double-blinded crossover study	ZO:1 g /day Period: ZO treatment group: 5 days Placebo group: 4 days of metoclopramide	48 gynaecologic cancer patients	Determine whether ZO had antiemetic effect in cisplatin-induced emesis	Addition of ZO to antiemetic regimen has no advantage in reducing nausea or vomiting in acute phase of cisplatin-induced emesis, but a side effect, occurred more often in metoclopramide arm compared to ginger arm (p=0.109)	Manusirivithaya S. 2004
Randomized, prospective, cross-over, double-blind study	All patients: Cyclophosphamide 0.5-1g i.v. I Group: ZO 1g prior CT and 1g 6 h after CT II Group: lactulose plus metoclopramide prior CT and metoclopramide after CT III Group: lactulose plus ondansetron prior CT and metoclopramide after CT Period: 3 cycles of CT	60 patients with malignancy confirmed by histopathology and at least 2 episodes of vomiting in previous chemotherapy cycle	Determine the antiemetic effect of ZO on nausea and vomiting induced by cyclophosphamide	The study shows that complete control of nausea was achieved in 62% patients with ginger, 58% with metoclopramide and 86% with ondansetron. (p<0.01) Complete control of vomiting was achieved in 68% patients with ginger, 64% with metoclopramide and 86% with ondansetron. (p<0.01)	Sontakke S. 2003

Tab.1. Single clinical studies on nausea and vomiting in adults/children. Legend: ZO (*Zingiber officinalis* root powder), CT (chemotherapy), ESAS (Edmonton's Symptom Assessment System), NCI (National Cancer Institute), CINV (Chemotherapy-Induced Nausea and Vomiting), MANE (Morrow Assessment of Nausea and Emesis).

## Cannabis sativa

*Cannabis sativa* preparations have been used for their psychotomimetic effect since 4000 years. In 1986 the Food and Drug Administration authorized the use of its active element, delta-9-tetrahydrocannabinol (THC), for medical purposes (Walsh D. 2003) to treat nausea and vomiting side effects in patients receiving chemotherapy.

Cannabinoids interact with various neurotransmitters and neuromodulators, such as gamma-aminobutyric acid (GABA), histamine, serotonin, dopamine, glutamate, norepinephrine, prostaglandins and opioid peptides.

There are at least two types of cannabinoid receptors, CB1 and CB2, to which potent and selective antagonists have been developed. The blockage of CB1 cannabinoid receptors induces vomiting, suggesting the existence of an endogenous cannabinoid system within the emetic circuits. This also suggests that the THC anti-emetic activity would be due to the stimulation of the CB1 receptor. Besides, THC and its synthetic analogues were able to prevent the inducing of this condition.

In a systematic review, the authors analyze 96 documents obtained from 12749 articles extracted from the databases (Machado Rocha FC, 2008). The authors conclude that, the cannabinoids efficacy can be higher when combined with other anti-emetic drugs than alone. Because the cannabinoid mechanism is different from other medications, they can benefit refractory patients or be used as auxiliaries to enhance the effect of existent anti-emetic medications. Thus, smaller doses of cannabinoids in combination with modern anti-emetic medications might eventually not only enhance the anti-emetic efficacy, but also reduce the cannabinoid collateral effects. In the last 10 years only some RCTs have been produced on the cannabis extract and THC in cancer patients and among these, only one relating to the treatment of cancer-related nausea (see Tab.2).

**Dosage:** The daily-recommended dose for chemotherapy-induced nausea and vomiting is an orally administration of 2.5-10mg of THC. The dose varies depending on the symptom and the pharmaceutical formulation (Walsh D. 2003, Ben Amar M. 2006, Grotenhermen F. 2012).

**Side effects:** The active compounds were generally well tolerated but the use of *Cannabis sativa* extracts or THC is limited by frequent side effects and toxicity that severely limit their use (e.g. hallucinations and dysphoria), as well as for its high potential for dependence. Furthermore, there are no extracts that are both active in reducing the psychotropic effect and not immunosuppressive (Firenzuoli F. 2009). However, no safety concerns were identified in cancer patients during clinical studies by Johnson JR. (2010), Meiri E. (2007) and by Cannabis-In-Cachexia-Study-Group (2006) (see Tab 2).

**Drug interactions:** To date there are no known drug interactions but caution is advised in the use.

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Multicenter, phase III, randomized, double-blind, placebo-controlled, clinical study	I Group: 2.5 mg THC and 1 mg cannabidiol II Group: 2.5 mg THC III Group: Placebo Period: 6 weeks	243 patients with advanced cancer	Compare the effects of cannabis extract, THC, and placebo on appetite and quality of life.  Criteria: VAS, QLQ-C30	CE at the oral dose administered was well tolerated by these patients with CACS	CICSG 2006
Randomized, double-blind, placebo-controlled study	All patients: dexamethasone 20 mg Day 1: ondansetron (16 mg) or dronabinol (2.5 mg) prior CT and dronabinol (2.5 mg) after CT Day 2: dronabinol (10 mg),	61 patients	Compare the efficacy and tolerability of dronabinol, ondansetron, or the combination CINV in 5 days	Dronabinol or ondansetron was similarly effective for the treatment of CINV. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone	Meiri E. 2007

	ondansetron (16 mg) or combination Day 3-5: dronabinol (10-20 mg), ondansetron (8-16 m) or combination Period: 5 days				
multicenter, double-blind, randomized, placebo-controlled, parallel-group trial	THC:CBD Group: 100 µl spray with 2.7 mg THC and 2.5 mg CBD. 1 spray every 3 hours THC Group: 100 µl spray 2.7 mg THC. every 3 hours Period: 20 days	177 patients with cancer pain, who experienced inadequate analgesia despite chronic opioid dosing	Compare the efficacy of an extract, THC:CBD and THC extract, vs. placebo, in relieving pain in advanced cancer Criteria: NRS, BPI-SF, QLQ-C30, EORTC	THC: CBD extract, a non-opioid analgesic, endocannabinoid system modulator, has been shown to be a useful adjunctive treatment for relief of pain in patients with advanced cancer who experience in adequate analgesia despite chronic opioid therapy. (p=0.004)	Johnson JR. 2010

Tab.2 Single clinical studies on nausea and vomiting in adults. Legend: BPI-SF (Brief Pain Inventory-Short Form), CE (*Cannabis sativa* Extract), CINV (delayed chemotherapy-induced nausea and vomiting), CICS (Cannabis-In-Cachexia-Study-Group), CT (chemotherapy), EORTC (European Organisation for Research and Treatment of Cancer), NRS (Numerical Rating Scale), QLQ-C30 (Quality of Life Questionnaire C30), THC (delta-9-tetrahydrocannabinol), VAS (Visual Analog Scale), THC:CBD (tetrahydrocannabinol:cannabidiol).

#### Summary table

Plant	Clinical indications	Grading	Dosage
<i>Zingiber officinalis</i>	Treatment of nausea and vomiting in cancer patients	1A	1-4 g daily, taken in divided doses
<i>Cannabis sativa</i>	Authorized the use of delta-9-tetrahydrocannabinol (THC), for medical purposes to treat nausea and vomiting in cancer patients	2B	Orally administration of 2.5-5 mg of THC

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### *Nausea and vomiting and homeopathy*

A research was conducted in France in 2012 using the complex homeopathic medicine Cocculine\* (Pérol, 2012) in the control of CINV in non-metastatic breast cancer patients treated by standard chemotherapy regimens. The study was a randomized, multi-centered, double-blind, placebo-controlled Phase III trial.

From September 2005 to January 2008, 431 patients were randomized: 214 to Cocculine (C) and 217 to placebo (P).

Patient characteristics were well-balanced between the 2 arms. Overall, compliance to study treatments was excellent and similar between the 2 arms. A total of 205 patients (50.9%; 103 patients in the placebo and 102 in the homeopathy arms) had nausea FLIE scores > 6 indicative of no impact of nausea on quality of life during the 1st chemotherapy course. There was no difference between the 2 arms when primary endpoint analysis was performed by chemotherapy stratum; or in the subgroup of patients with susceptibility to nausea and vomiting before inclusion. In addition, nausea, vomiting and global emesis FLIE scores were not statistically different at any time between the 2 arms of the study. The frequencies of severe (Grade  $\geq$  2) nausea and vomiting were low in our study (nausea: P: 17.6% vs. C: 15.7%,  $p=0.62$ ; vomiting: P: 10.8% vs C: 12.0%,  $p=0.72$  during the first course).

\*Cocculine<sup>®</sup> is a complex of 4 active elements incorporated in the same tablets. The placebo tablets were identical seemingly in the active tablets (packaging, colour, shape). The placebo tablets were inert and contained only (Saccharose (75%), lactose (24%), and Magnesium stearate (1%)) without any homeopathic components.

### **Conclusions of the literature and authors**

According to the study, adding a complex homeopathic medicine (Cocculine) to standard anti-emetic prophylaxis does not improve the control of CINV in early breast cancer patients.

### **References**

Pérol D, Provençal J et al. Can treatment with Cocculine improve the control of chemotherapy-induced emesis in early breast cancer patients? A randomized, multi-centered, double-blind, placebo-controlled Phase III trial. *BMC Cancer* 2012; 12:603

## Neuropathy

### *Post-chemotherapy neuropathy and acupuncture/TCM*

The reviews of Visovsky et al. (2007) and Lu et al. (2008) on the effect of acupuncture in cancer symptoms have analysed only one study (Wong 2006) about the post-chemotherapy neuropathy which is reported in the table. According to the authors, it is not possible to draw conclusions and more research is needed.

Zhou et al. (2009) argue that Thalidomide and Bortezomid are very effective in the treatment of multiple myeloma but cause a sensory neuropathy of difficult resolution which often limits the dose and duration of treatment. They conclude that acupuncture has been proven effective and has fewer side effects than analgesics in the treatment of diabetic neuropathy and HIV neuropathy but was never tested in the treatment of toxic neuropathies.

The guidelines of the Society for Integrative Oncology 2009 (Deng et al.) conclude that “acupuncture treatment is recommended as an aid (grade of recommendation 2C (weak recommendation, low or very low quality evidence) in the chemotherapy-induced neuropathy”.

The review of Cassileth et al. (2010) has studied the promising approaches of complementary medicines for neuropathic pain. The authors state that complementary approaches like massage, acupuncture and mind-body therapies such as hypnosis and meditation are inexpensive, non-invasive and without side effects unlike of drug therapy. They conclude that the evidence of effectiveness particularly for acupuncture continues to increase, as demonstrated by RCTs on chronic pain.

The review of Lu et al. (2013) on acupuncture in cancer pain reports 2 works statistically significant compared to controls (Alimi 2003 and Schroeder 2012, in details in our table) relating to chemotherapy-induced neuropathy.

The systematic review of Franconi G. et al. (2013) has identified 8 relevant papers out of 3,989 publications. One was an experimental study which showed that electroacupuncture suppressed chemotherapy-induced peripheral neuropathy (CIPN) pain in rats. The others were 7 very heterogeneous clinical studies, 1 controlled randomised study using auricular acupuncture (Alimi 2003), 2 randomized controlled studies using somatic acupuncture (Xu 2010, Tian 2011), and 4 (Wong 2006, Bao 2011, Donald 2011, Schroeder 2012) case series/case reports. All studies suggested a positive effect of acupuncture in CIPN (see table). The conclusions of the authors were that all the clinical studies reviewed had important methodological limitations; therefore further studies with robust methodology are needed to demonstrate the role of acupuncture for treating CIPN resulting from cancer treatment.

There are also some relevant single clinical studies on neuropathy in adults that are reported below.

Alimi and al. (2003) in a high quality RCT (see the chapter on Pain) evaluate the effectiveness of auricular acupuncture in chronic neuropathic pain, central or peripheral. They conclude that the reduction in pain intensity (VAS) is a clear benefit of auricular acupuncture for those patients who continue to have pain despite conventional analgesic therapies.

Wong and Sagar (2006) carried out a study with acupuncture where only 5 patients had improvement in balance, posture and gait while reducing the dosage of analgesics.

Xu et al. published in 2010 in Chinese language a RCT of 64 cases of peripheral neuropathy from chemotherapy drugs (Paclitaxel or Oxaliplatin) randomized into 2 groups (acupuncture versus intramuscular injection of Cobamamide ). The data showed a significant improvement of symptoms in the acupuncture group (66.7 % 20 /30) compared to the other group (40% 12/30), with statistically significant difference (P <0.05).

Bao et al. (2011) firstly presented in literature a case of peripheral neuropathy induced by Bortezomid in patient with multiple myeloma treated with acupuncture who presented a significant improvement of symptoms.

Donald et al. (2011) conducted an observational study on 18 patients with chemotherapy-induced neuropathy treated with 6 weekly sessions of acupuncture. They found an improvement in symptoms of neuropathy and a reduction in the use of analgesic and sleep disorders in 82% of the patients. The encouraging results suggest that acupuncture may be a therapeutic option for these patients and controlled trials using validated patient-reported outcome measures are justified.

Schroeder et al. (2012) conducted a pilot study to evaluate the therapeutic effect of acupuncture on chemotherapy-induced neuropathy in 6 patients treated for 10 weeks, in addition to the current medical therapy. The control group consisted of 5 patients who practiced only current medical therapy. After 3

months have found an improvement of nerve conduction in 5 of 6 patients treated with acupuncture compared to 1 of 5 patients of the control group.

Rostock et al. (2013) in a randomized trial with a group sequential adaptive design in patients with CIPN, compared EA (n.14) with hydroelectric baths (HB, n.14), vitamin B1/B6 capsules (300/300mg daily; Vit. B, n. 15), and placebo capsules (n. 17). CIPN complaints improved by  $0.8 \pm 1.2$  (EA),  $1.7 \pm 1.7$  (HB),  $1.6 \pm 2.0$  (Vit. B), and  $1.3 \pm 1.3$  points (placebo) on a 10 point numeric rating scale without significant difference between treatment groups and placebo. In addition no significant differences in sensory nerve conduction studies or quality of life (EORTC QLQ-C30) were found. The conclusions of authors were that the used EA concept, HB, and Vit. B were not superior to placebo. Since, contrary to these results, studies with different acupuncture concepts showed a positive effect on CIPN, the effect of acupuncture in this condition remains unclear. Further randomized, placebo controlled studies are necessary.

Type of Study	Therapeutic Protocol	N. patients and disease	End points criteria	Results	Author, year
RCT 1) auricular acupuncture 2) sham auricular acupuncture 3) auricular seeds at non acupoint	1) measuring electrodermal responses of each ear with el. microvoltmeter 2) points outside the pain areas 3) auricular seeds outside the pain areas  6 auricular points on average 44m/session 2 months	90 patients randomized (29 group 1, 30 group 2, 31 group 3) cancer pain arising after treatment of cancer	VAS (0-100mm)	pain intensity decreased by 36 % at 2 months in the group receiving acupuncture (P<0.0001); there was little change for patients receiving placebo (2%).	Alimi, 2003
Prospective case series acupuncture (no control)	CV6 ST36 LI11 EX-LE10 and EX- UE9 weekly	5 patients with CIPN (chemotherapy-induced peripheral neuropathy)	Pain score and WHO CIPN grade	Improvement of symptoms	Wong, 2006
RCT 1) acupuncture group 2) control group	1) LI4 LR3 ST36 CV6 and LI11 and other points not reported 2) treated with intramuscular injection of cobamamide	64 patients randomized (30 group 1, 30 group 2) cases of peripheral neuropathy induced by Paclitaxel or Oxaliplatin	Questionnaire of peripheral neuropathy	acupuncture more effective than Cobamamide (p< 0.05).	Xu, 2010
Case report	bilaterally: LI4 TE5 LI11 ST40 EX-LE10 auricular acupuncture (shenmen, zero) and 2 additional points where electrodermal signal was detected once per week for six treatments	1 patient with bortezomib-induced CIPN	VAS pain score	no more symptoms From 8 VAS to 2 VAS	Bao, 2011
Retrospective case series	most commonly used points: SP6 and ST36 LV3 6 weekly acupuncture sessions (30-45 minutes)	18 patients CIPN	subjective symptoms	82% (n.14) patients reported an improvement of neuropathy symptoms (evaluation form was filled by a therapist not involved in patient care)	Donald, 2011
Retrospective controlled non randomized pilot trial 1) acupuncture and best medical care 2) best medical care	1) bilaterally: ST34 EX-LE12 and EX-LE10 2) best medical care 10 weekly	n.11 (6 group 1, 5 group 2) CIPN	Measurement nerve conduction	acupuncture significantly improved nerve conduction velocity and amplitude (in 5/6 patients acupuncture vs. 1/5 controls)	Schroeder, 2012
RCT 1) electroacupuncture(EA) 2) hydroelectric baths (HB)  3) high doses of Vit B1 and B6  4) placebo	1) 8 ± 1 sessions of EA: LV3 , SP9 , GB41 , GB34 in patients with CIPN in the lower extremities) and LI4, LI11, SI3 HT3 in patients with CIPN in the upper extremities 2) 8 ± 1 sessions of HB into a special water basin with water at a temperature of about 35°C 3) 100 mg thiamine nitrate, 100 mg pyridoxine hydrochloride) per day for 3 weeks 4) 3 lactose capsules per day. for three weeks	60 patients randomized (14 group 1, 14 group 2, 15 group 3, 17 group 4)  (analysed 14,13,15, 17)  CIPN	detailed questionnaires numerical rating scale (NRS) from 0 to 10  neuropathy score (0–15 points)  electroneurographical tests	CIPN complaints improved by 0.8±1.2 (EA), 1.7 ± 1.7 (HB), 1.6 ± 2.0 (Vit. B), and 1.3 ± 1.3 points (placebo) on a 10-point numeric rating scale without significant difference between treatment groups or placebo. no significant differences in sensory nerve conduction studies	Rostock, 2013

## Conclusions of the literature and the authors

According to the guidelines of the Society for Integrative Oncology (SIO 2009), it is impossible to conclude whether acupuncture could be used to improve symptoms related to post-chemotherapy neuropathy in cancer patients (Grade 2C, weak recommendation, low or very low quality evidence).

Deng et al. (2013) in their guidelines on lung cancer recommend acupuncture in patients with peripheral neuropathy related to the tumor as an adjunctive treatment when there is inadequate control of symptoms (Grade 2C, weak recommendation, low or very low quality evidence).

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### *Neuropathy and homeopathy*

Even if there are not researches related to neuropathy in cancer patients, there is one interesting study on patients with diabetic polyneuropathy.

The feasibility and outcomes of homeopathic therapy in a group of type-2 diabetes mellitus patients with diabetic neuropathy were studied in a prospective observational study. Patients were followed from baseline (T0) for 6 months (T1) and for 12 months (T2), treatment was adjusted as necessary. Primary outcome was diabetic neuropathy symptom (DNS) score, secondary outcomes were clinical evolution and short-form-36 (SF-36)-evaluated quality of life (QOL).

Homeopathy was used in 45 patients, 32 of whom completed the observation study and in parallel the conventional therapy outcomes were observed in 32 patients, 29 of whom completed the study. DNS improved in both groups during the observation period, but the change with respect to baseline was statistically significant only in homeopathic group at T1 (P=0.016). Over the course of the observation there was a substantial stability of the electroneurophysiological values, blood pressure and body weight in both groups, a slight decrease of fasting blood glucose and glycated hemoglobin in homeopathic group. QOL scores showed an improvement in homeopathic group only.

### **Conclusions of the literature and authors**

Complementary homeopathic therapy of diabetic neuropathy was feasible and showed promising effects in symptom scores.

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Pomposelli R, Piasere V, Andreoni C, Costini G, Tonini E, Spalluzzi A, Rossi D, Quarenghi C, Zanolin ME, Bellavite P. Observational study of homeopathic and conventional therapies in patients with diabetic polyneuropathy *Homeopathy* 2009 Jan;98(1):17-25

### *Peripheral neuropathy and anthroposophic medicine*

Peripheral neuropathy is frequent in relation to some chemotherapeutic agents, such as taxanes, vincristine, platinum compounds, and other oncological treatments (e.g. bortezomib, thalidomide, lenalidomide). It can be associated with pain. Neurotoxic side effects of cancer therapy are second in frequency to hematological toxicity and preventive and therapeutic strategies are still unsatisfying (Windebank et al. 2008; Moya del Pino 2010).

At least one randomised phase II trial described specifically the effect of *Viscum album* L. extracts on chemotherapy induced neuropathy. Bar Sela et al. (2013) enrolled 72 patients with NSCLC (non-operable St IIIA/B-IV; 65% stage IV, 63% squamous histology) in order to study the effects of the addition of a *Viscum album* L. extract (Iscador® Qu 10 mg, every 2<sup>nd</sup> day, after induction) to standard chemotherapy (carboplatin combined with gemcitabine or pemetrexed). Severe grade 3-4 non hematological chemotherapy toxicities (16% vs. 41%) were less frequent in the Iscador group. Specifically, the difference in favour of Iscador was significant ( $p = 0,03$ ) for chemotherapy-induced neuropathy.

The addition of anthroposophic medications has been suggested, such as *Argentum/Quarz*, *Crotalus terrificus D30*, *Rhus toxicodendron comp.* or *Stibium met. praep D6* and others, sc. 2-3 times weekly by a peer-reviewed data collections on single AMPs (Vademecum) (GÄAD 2013) and by Debus (2009).

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## Pain

### *Pain and acupuncture/TCM*

There is a great deal of evidence in literature regarding non-oncological pain. A recently published meta-analysis study (Vickers et al. 2012) investigated the effect size of acupuncture for chronic back and neck pain, osteoarthritis, chronic headache, and shoulder pain.

The authors used individual patient data gathered from 29 high quality, large acupuncture RCTs. A meta-analysis based upon individual patient data is considered superior to regular meta-analyses that use summary data because of its enhanced data quality and increased precision. A total of 17,920 patients were included in the study. The results indicated that acupuncture was superior to both the sham and the no-acupuncture control for each pain condition ( $p < 0.001$ ). The specific effect sizes (less pain) of true acupuncture was 0.23 [95% confidence interval (CI), 0.13–0.33], 0.16 (95 % CI, 0.07–0.25), and 0.15 (95% CI, 0.07–0.24) SDs lower than sham controls for back and neck pain, osteoarthritis, and chronic headache, respectively, strongly suggesting that acupuncture is more than a placebo. The author argued that acupuncture is effective for the treatment of chronic pain and therefore a reasonable referral option.

A systematic review (Sun et al. 2008), quantitatively evaluated the efficacy of acupuncture and related techniques as adjunct analgesics for acute postoperative pain management in different types of surgery including 15 RCTs, comparing acupuncture with sham control in the management of acute postoperative pain. Weighted mean difference for cumulative opioid analgesic consumption was  $-3.14$  mg,  $-8.33$  mg, and  $-9.14$  mg at 8, 24, and 72 h, respectively. Postoperative pain intensity (visual analogue scale, 0–100 mm) was also significantly decreased in the acupuncture group at 8 and 72 hours compared with the control group. The acupuncture treatment group was associated with a lower incidence of opioid related side-effects such as nausea, dizziness etc. The conclusions are that the perioperative administration of acupuncture may be a useful adjunct for postoperative analgesia. Further large, well-designed studies are required to confirm these findings and to answer questions regarding the most efficacious type of acupuncture and optimal timing of administration.

The conclusions of the literature in reference to cancer-related pain are less certain. Alimi et al. (2003), published a RCT reporting the efficacy of auricular acupuncture in cancer patients with neuropathic pain. The 90 patients were randomised in 3 groups, to compare true acupuncture (29 patients, needles inserted at acupuncture points) to sham acupuncture (30 patients, acupuncture at placebo points) and to seeds fixed at placebo points (31). Patients were treated for 2 months. Pain intensity decreased by 36% at 2 months in the group receiving acupuncture ( $p < 0.0001$ ); there was little change for patients receiving placebo (2%). The authors concluded that observed reduction in pain intensity (VAS) represents a clear benefit from auricular acupuncture in pain, despite stable analgesic treatment.

Deng et al. (2004) are of the same opinion and refer to a RCT conducted by Alimi (2003) on auricular acupuncture. A review (Cohen et al. 2005) relates the fact that in the west there are limited studies, whereas the numerous studies conducted in China are of poor quality. The authors examined 7 studies on cancer-related pain in general, adenocarcinoma or breast or bone cancer pain (published between 1985 and 2003), three of which were RCTs. Alimi's study was the only one that was of high quality and gave promising results. The conclusion of these 3 studies is that acupuncture can be an important additional treatment for cancer patients, even in those who do not fully respond to conventional therapy.

Another review (Lee et al. 2005) examines 7 studies - 3 RCTs and 4 non-controlled studies. In 4 studies somatic acupuncture is examined, in 2 auricular acupuncture and in one electro-acupuncture. Both the subjects examined and the type of pain is heterogeneous and only 1 of the 3 RCTs is of high quality. The conclusion is that the use of acupuncture as an additional therapy in oncological pain is not sustained by the available data. However, the best trial (Alimi), demonstrates promising results.

Filshie and Rubens (2006) claim that there is positive evidence that acupuncture can reduce pre and postoperative pain but there are few RCTs on chronic oncological pain, even though numerous observational studies demonstrate its effectiveness. They also underline the high quality of Alimi's study.

Numerous studies suggest that acupuncture can help various types of pain including postoperative pain in breast surgery or pain resulting from other treatments. There is consequently a reduction in the use of pain killers and improved mobility. A review (Bardia et al. 2006) examines the efficacy of different CAMs and in reference to acupuncture, the review considers 3 RCTs, two of which are of low quality and only one (Alimi 2003) of high quality. It concludes, confirming that acupuncture seems to be a promising therapy for controlling oncological pain but it can not yet be recommended as being effective.

Lu et al. (2008), report that there are still very few clinical trials, but the results point to the benefits of acupuncture in oncology. Furthermore, the numerous RCTs on chronic post operative neuropathic pain (non

small cell lung carcinoma, breast cancer, bladder cancer, prostate cancer, ovarian cancer) have shown that acupuncture is often used as a complementary method along with usual care to provide additional pain reduction and to lessen the need for pharmaceutical analgesic medicine.

According to the Guidelines for the Practice of Integrative Oncology, (Deng et al. USA 2009) of the Society for Integrative Oncology (SIO), acupuncture is recommended as a complementary therapy when it is difficult to control pain and when the side effects of other therapies are clinically significant (degree of recommendation 1 A, strong recommendation, high quality evidence).

The review by Peng et al. (2010 – Chinese language) included all the RCTs, until 2008, that compared acupuncture to a placebo or to the use of Chinese herbs. Seven trials (n. 634 patients) were included and 1 high quality trial demonstrated that auricular acupuncture was significantly superior to a placebo in reducing pain. The 6 trials of low quality without a placebo showed some positive effects of therapy with acupuncture. The conclusions are that acupuncture is effective in relieving pain but further high quality RCTs are necessary.

According to Lu and Rosenthal (2010) recent evidence demonstrates the use of acupuncture on cancer patients suffering from pain and dysfunction after surgery of neck cancers and arthralgia associated to aromatase inhibitors in breast cancer.

The National Comprehensive Cancer Network (NCCN® 2013) guidelines for adult cancer pain recommends the use of physical modalities (acupuncture or acupressure, bed, bath, physical therapy etc.) cognitive modalities (relaxation training, imagery/hypnosis etc.) and spiritual care, as part of integrative interventions, in conjunction with pharmacologic intervention as needed. To support this evaluation, they refer to a meta-analysis (Sheinfeld 2012) of psychosocial interventions on cancer pain that highlights the importance of a multi model approach to the management of cancer pain. These integrative interventions may be particularly important in vulnerable populations, for example frail, elderly, or pediatric patients, in whom standard pharmacological interventions may be less tolerated. All recommendations are category 2A; there is uniform NCCN consensus that the intervention is appropriate.

A Cochrane review (Paley 2011) included 3 RCTs (204 participants). Only one study (Alimi) was of high quality and demonstrated the efficacy of auricular acupuncture. One study (Chen 2008) comparing acupuncture with medication; the second study (Dang 1998) compared acupuncture, point-injection and medication in participants with stomach cancer.

Although both studies have positive results in favour of acupuncture, they should be viewed with caution due to methodological limitations, small sample sizes, poor reporting and inadequate analysis. The conclusion is: there is insufficient evidence to judge whether acupuncture is effective in treating cancer pain in adults.

Choi et al. (2012), a total of 15 RCTs, met the inclusion criteria (1,157 patients); 14 studies were conducted in China (n.1070) and one in France (Alimi n.87). Twelve trials were published in Chinese and 3 in English. Randomised clinical trials were included if acupuncture was used as the sole treatment or as a part of a combination therapy for cancer pain. Studies were included if they were controlled with a placebo or against a drug-therapy or no-treatment group. All of the included RCTs were associated with a high risk of bias (Cochrane criteria). The majority of acupuncture treatments or combination therapies with analgesics exhibited favorable effects compared with conventional treatments in individual studies. However, a meta-analysis suggested that acupuncture did not generate a better effect than drug therapy (n=886; risk ratio (RR) 1.12; 95% CI 0.98 to 1.28; P=0.09). The comparison between acupuncture plus drug therapy and drug therapy alone demonstrated a significant difference in favor of the combination therapy (n=437; RR 1.36; 95% CI 1.13 to 1.64; P=0.003). The results of this systematic review provide no strong evidence for the effectiveness of acupuncture in the management of cancer pain.

The review of the U.S. National Cancer Institute (2007-2009, revised 2013) reports 7 clinical studies in the English language; 3 RCTs, 2 studies conducted in China and one in France (Alimi), while 4 studies were case series. The authors state that although most of these studies were positive and demonstrated the effectiveness of acupuncture, the findings have limited significance due to methodological problems.

The review of Garcia et al. (2013) included 11 RCTs on pain. No large trials were identified that had low risk of bias (ROB) and positive results. The most common reasons reviewers assigned high ROB were problems with blinding patients and small sample size. Two blinded, sham-controlled trials (25 patients: 13 electroacupuncture and 12 sham in patients after thoracotomy; n. 38: 20 acupuncture and 18 sham for management of aromatase inhibitor-associated joint pain in women with breast cancer) with positive findings were methodologically sound but had small sample sizes. In an initial pilot cross-over study (n. 19) the authors concluded acupuncture reduced joint symptoms and improved functional ability. A subsequent blinded, sham-controlled trial (n. 38) 19 showed that the worst pain scores were significantly lower in the true acupuncture versus sham group (P <0 .003). A later cross-over trial (n. 106: 52 acupuncture and 54

sham) did not find perioperative stimulation with intradermal acupuncture needles was more effective than sham, but authors concluded that intradermal acupuncture may have provided less intense stimulation than the electroacupuncture used in the previous trial. In reference to Alimi's trial, the authors reported ROB was unclear because issues of blinding were not discussed, and after the study began, the recruitment strategy was changed. Of the 11 trials examining acupuncture for pain, nine were positive, but eight had high ROB.

Deng et al. (2013) in their guidelines on lung tumours "Acupuncture for chemotherapy induced peripheral neuropathy (CIPN) and cancer related pain", selected 19 studies, 12 of which were RCTs, one a prospective trial, and 6 case series trials. The positive results are not considered sufficient in order to affirm the efficacy of acupuncture given the methodological problems. They conclude that in patients with lung cancer related pain and peripheral neuropathy, acupuncture is suggested as an adjunct treatment in patients with inadequate control of symptoms (Grade 2C). After initial review for CIPN (chemotherapy induced peripheral neuropathy), 5 articles were selected: the studies were of low quality and the data given were inconclusive. The RCTs involving head and neck cancer and breast cancer related pain showed improvement in pain scores (Brief Pain Inventory). No difference was seen for post-thoracotomy pain versus sham acupuncture.

The review by Lu and Rosenthal (2013) examines the National Comprehensive Cancer Network guidelines for adult cancer pain, the Cochrane Systematic Review (2012) and the Systematic Review of Choi (2012). It also analyzes the study by Sun et al. (post surgical gastroparesis, 2008), Mehling et al. (postoperative pain from tumours in various locations, 2007) and Wong et al. (post-thoracotomy 2006). As well, it provides "actionable" acupuncture protocols for specific cancer pain conditions and related symptoms (postoperative nausea and vomiting, postsurgical gastroparesis syndrome etc.). The same authors (2013) maintain that "Clinically, the role of acupuncture applying to cancer pain management is twofold: one is to use acupuncture, along with opioids, to alleviate specific cancer pain conditions; the second is to use acupuncture to minimize opioid-related side effects, including opioid-induced constipation, pruritus, and nausea/vomiting".

Although far from conclusive, accumulated evidence from clinical and animal studies has suggested that acupuncture may be beneficial to cancer patients with pain. Acupuncture protocols generated from RCTs should be adopted by clinicians who are using acupuncture in the field. Moreover, oncology acupuncture requires that clinicians possess knowledge and skills in both acupuncture and allopathic oncology.

**Single clinical studies on pain in adults**

Type of Study	Therapeutic Protocol	N. patients and disease	Endpoints criteria	Results	Author, year
<p>RCT 1) auricular acupuncture 2) sham auricular acupuncture 3) auricular seeds at non acupoint</p>	<p>1) measuring electrodermal responses of each ear with el. microvoltmeter 2) points outside the pain areas 3) auricular seeds outside the pain areas</p> <p>6 auricular points on average</p> <p>44 m/session 2 months</p>	<p>n. 90 randomized (29 group 1, 30 group 2, 31 group 3) Cancer pain arising after treatment of cancer</p>	<p>VAS (0-100mm)</p>	<p>pain intensity decreased by 36 % at 2 months in the group receiving acupuncture (P&lt;0.0001) there was little change for patients receiving placebo (2%).</p>	<p>Alimi, 2003</p>
<p>RCT double blind 1) electro-acupuncture + usual care 2) sham acupuncture + usual care</p>	<p>1) LI4 GB34 GB 36 TE8 ipsilateral to the side of the thoracotomy 60Hz altern. wave 30 m/session 2) blunt tip needles in the same acupoints and pseudostimulation</p> <p>twice daily 7 post operative days</p>	<p>n. 27 enrolled n. 25 randomized (13 group 1, 12 group 2)  thoracotomy in operable non-small cell lung cancer</p>	<p>VAS (0-100mm)</p>	<p>electro-acupuncture (EA) may reduce narcotic analgesic use in the early postoperative period in patients with thoracotomy Cumulative dose of patient-controlled analgesia morphine used on day 2 was significantly lower in EA group (7.5 +- 5 mg vs. 15.6 +-12mg; p&lt;0.05)</p>	<p>Wong, 2006</p>
<p>pilot cross over study</p>	<p>twice weekly for 6 weeks full body TE5 GB41 GB34 LI4 ST41 KI3 specific point protocols shoulder LI15 SJ14 SI10 wrist SJ4, LI5 fingers SI5 SI3 ba xie LI3 lumbar GV3 GV8 BL23 hip GB30 GB39 knee SP9 SP10 ST34 auricular acupuncture alternative ears with each treatment: Shenmen kidney liver upper lung sympathetic twice weekly for 6 weeks</p>	<p>n.21 enrolled  postmenopausal women breast cancer with aromatase inhibitor</p>	<p>Brief Pain Inventory-Short Form (BPI-SF) Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index at baseline, 6 and 12 weeks</p>	<p>acupuncture reduced joint symptoms and improved functional ability improvement in the mean BPI-SF worst pain scores (p = 0.01), pain severity (p = 0.02), pain-related functional interference (p = 0.02) WOMAC function subscale (p = 0.02 )  no adverse events</p>	<p>Crew, 2007</p>

<p>RTC</p> <p>1) massage and acupuncture +usual care on postoperative days 1 and 2</p> <p>2)usual care alone</p>	<p>massage (standard and acupressure-type foot massage) acupuncture GI4 SP6</p> <p>auricular points corresponding to the area of pain</p>	<p>150 patients were eligible</p> <p>n.138 randomized (93 group 1, 45 group 2)</p> <p>postoperative cancer</p>	<p>pain numeric rating scale (NRS) (0-10) during the previous 24 hours</p>	<p>statistically significant improvement in pain for the intervention group :decrease (p =0.038)</p> <p>Among patients reporting moderate-to-severe (at least 3/10) pain at base-line on POD1 (day 1postoperative), average pain scores improved in the intervention group (p &lt; 0.0001)</p>	<p>Mehling, 2007</p>
<p>RCT</p> <p>1) preoperative implantation of small intradermal needles</p> <p>2) preoperative placement of sham needles</p>	<p>1) on each side of the spine corresponding to the BL12 to BL19 ST36, ear Shenmen</p> <p>2) sham needles at the same schedule</p> <p>for 4 weeks</p>	<p>n.162 randomized (81 group 1, 81 group 2)</p> <p>post thoracotomy unilaterally cancer</p>	<p>Brief Pain Inventory scores (BPI) at the 30 day follow up</p> <p>BPI scores at 30 days</p> <p>BPI scores for post discharge 60, 90 days</p> <p>Numerical Rating Scale (NRS) at rest, on movement, on coughing in first 5 days after surgery</p> <p>Medication Quantification Scale (MQS) in first 5 days after surgery</p>	<p>at 30 days pain scores were marginally higher in the intervention group (p=0.9).</p> <p>no significant difference any follow up for BPI</p>	<p>Deng, 2008</p>
<p>Prospective clinical trial</p>	<p>acupuncture plus usual care</p> <p>ST36, SP6, LI11, LI4, LV3, SP9, yintang, GV20, CV6, shenmen.</p> <p>Ashi point</p> <p>12 sessions</p> <p>8 weeks</p>	<p>n.32</p> <p>advanced ovarian or breast cancer</p>	<p>QOL assessment tool measures of pain severity and interference, physical and psychological distress, life satisfaction and mood states</p>	<p>improvement immediately post treatments in pain, anxiety, fatigue, and depression</p> <p>significant improvement over time in anxiety, depression and pain (P = .0002) with sustained benefit at 12 weeks</p>	<p>Dean-Clower, 2010</p>
<p>RCT</p> <p>1) true acupuncture (TA)</p> <p>2) sham acupuncture</p>	<p>1) acupuncture TE5 GB41 GB34 LI4 ST41 KI3 joint-specific points: SP9 SP10 ST34 SI5 baxie LI3 GV3 GV8</p>	<p>n.51 enrolled n.43 randomized (23 group 1, 20 group 2)</p>	<p>Brief pain inventory short form (BPI-SF) worst pain scores at 6 weeks</p>	<p>the mean BPI-SF was lower in the TA compared with the SA (p &lt; 0.001) in eighty percent for participants</p>	<p>Crew, 2010</p>

(SA)	BL23 LI15 TE14 SI10 GB30 GB39 TE4 LI5 auricular acupuncture alternative ears with each treatment: Shenmen kidney liver upper lung sympathetic  2) superficial needles insertion at non acupoint; twice weekly for 6 weeks	n.38 evaluable  breast cancer with aromatase inhibitor	Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) at 3 and 6 weeks  Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands(M-SACRAH) at 3 and 6 weeks	significant differences in pain severity and pain related interferences (p = 0.003; p = 0.002 respectively)  similar findings were seen for the WOMAC and M-SACRAH scores  no significant adverse event reported	
RCT 1) acupuncture 2) usual care.	1)acupuncture LI4 SP6 GV20 luozhen Ear Shenmen  Ashi points  once a week for 4 weeks  2) the median time from the surgery was 34 months	n.70 randomized n. 58 evaluable (28 group 1, 30 group 2)  neck dissection radiation therapy	Costant Murley instruments Composite score of pain (CMS), function and activities (0-100mm)  NRS (numerical rate of scare) (0-10)	acupuncture was significant superior to control for all outcomes measures  medication use decreased in both groups but the difference were not statically significant (p=0.4)  no serious adverse events statistically significant interaction in NRS between time and acupuncture (p< 0.001)  CMS improve more in the acupuncture group (p=0.008)	Pfister, 2010
RCT double blind 1) acupuncture (TA) 2) sham acupuncture (SA)	1) acupuncture CV4 CV6 CV12 and bilateral LI4 PC6 GB34 ST36 KI3 BL65 2) sham needles (non penetrating retractable needles) in sham acupuncture  sessions 8 weekly	n. 51 randomized n. 47 analyzed (23 group 1, 24 group 2)  breast cancer with aromatase inhibitors	VAS (0-100 mm)  Health Assessment Questionnaire Disability Index (HAQ-DI)	no statistically significant difference in reduction (p = 0.31) between the 2 groups	Bao, 2013

## Conclusions of the literature and the authors

The majority of high quality studies refer to the efficacy of acupuncture in non oncological pain. The most important study is a meta-analysis published by Vickers et al. in 2012; the authors argued that acupuncture is effective for the treatment of chronic pain and therefore a reasonable referral option and a promising option for the cancer population.

A systematic review (Sun et al. 2008) for acute postoperative pain management argued that postoperative pain intensity was significantly decreased in the acupuncture group and the acupuncture treatment group was associated with a lower incidence of opioid-related side-effects such as nausea, dizziness etc.

The efficacy of acupuncture on cancer-related pain is less certain. The first RCT of high quality is that of Alimi et al. (2003) where pain is treated with auricular acupuncture. In general, both positive and negative studies lead to the conclusion that it is difficult to ascertain the efficacy of acupuncture. The Cochrane Review of 2011 confirms this and adds that positive results in favour of acupuncture should be viewed with caution due to methodological limitations, small sample sizes, poor reporting and inadequate analysis. Choi in 2012 and Garcia in 2013 draw the same conclusions.

Nevertheless, the majority of authors believe that the results are promising. The English Guidelines (2006) indicate the use of acupuncture for patients who do not respond to conventional analgesic therapy or who refuse this type of therapy. The 2009 SIO Guidelines also maintain that acupuncture can be recommended as a complementary therapy for cancer patients when it is difficult to control their pain and when the side effects of other therapies are clinically significant (1A, strong recommendation, evidence of high quality). Deng et al. (2013), in their guidelines for lung tumours, recommend acupuncture as an additional treatment in patients where pain control is inadequate (Grading 2C).

The National Comprehensive Cancer Network (NCCN® 2013) guidelines for adult cancer pain recommends (category 2A - uniform NCCN consensus that the intervention is appropriate) a multi model approach to the management of cancer pain particularly in vulnerable populations (frail, elderly, or pediatric patients) in whom standard pharmacological interventions may be less tolerated. The review by Lu et al. (2008) also suggests that acupuncture can be used for chronic neuropathic pain, for postoperative non small lung carcinoma pain and for postoperative pain in patients with breast, prostate or ovarian tumours. The same authors (2013) concluded that acupuncture and auricular acupuncture are beneficial for treating pain as a sole therapy or in addition to other therapies, including pharmacological ones.

To concluded, in accordance with the 2009 SIO Guidelines, the grading is 1A (strong recommendation, evidence of high quality).

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### *Pain and herbal medicine*

Different medicinal plants are traditionally used for the relief of generic pain, among them *Salix* spp, *Harpagophytum procumbens*, *Tanacetum parthenium*, *Cinnamomum camphora*, *Cannabis sativa* and *Papaver somniferum*. However, the only ones with scientific evidence in the treatment of cancer-related pain are *Cannabis sativa* and *Papaver somniferum* (also known as Opium).

Although there are many *in vitro* studies on the action of opium in pain, since 2003 only one RCT was conducted on human cancer pain. Lukasewycz S. et al. (2010) investigated whether opium in combination with *Atropa belladonna*, containing the muscarinic receptor antagonists atropine and scopolamine, as a rectal suppository could improve post-RALP (Robotic assisted laparoscopic radical prostatectomy) pain.

Briefly, 99 patients undergoing RALP entered a randomized, double-blind, placebo-controlled trial. The data showed that, in a preoperative treated group, postoperative pain was significantly improved during the first 2 postoperative hours. Similarly, 24-hour morphine consumption was significantly lower in patients who received the treatment. No adverse effects were observed, but more studies are necessary to analyze the 2 major side-effects of opioids (physical dependence and tolerance).

### ***Cannabis sativa***

*Cannabis sativa* (CS) has been studied for its use in pain as well as in nausea and vomiting related to cancer treatment (see also "nausea and vomiting and herbal medicine" paragraph).

Baker D. in a review (2003) described how the cannabinoids inhibit pain either via CB1 or by a CB2-like activity in supraspinal, spinal, or peripheral regions, dependent on the type of nociceptive pathway being studied. This finding is consistent with high concentrations of CB1 receptors on primary afferent nociceptors, particularly in the dorsal spinal cord, whereas peripheral CB2-like receptors have been implicated in the control of "inflammatory" pain.

Some systematic reviews (Hoskin RD. 2008, Lynch ME. 2011, Grotenhermen F. 2012) evidenced an antinociceptive action of CS and cannabinoids. In particular, Hoskin RD (2008) exposed the therapeutic activity of CS in cancer and non-cancer pain and reported experimental works from 1997 to 2008 with evidences for antinociceptive action of cannabis and THC. Lynch ME et al. (2011) analyzed, in a systematic review, the use of cannabinoids in chronic non-cancer pain conditions including neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain. The authors selected 18 trials that met the inclusion criteria; 15 of them demonstrated a significant analgesic effect of cannabinoid as compared to a placebo. Grotenhermen F. (2012) exposed the different use of cannabis and cannabinoids in pain treatment and showed that cannabinoids are particularly effective against (chronic) neuropathic pain and in multiple sclerosis pain, but have little or no effect in patients with acute pain.

In addition to numerous *in vitro* studies, a recent report on anosteolytic sarcoma murine model suggests a gain of function in the cancer-induced bone pain treatment with cannabinoids. Unlike opiates that can produce paradoxical hyperalgesic actions and enhance bone destruction, the CB2 selective agonists have been shown to reduce bone loss and bone fracture while lacking many unwanted side effects seen with current treatments for bone cancer pain (Lozano-Ondoua AN. 2010).

However, there is a lot of scientific evidence about the action of *Cannabis sativa* in the treatment of generic pain while few of these are RCTs on the pain cancer related treatment (Tab1).

**Drug interactions:** Some evidences show that cannabis may have synergistic interaction with morphin and opioids in the treatment of pain (Cichewicz DL. 2003-2004, Roberts JD. 2006).

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Multicenter, double-blind, randomized, placebo-controlled, parallel-group trial	THC: CBD Group: 100µl spray with 2.7 mg THC and 2.5 mg CBD. 1 spray any three-hours THC Group: 100 µl spray 2.7 mg THC. any three-hours Period: 20 days	177 patients with cancer pain, with inadequate analgesia despite chronic opioid dosing	Compare the efficacy of the extract THC: CBD and a THC extract vs placebo in relieving pain in advanced cancer Criteria: NRS, BPI-SF, QLQ-C30, EORTC	THC: CBD extract, a non-opioid analgesic, endocannabinoid system modulator, is a useful adjunctive treatment for relief of pain in patients with advanced cancer and adequate analgesia despite chronic opioid therapy. (p=0.004)	Johnson JR. 2010
Randomized, double-blind, placebo-controlled, graded-dose study	A novel cannabinoid formulation low dose GROUP: 1-4 sprays/day medium dose GROUP: 6-10 sprays/day high dose GROUP: 11-16 sprays/day Period: 5 weeks	360 patients with active cancer and chronic pain	Evaluate the pharmacokinetics after controlled administration of oromucosal, specifically to determine if CBD modulates THC disposition. Criteria: BPI-SF, QLQ-C30, PAC-QoL, MADRS	The proportion of patients reporting analgesia was greater in formulation than placebo overall (P = 0.035), and specifically in the low-dose (p= 0.008) and medium-dose (p= 0.039) groups	Portenoy RK. 2012

Tab.1. Single clinical studies on *Cannabis sativa* in adults. Legend: BPI-SF (Brief Pain Inventory- Short Form), CBD (cannabidiol), Montgomery-Asper Depression Rating Scale (MADRS), QLQ-C30 (Quality of Life Questionnaire version 3), PAC-QoL (Patient Assessment constipation Quality of Life), THC (tetrahydrocannabinol).

### Other Medicinal Plants

*Salix* species (Ss) family *Salicaceae*, consist of several species of willow tree. *Salix* species with well-described analgesic and antipyretic properties of willow bark have been well known in ancient Egypt, Greece, India and the Roman Empire. Today, willow bark is used orally for headaches, pain, myalgia, osteoarthritis, dysmenorrhea, gouty arthritis, ankylosing spondylitis, and also for fever, common cold, influenza, and weight loss.

**Side effects:** Ss extracts can cause gastrointestinal adverse effects, but these appear to be less frequent than those caused by NSAIDs. Ss may cause itching and rash, as well as serious allergic reactions, including anaphylaxis, in people who are allergic to aspirin. Salicylates can inhibit prostaglandins, which can reduce renal blood flow. Salicin can cause renal papillary necrosis and the risk for toxicity is greater with high acute doses or chronic use (Zareba G. 2009).

*Harpagophytum procumbens* (HP), also known as devil's claw, is a perennial plant belonging to the family of Pedaliaceae used for arteriosclerosis, osteoarthritis, rheumatoid arthritis, gout, myalgia, fibrositis, lumbago, tendonitis, pleuritic chest pain, gastrointestinal upset or dyspepsia, fever and migraine headache.

The major chemical constituents of HP are iridoid glycosides (primarily harpagoside, harpagide, and procumbide), sugars, triterpenoids, phytosterols, aromatic acids, and flavonoids.

It has been suggested that harpagoside inhibits both the COX and lipoxygenase inflammatory pathways (Fiebich BL. 2012). HP seems to inhibit COX-2 (but not COX-1) and nitric oxide synthetase, a modulator of inflammation. There is also some evidence that devil's claw products might influence heart rate and blood flow as well as have antiarrhythmic effects. HP is generally well tolerated.

**Dosages:** The daily dosage of HP suggest are 0.5-1.0 g of dried root (tablet or capsule) three times daily, 1,8-2,4mg/daily (50-100 mg harpagoside) of dried root for arthritis and musculoskeletal pain and inflammation.

**Drug interactions:** HP has been shown to inhibit certain cytochrome P450 enzymes; therefore, it may have an impact on numerous pharmaceutical drugs also metabolized via these enzymes, including Coumadin, antihypertensives, statin drugs, anti-epileptic and anti diabetic agents, antidepressants, and proton pump inhibitors (Monograph, 2008).

**Side effects:** The most common adverse effects are diarrhea, nausea, vomiting and abdominal pain. HP can cause allergic skin reactions, dysmenorrhea and hemodynamic instability, frontal headache, tinnitus, anorexia and loss of taste. Due to reports that devil’s claw increases stomach acid, it might decrease the effectiveness of anti-acids.

*Tanacetum parthenium* (TP), also known as bachelor’s button, feverfew, mutterkraut and Santa Maria, of the family Asteraceae has been used for many years as a treatment for fever and for relief of dysmenorrhea and arthritis.

Unlike salicylates or NSAIDs, feverfew is not an inhibitor of COX-1 or COX-2. Feverfew appears to prevent the release of arachidonic acid from platelets and inhibit the action of phospholipase A2.

The most important biologically active principles are the sesquiterpene lactones, the principal one being parthenolide. Parthenolide is found in the superficial leaf glands (0.2%–0.5%), but not in the stems, and comprises up to 85% of the total sesquiterpene content.

**Dosages:** The daily dosage suggested for migraine headaches is 100–300 mg (standardized to 0.2–0.4% parthenolides), up to 4 times daily. Feverfew may be used to prevent or stop a migraine headache. Feverfew supplements may also be CO<sub>2</sub> extracted. For these, take 6.25 mg, 3 times daily, for up to 16 weeks. For inflammatory conditions: 60-120 drops, 2 times daily of a 1:1 w/v fluid extract, or 60-120 drops twice a day of 1:5 w/v tincture.

**Drug interactions:** TP may inhibit platelet aggregation, so it is contraindicated in anti-aggregating therapies. Furthermore, pregnant women should not use it because the leaves have been shown to possess potential emmenagogue activity, and it is not recommended for lactating mothers or for use in children.

**Side effects:** TP may alter bleeding time and should not be used concomitantly with warfarin. Other adverse effects include oral ulcers, nausea, vomiting, diarrhea, and flatulence. It hastens and enhances menstrual flow and use during pregnancy may result in spontaneous abortions (Pareek A. 2011).

*Cinnamomum camphora* (CC), synonym *Laurus camphora*, family Lauraceae has been applied topically as an analgesic and antipruritic. The applicable parts of CC are the bark and wood.

Camphor has been used to treat warts, cold sores, hemorrhoids and osteoarthritis. It has frequently been used topically to treat respiratory tract diseases involving mucous membrane inflammation and is sometimes used topically to treat cardiac symptoms.

CC is also used topically as an eardrop and for treating minor burns. In inhalation therapy, CC is used as an antitussive while orally it is used as an expectorant, antifatulent and for treating respiratory tract diseases. Camphor is FDA-approved for topical use as an analgesic and anesthetic in concentrations of 3% to 11% (Zareba G. 2009).

**Summary table**

Plant	Clinical indications	Grading	Dosage
<i>Cannabis sativa</i>	Authorized the use of delta-9-tetrahydrocannabinol (THC), for medical purposes to treat pain, nausea and vomiting in cancer patients	2B	Orally administration of 2.5-5 mg of THC

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### *Pain and homotoxicology*

There are no researches on pain treated with classical homeopathy, except 2 researches on back pain and fascitis.

In breast cancer patients, post-treatment pain often appears after several months and strongly impairs health-related quality of life. Conventional methods of pain reduction are often ineffective. Injection therapy with Traumeel (Heel GmbH, Baden-Baden, Germany), a medication with analgesic properties used in homotoxicology for the treatment of the pain associated with trauma as well as a mediator of inflammation, was proposed as an innovative approach for pain relief after breast cancer treatment.

Nine patients, still suffering from a high level of pain after breast cancer therapy despite use of postoperative treatment with conventional analgesics, were invited to participate. Traumeel injection and procaine injection were administered once a week for three to 10 sessions. The level of pain was assessed by a pain score and physical and psychological status by a questionnaire before and directly after injection and again at follow-up visits after 3 and 6 months.

After the last injection, all patients experienced a marked reduction of their level of pain on average from 7.6 +/- 1.5 to 2.4 +/- 1.4 points on a scale from 1 to 10 points. After a follow up observational phase of 3 and 6 months, pain score ratings increased slightly again in some patients but remained consistently low in others. In any case, the ratings of pain levels did not reach the values assessed before the start of Traumeel injection. Similarly, health-related quality of life improved with this injection therapy. The perception of pain relief with Traumeel injection was high in 8 of 9 patients, reflecting an overall perceived positive outcome and tolerability of this treatment.

### **Conclusions of the literature and authors**

This case series is a first encouraging approach of homotoxicology for pain relief in breast cancer patients.

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## Radiodermatitis

### *Radiodermatitis and herbal medicine*

The herbal medicines used in radiodermatitis treatment are *Silybum marianum* and *Aloe vera*. Although the traditional use and some reviews indicate the use of *Aloe vera* in the treatment of dermatitis, to date only one systematic review examines the literature on the use of this medicinal plant in the radiodermatitis. The authors analyzed one earlier systematic review on *Aloe vera*, 5 published RCTs (1 on pediatric cancer patients, 3 on women with breast cancer and 1 on patients undergoing in radiotherapy), and 2 additional RCTs not published. There is no evidence from clinical trials to suggest that topical *Aloe vera* is effective in preventing or minimizing radiation-induced skin reactions in cancer patients. Further methodologically rigorous, sufficiently powered research studies should be conducted to evaluate the effectiveness of currently used and novel therapies for the prevention, minimization and management of radiation-induced skin reactions (Richardson J. 2005) (see also mucositis paragraph).

### *Silybum marianum*

*Silybum marianum* (SM), also known as milk thistle, has been used for centuries in the treatment of liver-related diseases. It is native to the Mediterranean and grows throughout Europe and North America but also in India, China, South America, Africa and Australia (Dixit N. 2007, Fehér P. 2011).

The major SM bioactive flavonoligans in silymarin include silychristins A and B, silydianin, silybin A and B and isosilybin A and B.

Although there is a large literature on the SM anti-cancer activity and its preventive action on skin tumors UVB-induced, only one clinical study has analysed its effects on radiodermatitis induced by RT. Becker-Schiebe M. et al. (2011) have examined the effect of a silymarin-based cream and have shown how the treatment is active to prolong significantly the time of treatment-related toxicity. However, as the cream is made from both SM and other natural components synergistic actions cannot be excluded (see Tab.1).

Numbers of studies have established the cancer chemopreventive role of silymarin in both *in vivo* and *in vitro* models of several tumors, like prostate, colon, mammary, ovarian, renal and lung cancer. A systematic review of Saller R. et al. (2007) evaluated and selected more than 700 papers to identify the complex mechanisms of action of silymarin. Silymarin was found to modify specifically the functions related to various transporters and receptors located in the cell membranes. In the cytoplasm, some antioxidant properties and the inhibition of the lipoxygenase pathway seem quite selective and could concur to the antitoxic effects. Some effects like the inhibition of inducible nitric-oxide synthase, of nuclear factor  $\kappa$  B, and reduction of collagen synthesis are indicative of DNA/RNA-mediated effects. However, the data presented do not solve the question of silymarin mechanism of action. This component contributes to modulate imbalance between cell survival and apoptosis through interference with the expressions of cell cycle regulators and proteins involved in apoptosis and shows anti-inflammatory as well as anti-metastatic activity (Ramasamy K. 2008).

Furthermore, various studies show that these major components can reverse, inhibit or retard the process of skin carcinogenesis at one or at all of the three stages of carcinogenesis UVB-induced. In these papers are shown the protective effects of silymarin and silybin against chemically and UVB-induced skin damages both in cell cultures and animal experiments (Dixit N. 2007, Dinkova-Kostova AT. 2008, Vaid M. 2010, Adhikari M. 2012).

**Dosage:** SM seed extract, 150 to 175 mg capsule, standardized to 80% silymarin, 3 times daily. Seed extract bound to phosphatidylcholine 360 mg capsule, 3 times daily (Rainone F. 2005).

**Side effects:** Silymarin has very low toxicity and a good safety profile. At high doses, a laxative effect is observed due to increased bile secretion and bile flow.

Adverse effects related to the gastrointestinal tract such as dyspepsia, bloating, nausea, and diarrhea were reported. Serious adverse effects are rare, and include gastroenteritis associated with collapse and allergy (Dixit N. 2007).

**Drug interactions:** Silybin inhibits the activities of CYP2D6, CYP2e1, and CYP3A4, but at physiologic concentrations far higher than those given clinically. Some studies show that there are no significant effects on concomitantly administered indinavir. No indinavir interaction was reported by Rainone F. (2005) when

analyzing a study (Piscitelli SC, 2002) on 10 healthy volunteers who received 175 mg of SM 3 times daily for 3 weeks. Also Di Cenzo R. (2003) and Mills E. et al. (2005) did not find any indinavir-interaction.

Type of study	Therapeutic protocol	N. patients and disease	End point and Criteria	Results	Author, year
Prospective study	Silymarin-based cream (0.25% SM content, Leviaderm®), 3 times a day 2 weeks before beginning RT, during RT 2 hours before radiation, and 2 weeks after it	101 patients evaluated after breast-conserving surgery followed by RT with 50.4 Gy plus boost 9-16 Gy	Evaluate the efficacy of silymarin-based cream (Leviaderm®) in the treatment of RT-induced vs., standard care  Criteria: RTOG and VAS	Silymarin-based cream (Leviaderm®) may be a promising treatment for preventing acute skin lesions caused by RT in breast cancer patients (p< 0.0001)	Becker-Schiebe M, 2011

Tab.1. Single clinical studies on radiodermatitis in adults. Legend: SM (*Silybum marianum* extract), ROTG (Radiation Therapy Oncology Group scale), VAS (Visual Analogue Scale).

#### Summary table

Plant	Clinical indications	Grading	Dosage
<i>Aloe vera</i>	Treatment and prevention chemotherapy side effects	2B	Aloin-free aloe gel, titrated in polysaccharides, or pure polysaccharides (acemannan) 200-400 mg per dose
<i>Silybum marianum</i>	Treatment of liver-related diseases and preventive action on skin damage UVB-induced	2B	SM seed extract, 150 to 175 mg capsule, standardized to 80% silymarin, 3 times/day

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### *Radiodermatitis and homeopathy*

A first study (Balzarini A, 2000) tested the effect of Belladonna 7CH and X-ray 15CH associated in the treatment of acute radiodermatitis. A randomized double-blind placebo-controlled clinical trial involving 66 patients operated on for breast cancer and undergoing radiotherapy was conducted. The efficacy of the treatment was assessed by the comparison of these parameters taken individually and by calculating an Index of Total Severity (sum of the scores of the four parameters) during radiotherapy, and during recovery, 15 and 30 days after the end of radiotherapy.

In a second study (Schlappack O, 2004) 25 patients were treated homeopathically for radiation-induced itching. Fourteen patients developed itching during their course of post-operative radiation at 27 days median (range: 14-40). Eleven patients experienced itching in the radiation field after completion of treatment (median 21 days) after the end of their radiation treatment. A single dose of an individually selected homeopathic medicine in 30C dilution was given in the clinic, on the basis of repertorisation. Patients were asked to record a visual analogue scale (VAS) before prescription of the homeopathic medicine and at follow-up. Patients were evaluated at median 3 days (range: 1-27 days) after administration of the homeopathic medicine. In total, 14 of 25 patients (56%) responded to the first medicine. Nine patients had a second medicine, seven responded. Altogether 21 of 25 (84%) patients were successfully treated. The following medicines were employed successfully: Fl-ac 9/13, Rhus-t 3/5, Caust 2/3, Ign 2/2, Psor 2/2, gamma-ray 2/2 and Kali-bi 1/1.

The VAS measurements before and after homeopathic treatment showed a reduction of the median value of 64 mm (range: 20-100 mm) to 34 mm (median; range: 0-84 mm). Homeopathic treatment of radiation-induced itching appears quite successful. The most frequently indicated and most frequently effective medicine was Fluoric acid. An approach that allows greater understanding of the patient as a whole in the short time available in a busy clinic may be required.

Type of study	Therapeutic protocol	N. patients and disease	End points criteria	Results	Author, year
Prospective randomised double blind (subject and observer blind) placebo controlled trial with 2 parallel arms	Clinical homeopathy a) homeopathic medicines - Belladonna 7CH, 3 granules twice daily and X-ray 15CH, 3 granules once daily b) placebo Outcomes	66 women after conservative surgery for breast cancer and being treated with radiotherapy Age: mean 52.7 years, range 28.3 to 70 (7.0 in text, presumed error) years	Skin reactions to radiotherapy	Skin reactions to radiotherapy assessed by physician observers using ordinal and nominal scales as follows: Skin colour: normal 0; pink 1; red / violet 2 Heat to touch: normal 0; faint 1; intense 2 Edema: absent 0; present 1 Hyperpigmentation: absent 0; present 1 efficacy of the treatment was assessed by the comparison of these parameters	Balzarini, 2000

### **Conclusions of the literature and authors**

The homeopathic medicines are effective on the heat of the skin. The limited number of patients and the posology employed could have interfered with the significance of the results. Chemotherapy and hormonotherapy do not seem to affect the results. Both studies underline that the differences of the scores of the Index of Total Severity during Radiotherapy were not statistically significant, but showed a trend towards a better activity of the homeopathic medicine compared to placebo. Analysis of the data on Total Severity during recovery, showed a statistically significant benefit of the active medicines over placebo.

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## Xerostomia

### *Xerostomia and acupuncture/TCM*

The Guidelines of Filshie and Hester (2006) indicate xerostomia as a specific condition to consider for treatment with acupuncture in patients who do not respond to conventional treatment.

The reviews (Sagar 2008, Lu 2008) of some pilot clinical studies (Bloom 2000, Johnstone 2001, Wong 2003) suggest that acupuncture could improve radiotherapy-induced xerostomia in patients with head and neck cancer, also in patients who do not respond to pilocarpine.

The SIO Guidelines 2009 (Deng et al.) conclude that “acupuncture is recommended as complementary therapy for xerostomia induced by radiation (Grading 1B, strong recommendation, moderate quality evidence)”.

The review by Jensen et al. (2010) examined 72 articles published from 1989 to 2008; the authors conclude there is evidence that xerostomia could be prevented or minimized with acupuncture and other treatments.

Four articles are included related to acupuncture therapy (2 of them are RCTs): one (Johnstone 2001) demonstrated the efficacy of the auricular acupuncture treatment in 18 patients who did not respond to oral therapy with pilocarpine; the other 3, visible in the table (Blom 1996 and 2000, Cho et al. 2008), demonstrate that acupuncture increases the quantity of saliva and that the improvement of xerostomia is correlated to the quality of life. The conclusions of the authors were that acupuncture can be a possible means of treating irradiation induced xerostomia in patients with reduced function of salivary glands, without side effects.

A review by O' Sullivan et al. (2010) included 3 trials (Bloom 1996, Cho 2008, Pfister 2010, see the Table): all reported significant reduction in xerostomia versus baseline Salivary Flow Rates ( $p < 0.05$ ). The conclusions were that limited evidence suggests the beneficial effect of acupuncture for irradiation induced xerostomia. Although current evidence is insufficient to recommend this intervention, it is sufficient to justify further studies.

In the review of Zhuang et al. (2013) are included 4 studies in patients with radiation-induced xerostomia, reported in the table: 3 RCTs (Bloom 1996, Cho 2008, Pfister 2010) investigating the therapeutic effect of acupuncture (110 patients 54 acupuncture group, 56 control group) and one RCT (Meng 2012) on the preventive effect of acupuncture. Because of the considerable variation among included studies, the meta-analysis was not possible. Two included RCTs used placebo controls (Bloom 1996 superficial acupuncture, Cho 2008 sham acupuncture), and both observed significant improvement in the salivary flow rates between acupuncture and control groups. However, no significant differences were found. According to the authors of the review this result calls into question whether non acupoint needling is an effective and credible placebo. Though non acupoint needling has been used extensively, many studies have argued that this control option is physiologically active and may not be an appropriate placebo (Birch 2006). The effect produced by acupuncture is usually attributed to 3 components: a non specific placebo effect, which is related to patients' expectation and the interaction between patients and acupuncturists; physiological effect due to needles being inserted into the skin; and specific effect due to needling manipulation at specific acupoints (White 2001). Three included RCTs suggested that acupuncture for radiation-induced xerostomia can improve patients' subjective symptoms. Only 1 study (Meng, 2012) evaluated the preventive effect of acupuncture for radiation-induced xerostomia and showed positive changes in salivary flow rates (both unstimulated and stimulated) and dry mouth related symptoms. Acupuncture treatment was well tolerated by all patients and no severe adverse effects were observed. The conclusions of the authors are that there is insufficient evidence to judge whether acupuncture is safe and whether it is effective in preventing or treating radiation-induced xerostomia. Significant research remains to be done before acupuncture can be recommended for routine use in radiation-induced xerostomia.

Garcia et al. in their review (2013) on various symptoms, among them xerostomia, included 4 studies (the same of the previous review), all with high risk of bias (ROB) owing to low statistical power or problems with patient blinding. Two of these studies reported negative results (Blom 1996, Cho 2008) and 2 were positive (Pfister 2010, Meng 2012), so the reduction of incidence and gravity of symptoms of xerostomia is different between the acupuncture group and the usual care and it is statistically significant ( $p < 0.003$ ,  $p < 0.02$ ). Efficacy remains undetermined because of unclear or high ROB among studies.

Furness et al. in a Cochrane review (2013) on non pharmacological interventions for the treatment of dry mouth (not all caused by radiotherapy treatment) included 9 RCTs with a total of 366 participants randomized. Five studies with a total 153 participants evaluated acupuncture. Three of 5 studies (Bloom 1992, 1996, Cho 2008) evaluated acupuncture compared with placebo (see the Table), 1 (List 1998) acupuncture with both manual and EA stimulation, 1 (Pfister 2010, reported in the table) acupuncture with

usual care. The pooled estimate of 2 trials (70 participants, low quality evidence) reported no difference between acupuncture and control in dry mouth symptoms (SMD-0.34, 95% CI -0.81 to 0.14, P value 0.17, I<sub>2</sub> = 39%) in a form suitable for meta-analysis. There was a very small increase in unstimulated whole saliva (UWS) at the end of 4 to 6 weeks of treatment in 3 trials, 71 participants, low quality evidence (MD 0.02 ml/minute, 95% CI 0 to 0.04, P value 0.04, I<sub>2</sub> = 57%), and this benefit persisted at the 12-month follow-up evaluation in 2 trials, 54 participants, low quality evidence (UWS, MD 0.06ml/minute, 95% CI 0.01 to 0.11, P value 0.03, I<sub>2</sub> = 10%). For the outcome of stimulated whole saliva (SWS) 3 trials (71 participants, low quality evidence), there was a benefit favouring acupuncture (MD 0.19 ml/minute, 95% CI 0.07 to 0.31, P value 0.002, I<sub>2</sub>= 1%). This effect also persisted at the 12-month follow-up evaluation (SWS MD 0.28 ml/minute, 95% CI 0.09 to 0.47, P value 0.004, I<sub>2</sub> = 0%) (2 trials, 54 participants, low quality evidence). The conclusions were that there is some low quality evidence that acupuncture produces a small increase in saliva production in patients with dry mouth following radiotherapy. Reported adverse effects of acupuncture are mild and of short duration.

Below a list of interesting studies.

Bloom et al. (1996) were the first to report a RCT in which the treatment with acupuncture and auricular acupuncture induced a persistent increase of salivary flow in 36 patients with severe xerostomia from radiotherapy observing an improvement of 68% with acupuncture and auriculotherapy treatments compared to an improvement of 50% in the placebo-group. The next follow-up, after 32 months in 2000, confirmed the previous results: a statistical significant improvement of xerostomia in subjects treated with acupuncture and auricular acupuncture, compared to the patients not treated in 6 months and even in 3 years.

Subsequently some works obtained positive results with acupuncture and auricular acupuncture (Johnstone 2001, 2002) but without control group.

Wong et al. (2003) used electrostimulation in 36 patients randomised in 3 groups with different point of acupuncture. After 6 months of treatment, the increase of salivation was statistically significant from 3 to 6 months. In studies in which fMRI has been used, there were a connection between the stimulation in the LI-2 point and the activation in cerebral area which is responsible for the production of saliva.

In a work (Cho et al. 2008), 12 patients suffering of xerostomia caused by radiotherapy have been treated in 2 randomized groups, one with true acupuncture (ST6, LI4, ST36, SP6) and the other one with false acupuncture (treating points that are 2 cm distant from the true points). In both of groups an improvement from subjective symptoms could be observed, but it was not significant.

An interesting study conducted by Deng et al. (2008) used functional magnetic resonance imaging to evaluate changes in saliva production associated with acupuncture at point LI-2. Manual stimulation of LI-2 acupoint of the non-dominant hand was associated with neuronal activations that were absent during sham acupuncture (Streitberger needle at a non-acupoint on the ulnar side of the ipsilateral forearm, 3 cm lateral to PC-6, non penetrating the skin manually manipulated by twisting). Furthermore, neuroimaging signal changes appeared to correlate with saliva production. Mean saliva production in grams during the true versus sham acupuncture was 2.72 (standard deviation, 1.42) and 2.38 (standard deviation, 1.43), respectively.

Meidell and Rasmussen (2009) treated 82 patients suffering xerostomia for 2 years; 14 of them have been included in a study with 10 acupuncture treatments for 5 weeks. The results show improvement of the dryness of the mouth in all patients. Garcia et al. (2009) in a short pilot study on 19 patients verified a significant difference in quality of life after acupuncture treatment in the fourth and the eighth week respect the initial situation.

The randomised controlled study of Pfister et al. (2010) evaluated if on 58 patients with passed surgical intervention the acupuncture treatment (during 4 weeks in 28 cases) reduces pain, shoulder dysfunction, and the xerostomia compared to usual therapy (in 30 cases). The results demonstrated significant statistically improvements of the pain (p<0.008) and the xerostomia (p<0.002) in the acupuncture group respect the conventional therapy group.

A randomised controlled study by Wong et al. (2010) compared acupuncture treatment with electrostimulation respect the standard treatment with pilocarpine in 60 patients with xerostomia caused by radiotherapy, and did not find differences among the 2 groups.

Braga et al. (2011) made a controlled randomised study on 24 patients with xerostomia; 12 of them have been treated before and after radiotherapy with acupuncture, and 12 were not treated with acupuncture. The study shows a significant statistical difference between the 2 groups, with increase of salivation and reduction of xerostomia in the acupuncture group.

In China Meng et al. (2012) conducted 2 RCTs. In the first RCT, 40 patients with nasopharyngeal cancer were treated in the same days of radiotherapy and the results were compared to a controlled group of 46 patients exposed to standard care. At the end, the acupuncture group presented an improvement of the quality of life. The second pilot study of Meng et al. (2012) compared 23 randomised controlled patients divided in 2 groups, treated 3 times a week during the radiotherapy. The first group has been treated with true acupuncture and the second one with sham acupuncture. A significant statistical improvement has been observed in xerostomia and in the quality of life with the true acupuncture.

A recent RCT by Simcock et al. (2013, England) examined 145 patients with xerostomia caused by radiation. The patients have been randomised in 2 groups, the trial has demonstrated a significant improvement of symptoms in patients treated with 8 acupuncture sessions respect to patients of the second group treated with education oral care.

### Single clinical studies on xerostomia in adults

Type of Study	Therapeutic Protocol	N. patients and diseases	End point criteria	Results	Author, year
RCT 1) acupuncture 2) placebo acupuncture	1) true acupuncture 2) superficial acupuncture twice weekly for 6 weeks, then 2 week break and further 6 weeks treatment	n. 21 randomized (11 group 1, 10 group 2) n. 20 evaluated patients with xerostomia due to primary and secondary Sjögren's syndrome, irradiation and other causes	salivary flow rates stimulated (SSFR) and unstimulated (UWSFR)	both groups significantly increased salivary flow rates after the acupuncture treatment, The improved salivary values persisted during the observation year only in the acupuncture group	Bloom, 1992
RCT 1) acupuncture 2) placebo acupuncture	1) auricular points (2-4): shen men, sympathetic, kidney, mouth, stomach, gl.Parotis, subcortex Points (5-8) ST3 ST5 ST6 ST7 GV20 SI17 LI18 P6 HT7 LI4 LI10 LI11 SP8 SP6 KI3 KI5 KI6 SP3 ST36 LV3 2) superficial needling 1 cm away from the classical acupuncture point, 24 treatments	n. 41 randomized n.38 completed treatment (20 group 1, 18 group 2) head and neck cancer	salivary flow rates stimulated (SSFR) and unstimulated (UWSFR)	both groups significantly increased salivary flow rates after the acupuncture treatment, no differences statistically significant between groups Group 1 68%, Group 50% of patients increased salivary flow rates at the end of the observation period	Bloom, 1996
Retrospective study 1) acupuncture 2) placebo acupuncture	24 acupuncture treatments using two-way ANOVA (see Blom 1996)	70 patients with xerostomia due to primary and secondary Sjögren's syndrome, irradiation and other causes	Salivary flow rates (SFR)	Statistically significant differences in unstimulated and stimulated salivary flow rates ( $P < 0.01$ ) up to 6 months and 3 years follow-up	Bloom, 2000
Observational study 1) predetermined set of acupuncture points 2) predetermined set of acupuncture points 3) predetermined set of acupuncture points	Codetron treatment twice weekly for 6 weeks 1) SP6 ST36 (active electrode AE )CV24 (indifferent electrode IE) 2) SP6 ST36 P6 (AE), CV24(IE) 3) SP6 ST5 ST6 P6(AE)CV24 (IE)	n. 46 randomized n. 37 completed treatment (13 group 1, 10 group 2, 14 group 3) head and neck cancer	Five-item xerostomia symptom questionnaire with VAS	Improvement in xerostomia symptoms mean increase in the visual analogue scale score of 86 ( $p < 0.0005$ ) and 77 ( $p < 0.0001$ ) at 3 and 6 months after treatment completion, respectively in all 3 groups without statistically significant differences	Wong, 2003

RCT 1) real acupuncture  2) sham acupuncture	1) real acupuncture: ST6 LI4 ST36 SP6  2) sham non-acupoints 2 cm away from the real acupoints, twice weekly for 6 weeks, 20 minutes	n.12 randomized (6 group1, 6 group 2) with radiation--induced xerostomia in head and neck cancers	Measurement salivary flow rates  XQ (1-4 points)	Both groups showed a slight improvement with no significant difference, only RA significantly improved saliva secretion at 6 weeks, compared to before treatment (p <0.05) and the score for dry mouth, by 2.33 points versus 0.33 in the controls	Cho, 2008
Observational study	acupuncture ST4 5,6,7 LI3 SP6 twice a week for 5 weeks	n. 14 various cancers	VAS for: xerostomia, dysphagia and dysarthria Measure of salivary flow rates stimulated and unstimulated	VAS decreased from Md 7.5 before the baseline to 3.3 before the tenth treatment (P < 0.001)	Meidell, 2009
Pilot study	acupuncture: CV24 ST36 LI1 LU7 Ear shenmen, Point 0, Salivary gland 2'  twice a week for 4 weeks.	n.19 head neck cancer	Xerostomia inventory (XI) and patient benefit questionnaire (PBQ)  Sialometry	scores were significantly better after acupuncture on weeks 4 and 8 than at baseline XI: p = 0.0004 and 0.0001;PBQ: p = 0.0004 and 0.0011, respectively)  No side effects	Garcia, 2009
RCT:  1) acupuncture  2) usual care	1) weekly acupuncture (LI4 SP6 GV20, luozhen, and auricular shenman, bilateral LI2  2) no specific treatment, physical therapy, analgesia, and/or anti-inflammatory drugs	n.70 randomized, n.58 completed study (28 group 1, 30 group 2)  undergone neck dissection for cancer	Xerostomia Inventory Numerical  Rating Scale of Pain	Significant reductions in pain (P <0 .008) and xerostomia (P <0.02) and pain (P <0 .008)	Pfister, 2010
RCT 1) treatment group ALTENS (acupuncture-like transcutaneous electrical nerve stimulation) 2)control group standard mouth care only	1)ALTENS daily on acupuncture points Sp6 ST36 Li4 and P6 (on alternate days) bilaterally, CV24 (ground electrode)for 20' 2) standard mouth care without amifostine or pilocarpine after each radiation treatment	n.60 randomized (30 group 1, 26 group 2) head and neck cancer	whole saliva production (WSP) plus RIX symptoms visual analogue score (RIXV AS)	no statistically significant differences between the two groups ALTENS is not recommended as a prophylactic intervention	Wong, 2010

<p>RCT</p> <p>1)acupuncture before and during RT</p> <p>2)control group RT no acupuncture</p>	<p>1) Local (ST3,4, 5,6, 7 GB2 SI19 TB21), distal(LI4 LI11 LR3 ST36 KI3 KI5 GV20) and auricular (Shen-Men, Central Nervous System, Neurovegetative System, Kidney, Spleen Pancreas and Mouth acupoints)</p> <p>2) no acupuncture</p>	<p>n. 24 randomized (12 group 1, 12 group 2)</p> <p>with head and neck cancer radiation-induced xerostomia</p>	<p>salometry measuring the resting (RSFR)and stimulated (SSFR) salivary flow rates visual analogue scale (VAS) regarding dry mouth-related symptoms</p>	<p>improved salivary flow rates (RSFR, SSFR;p &lt; 0.001)</p> <p>decreased xerostomia related symptoms (VAS, p &lt; 0.05)</p>	<p>Braga, 2011</p>
<p>RCT</p> <p>1) acupuncture</p> <p>2) standard care</p>	<p>1) Body points Ren24, LU 7, KI6 earpoints Shenmen, Point Zero, Salivary gland 2-prime and Larynx</p> <p>2) 3 times/ week on the same days they received radiotherapy</p>	<p>n.86 randomized (40 group 1, 46 group 2) with nasopharyngeal carcinoma</p>	<p>Xerostomia Questionnaire and MD Anderson Symptom Inventory-Head and Neck (MDASI-H)</p> <p>measures unstimulated whole salivary flow rates (UWSFR) and stimulated salivary flow rates (SSFR)</p>	<p>significantly reduced scores for acupuncture vs in week 3 through the 6-months (P=0.003 at week3, all other P's &lt; 0.0001)</p> <p>unstimulated whole salivary flow rate, P = 0.0004), with greater saliva flow in the acupuncture group at week 7 (unstimulated whole salivary flow rate, P &lt; 0.0001;stimulated whole salivary flow rate, P =0.002)and 11 (unstimulated whole salivary flow rate, P &lt; 0.02; stimulated whole salivary flow rate, P &lt; 0.03) and at 6 months (stimulated whole salivary flow rate, P &lt; 0.003) and improved quality of life</p>	<p>Meng, 2012</p>
<p>RCT pilot study</p> <p>1) real acupuncture</p> <p>2) sham acupuncture during the course of radiotherapy</p>	<p>1) Body points: Ren 24, LU7, KI6 + sham needle at GB 32 Ear points :Shenmen, Point Zero, Salivary Gland 2-prime (SG 20) and Larynx</p> <p>2) non-penetrating needle device Park 0,5-1 cun from points + GB32 true</p> <p>4 real auricular points</p>	<p>23 randomized (11 group 1, 12 group 2) nasopharyngeal carcinoma</p>	<p>Xerostomia Questionnaire (XQ) and MD Anderson Symptom Inventory for Head and Neck Cancer (MDASI--HN).</p> <p>measures unstimulated whole salivary flow rates UWSFR) and stimulated salivary flow rates (SSFR)</p>	<p>XQ scores for acupuncture were significantly lower than sham controls starting in week 3 and lasted through the 1-month follow-up (all P's &lt;0.001 except for week 3, 0.006) No group differences for UWSFR and SSFR</p>	<p>Meng 2012</p>

<p>RCT cross over 1) oral care followed by acupuncture 2) acupuncture followed by oral care and education</p>	<p>weekly for 8 weeks LI2 LI20 bilaterally ear points bilaterally Salivary gland 2, modified point Zero and Shen men</p>	<p>n.145 randomized (75 group 1, 70 group 2)  head and neck cancer</p>	<p>Head and neck subscale saliva (stimulated and non-stimulated) production measures using Schirmer strips</p>	<p>acupuncture compared with oral care produced significant reductions in patient reports of severe dry mouth (OR = 2.01, P = 0.031) sticky saliva (OR = 1.67, P = 0.048), needing to sip fluids to swallow food (OR = 2.08, P = 0.011) and in waking up at night to drink (OR = 1.71, P = 0.013)</p>	<p>Simcock, 2013</p>
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## Conclusions of the literature and of the authors

The guidelines of Filshie et al. (2006) indicate that specific conditions which should be taken into consideration are: xerostomia in patients who do not respond to the conventional treatment.

According to the Guidelines of the Society for Integrative Oncology (SIO 2009), acupuncture can be considered as a method to stimulate the production of saliva in patients with xerostomia caused by radiation, particularly when they do not respond to pilocarpine. The degree of recommendation is 1B (strong recommendation, moderate quality evidence). These conclusions have been also confirmed by recent reviews and RCTs, which demonstrate acupuncture and auricular acupuncture are effective methods to treat xerostomia in cancer patients.

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### *Xerostomia and homeopathy*

The only trial found in the literature regarding the use of homeopathy on this symptom was conducted by Hail et al. (2005).

In this blind, placebo-controlled longitudinal study, 28 people diagnosed with dryness of the mouth were randomly assigned to receive either placebo or individually prescribed homeopathic medicines to evaluate the possible effects of homeopathy on oral discomfort.

All patients were first divided in 2 groups according to their medication and after that the 2 groups were randomly assigned according to a coin-toss to the experimental or control group. Most patients had systemic diseases (rheumatoid arthritis and/or Sjögren's syndrome) and took frequent daily medications. The randomly selected experimental group (n=15) received an individually prescribed homeopathic medicine and the control group (n=13) a placebo substance (sugar granules), both for 6 weeks. Oral dryness was evaluated by measurement of unstimulated and wax-stimulated salivary flow rates and visual analogue scale. With only two exceptions, the experimental group had a significant relief of xerostomia whereas no such effect was found in the placebo group. Stimulated salivary flow rate was slightly higher with homeopathy than placebo but no consistent changes occurred in salivary immunoglobulin (IgA, IgG) levels. In an open follow-up period those receiving homeopathic medicine continued treatment and the placebo group patients were treated with individually prescribed homeopathic medicines. The symptoms of xerostomia improved in both groups. The results of the trial suggest that individually prescribed homeopathic medicine could be a valuable adjunct to the treatment of oral discomfort and xerostomic symptoms.

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## Chapter 5

### CAM for type of cancer

#### Acupuncture/TCM

##### *Bladder cancer*

Beneficial effects of acupuncture have already been evaluated in the section dedicated to pain (see Tab. 1). Here we discuss the acupuncture capacity to treat cancer progression and pain in urinary function acting through purinergic receptors.

In a review, Burnstock G. (2011) shows how acupuncture, through a peripheral nerve stimulation, induces a release of ATP, co-transmitter together with noradrenaline in sympathetic nerves and with acetylcholine in parasympathetic nerves, and how this may interact with specific purinergic receptors (P2X3 and/or P2X2/3) present on low-threshold sensory nerve fiber in the skin.

These interactions activate a signal transduction via sensory ganglia until reaching a motor neuron in the brain stem that controls autonomic several functions including urogenital activities. These messages also elicit inhibitory neuromodulation in the cortex pain centre. Furthermore, the binding of ATP with P2X cell surface receptors has shown antitumor activity via induction of P2X receptor-mediated apoptosis, reducing cells growth, in a concentration dependent manner (see Fig. 1).

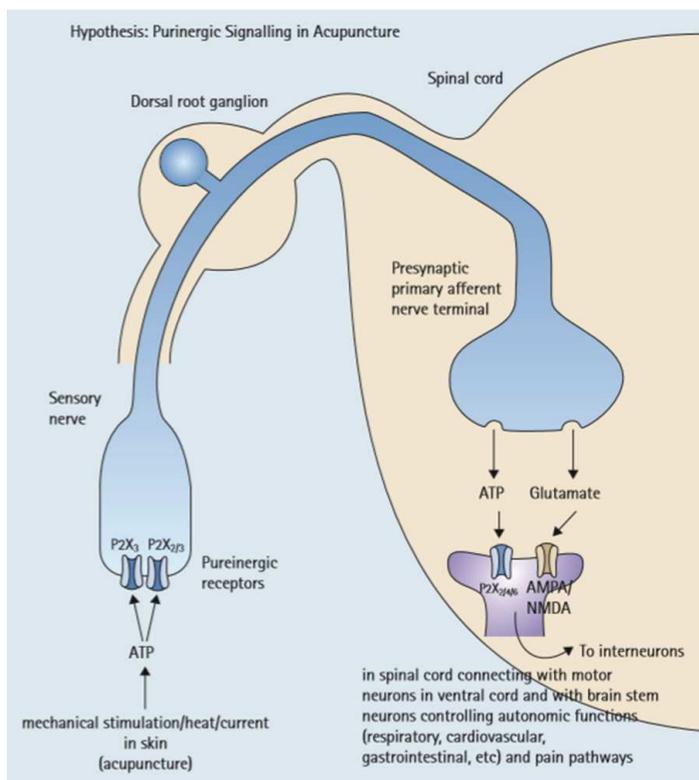


Fig.1. Purinergic signalling in acupuncture.

In bladder cancer, the combination of ATP with the established antitumor antibiotic drugs, like mitomycin C or mitoxantrone, has been shown to increase significantly, *in vitro* and *in vivo* (on mice), the cytotoxic action of drugs. The ATP acts in an additive manner; since the antitumor antibiotic drugs are cell cycle non-specific, whereas ATP has been shown to induce directly cell cycle arrest.

In this way it may be possible to combine an ATP with chemotherapeutic drugs known to work in different phases of the cell cycle, to prevent any overlap and to increase the chance of synergism.

In summary, there is strong evidence for a role for ATP acting through purinergic receptor subtypes in animal models and human tumour cell lines of prostate and bladder cancer. It is necessary to study whether this will be established for human tumours; therefore *in vivo* studies are needed to evaluate the action that

acupuncture can have on ATP release in patients with bladder cancer and both the induction of apoptosis of tumor cells and the modulation of pain (Burnstock G. 2011, 2013).

**Summary table**

Symptoms / Paragraphs	Grading
Pain (*)	1 A
Cancer progression (§)	

Tab.1. Summary Table. (\*) For detailed information, please refer to the symptoms paragraph (§). For detailed information, please see bladder cancer paragraph.

**References**

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*Blood cancer*

In the literature, no RTCs about the effect of acupuncture on blood cancer patients published in the last 10 years were found. However, 3 reviews and 1 systematic review analyzed the integration of acupuncture in the treatment of blood cancer.

In the first review, Wesa and Cassileth (2009) claimed that in patients with leukemia, the complementary therapies and especially acupuncture, are very beneficial for symptom management without adverse consequences, and with reports of less than one adverse event in over 10,000 acupuncture treatments.

Moreover, Zou Y. et al. (2009) pointed out that acupuncture has strong potential as an adjunctive therapy treatment of multiple myeloma with thalidomide or bortezomib-induced painful neuropathy and a better understanding might guide its use in the management of chemotherapy-induced neuropathic pain. However, other well-designed studies are needed to validate the protocol.

In the third review, Kelly et al. (2009) analyzed the integrative therapies in children with haematological malignancies. They stated that children with fear of needles and discomfort with the invasiveness of conventional treatments such as intrathecal chemotherapy injections and bone marrow aspirations may have added anxiety with the use of acupuncture; in this instance, acupressure or massage would be more appropriate options.

Finally, the systematic review of Liu J et al. (2011) analysed 716 reports involving 1,198 cancer patients, over more than 50 years. Although generally the works were of poor quality, the authors point out that 14.11% (169 patients) of the total were leukemic patients treated with traditional Chinese medicine; the use of acupuncture was relatively rare (1.8%; 22 patients of the total) and applied generally for the relief of cancer pain or attenuation of nausea and vomiting induced by chemotherapy.

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*Bone cancer*

In literature, we did not find systematic reviews or RTCs about the effect of acupuncture on patients with bone cancer. Some studies on cancer-induced bone pain (CIBP) have been already described in the pain paragraph (see Tab. 1).

Based on laboratory studies on animals, Paley CA et al. (2011), in a review, claimed that it is possible to conclude the effectiveness of acupuncture in treating CIBP reducing pain transmission and/or sensitization

at peripheral and central sites. However few clinical trials have been conducted. In this paper the authors explain how acupuncture acts reducing the CIBP through a combination of peripheral and central mechanisms. The acupuncture stimulates the SNC through the small myelinated A $\delta$  fibers in muscle and skin, which synapse with interneurons in the substantia gelatinosa (SG) of the spinal cord resulting in the release of inhibitory neuromodulators such as enkephalin, that reduce activity in nociceptive-specific and wide-dynamic range neurons. The application of acupuncture affects, via SNC fibres, the limbic system, where it modulates emotional responses to pain.

Clinical experience suggests that acupuncture is elective for treating CIBP, although there is no published information indicating the extent of its use in practice. To date, only a few studies with a low number sample groups, published over 10 years ago, have provided encouraging data on the efficacy of acupuncture in the treatment of CIBP. Further studies are needed to prove the effectiveness.

Furthermore, the study of T Bao et al. (2011) is interesting because the authors evaluated the efficacy of magnetic acupressure in reducing pain in cancer patients undergoing marrow aspiration and biopsy. Seventy-seven patients without previous acupuncture or acupressure experience were stratified and randomized to having magnetic acupressure delivered to the LI4 acupoint (38 patients) or (40 patients) to a sham site (no acupuncture point located in the first dorsal interosseous space of the hand).

The success of treatment was evaluated using a visual analogue scale (VAS). The data show that there is no significant difference between the median pain scores of patients treated at the LI4 site and the sham site ( $p=0.87$ ). However, severe pain ( $VAS \geq 7$ ) was reported in only one patient (2.7%) treated at the LI4 site compared with 8 patients (20%) at the sham site ( $p=0.03$ ). Moreover, magnetic acupressure at the LI4 is not invasive, well tolerated, and requires minimal training and expense.

### Summary table

Symptoms/Paragraphs	Grading
Pain (*) (§)	1A

Tab.1 (\*). For detailed information, please refer to the symptoms paragraph, (§). For detailed information, please see bone cancer paragraph.

### References

Bao T, Ye X, Skinner J, Cao B, Fisher J, Nesbit S, Grossman SA. The analgesic effect of magnetic acupressure in cancer patients undergoing bone marrow aspiration and biopsy: a randomized, blinded, controlled trial. *J Pain Symptom Manage*. 2011 Jun;41(6):995-1002

Paley CA, Bennett MI, Johnson MI. Acupuncture for cancer-induced bone pain? *Evid Based Complement Alternat Med*. 2011

### Brain cancer

Until today, few papers have been published about the application of acupuncture in brain cancer and these were described in the paragraphs related to the symptoms caused by surgery such as nausea and vomiting, and pain (see Tab. 1).

In this paragraph there were enlisted papers analysing the use of acupuncture in the treatment of brain cancer patients undergoing craniotomy.

Lu ZH et al. (2010) investigated the effect of electroacupuncture (EA) preconditioning on the serum level of S100 calcium-binding protein beta (S100beta) and neuron-specific enolase (NSE), 2 neural damage markers, in patients undergoing craniocerebral tumor surgery. The study enrolled 32 patients randomly assigned to two groups: electroacupuncture group (EAg) and control group (Cg).

The patients in EAg received electroacupuncture (Stimulus:1-4 mA, density wave frequency: 2/15 Hz) on Du16 and GB20 acupoints for 30 minutes, 2 hours before the operation, while patients in Cg received no treatment.

The anaesthesia was maintained with remifentanyl (4-8 mg/kg per hour), pumped intravenous drip of vecuronium (1.0-2.0 microg/kg each hour), and discontinuous intravenous dripped with vecuronium bromide (0.5-1 mg).

The data have shown that the 2 indices, measured with ELISA before operation, before skin incision, after tumor removal, at the end of operation, and at 24 hours after the operation, had significantly increased in comparison to before the operation ( $P<0.05$ ). Furthermore, at the end of the operation and 24 h post-

operation, the serum levels of S100beta and NSE in the EA group were significantly lower than those in the Cg (p<0.05).

The authors suggest that this decrease may have a potential protective effect on brain damage. This necessitates further studies.

In two different studies, An LX et al. (2010, 2011 - Chinese language) analysed the effect of acupuncture on the sevoflurane anaesthetic requirement for resection of supratentorial cancers and the speed of post-operation recovery. The authors analysed a total of 120 cases of supratentorial tumor resection patients who were randomized in 3 groups: general anesthesia (GA) group, EA-proximal acupoints group (EA-PA group) and EA-distant acupoints group (EA-DA group).

The patients in EA-PA group and EA-DA group received electroacupuncture (2 Hz/100 Hz beginning from the anesthesia induction until the end of the surgical operation.) on GB 20, BL 10, BL 2 and EX-HN 4 acupoints in EA-PA group and on LI 4, TE 5, BL 63, LR 3, ST 36 and GB 40 acupoints in EA-DA group. All patients were anesthetized by inhalation of propofol (2 mg/kg), sufentanil (0.3 microg/kg) and vecuronium bromide (0.1 mg/kg) and maintained with sevoflurane.

The data have shown that in comparison with GA group, the minimum alveolar concentration (MAC) of sevoflurane, both in EA-PA and in EA-DA groups, was significantly lower (p < 0.05, p < 0.01). The bispectral index was significantly higher (P < 0.05) in EA-DA groups if compared to GA group.

Finally, the autonomous respiration recovery time, tracheo-tube removing time, eye-opening time, voluntary motion recovery time, orientation force recovery time, and operating room-departure time of both EA-PA and EA-DA groups were significantly shorter (P < 0.05, P < 0.01) than those of GA group. The author concludes that EA of both proximal and distant acupoints can reduce the expired concentration and MAC of sevoflurane during anesthesia maintenance, and accelerate the recovery after anesthesia in supratentorial tumor resection patients.

Furthermore, Yang C et al. (2012) randomized 80 patients in a blinded controlled design to objectively test the hypothesis that EA decreases the amount of sevoflurane needed for anesthesia, facilitates the regulation of the physiological and pathological changes of the human body during surgery and improves the overall recovery profiles. In the study, the acupoints LI4, SJ5, ST36, BL63, LR3, and GB40 were connected to a dual channel electrical stimulator (frequency of waves: 2Hz/100Hz, altered/3sec; pulse duration: 0.6ms/0.2ms). The data demonstrated that EA-group required 9.62% less sevoflurane than the placebo EA-group (P<0.05). During recovery from anesthesia, the autonomous respiration recovery time, tracheo-tube removal time, eye-opening time, voluntary motor recovery time, orientation force recovery time and operating-room departure time of the EA-group were all significantly shortened, 35.86%, 27.07%, 38.38%, 30.11%, 34.95%, 28.80% than the corresponding placebo EA-group (P<0.05). Finally, the serum enkephalin values in the EA group were greater than in placebo EA-group.

### Summary table

Symptoms / Paragraphs	Grading
Nausea and vomiting (*)	1A

Tab.1 (\*) For detailed information please refer to the symptoms paragraph.

### References

An LX, Li J, Ren XJ, Liu YN, Wang BG. [Effects of electroacupuncture of different acupoint groups on sevoflurane anesthesia in patients undergoing resection of supratentorial tumors]. *Zhen Ci Yan Jiu*. 2010 Oct;35(5):368-74

An LX, He Y, Ren XJ, Li SQ, Han RQ, Wang BG. [Effect of electroacupuncture on Sevoflurane anesthesia in patients undergoing resection of supratentorial tumor]. *Zhongguo Zhen Jiu*. 2010 Aug;30(8):669-73

Lu ZH, Bai XG, Xiong LZ, Wang YH, Wang Y, Wang Q. Effect of electroacupuncture preconditioning on serum S100beta and NSE in patients undergoing craniocerebral tumor resection. *Chin J Integr Med*. 2010 Jun;16(3):229-33

Yang C, An L, Han R, Kang X, Wang B. Effects of combining electroacupuncture with general anesthesia induced by sevoflurane in patients undergoing supratentorial craniotomy and improvements in their clinical recovery profile & blood enkephalin. *Acupunct Electrother Res*. 2012;37(2-3):125-38

### Breast cancer

Numerous studies on breast tumours and TCM have been published. The majority of them have been reported in the chapters on the specific symptoms caused by surgery, radiotherapy and/or chemotherapy. These symptoms include anxiety and depression, CRF, vasomotor disorders, pain (post mastectomy, arthralgia, and musculoskeletal symptoms in breast cancer patients taking aromatase inhibitors), insomnia, lymphedema, nausea and vomiting (see Tab. 1). Breast tumours are also discussed in the chapter on the quality of life.

We did not find any studies in the literature on the progression of breast cancer and its treatment with TCM. As regards to guidelines, it must be pointed out, that up to now, no actual guidelines have been established in reference to the use of acupuncture in breast cancer.

Baum et al. (2006) refer to acupuncture in “Recommendations for the role of Complementary and Alternative Medicine (CAM) in the management of breast cancer”. The aim of the European Society of Mastology (EUSOMA) Workshop, Florence 2004, was to produce guidelines on the use of CAM for breast cancer. It was extremely difficult for all members of the workshop to reach a consensus on the current state of affairs but all accepted that practitioners of conventional medicine and of CAM are working in good faith to improve the length and QoL for women with breast cancer.

Recently, Liao et al. (2013) published a review with the aim of facilitating an understanding of the current practice and usefulness of herbal medicine and acupuncture as adjuvant in breast cancer therapy.

With reference to acupuncture, information from the literature on the following symptoms is reported: hot flashes, nausea and vomiting, pain, fatigue, anxiety, depression, insomnia, lymphedema and leukopenia. The authors report these contraindications and caution for the use of acupuncture in breast cancer patients: extreme needle phobia, very “strong reactors” to acupuncture, coagulopathy, immunocompromised patients or neutropenia (less 500/mm<sup>3</sup>)—risk of infection.

Conclusions of the authors are that acupuncture is a valuable non-pharmacological treatment option for symptom management in cancer patients but rigorously designed clinical trials are needed to improve the quality of the existing evidence base and support the use of CAM.

Price et al. (2013) in a longitudinal qualitative study, recruited 14 women diagnosed with breast cancer to receive up to 10 sessions of Traditional Acupuncture (TA) during chemotherapy. Patients were interviewed before, during, and after chemotherapy. Two practitioners of TA delivered treatment and were interviewed before and after the study. Practitioners had spoken substantially about using acupuncture to increase vitality and fortifying and strengthening the person to enable them to cope better, while the women reported that this “feeling better” could be about symptom relief (reported by most of the participants), combined with inducing a sense of calm or feeling more relaxed. They talked about feeling more composed, balanced, lighter, energised and better in themselves as well as more peaceful. During the interviews all the women, without exception, discussed these specific symptoms being helped by the acupuncture: extreme tiredness, nausea, and a disorientated feeling, extreme night sweats, disturbed sleep, headaches and eye pain: they reported that symptoms frequency and intensity were reduced immediately, sleep was improved and that they felt more relaxed at night. Several participants talked about help with emotional problems, reduction in anxiety levels was dramatic for two participants, almost immediately on starting acupuncture.

The women valued the whole experience of TA and reported receiving considerable benefit from it, providing further evidence of TA as a supportive and integrative treatment during chemotherapy.

#### Summary table

Symptoms / Paragraphs	Grading
Anxiety and depression (*)	2B (**)
Cancer Related Fatigue (*)	2C (**)
Pain (*)	1A
Insomnia (*)	2C (**)
Hot Flashes (*)	1B
Lymphedema	2C (**)
Nausea and vomiting (*)	1A

Tab. 1. Symptoms studied in the treatment of breast cancer. (\*) For detailed information please refer to the symptoms paragraph. (§) For detailed information please see breast cancer paragraph. (\*\*) In the absence of SIO grading, the grading was assigned by the authors.

## Conclusions of the literature and of the authors

Acupuncture is suggested as an adjunct treatment option in patients with treatment induced nausea and vomiting or cancer related pain (that is poorly controlled by usual post mastectomy care, aromatase inhibitors associated arthralgia). The authors point out that acupuncture can also be used in the treatment of hot flashes, insomnia, anxiety and depression. For fatigue, the use of moxibustion is advised in order to obtain better results. There is also a significant improvement in the quality of life which is described in a specific chapter.

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## Colon cancer

The literature reports very few studies (mostly in Chinese) on colon cancer and acupuncture. Some studies evaluate the effect of the immune function in progress on colon tumours.

Zhao et al. (2011 - article in Chinese) studied the effect of acupuncture on the immune function of patients with colorectal cancer liver metastases. Sixty cases were treated with acupuncture (ST 36 SP6 PC 6 ST37 LI 4 KI 3 LR 3 SP9 GB34) and moxibustion (CV 8 CV4 CV6 ST 36). The value of T lymphocyte subsets such as CD 3, CD 4, and CD 8, as well as Natural Killers (NK) cells, examined with flow cytometry, increased after treatment, and there were significant differences between them before and after treatment. The conclusions of the authors were that acupuncture can improve the immune function of patients with colorectal cancer liver metastases.

Zhang et al. (2011 - article in Chinese) conducted a RCT on the same topic to verify the clinical therapeutic effect of warming needle moxibustion on improvement of the gastrointestinal and immune function in patients with post operation of colorectal cancer. 105 patients were randomized into: acupuncture and moxibustion group, Chinese medicine group and routine treatment group, 35 in each group. The acupuncture and moxibustion group was also treated with warming needle moxibustion on the 1<sup>st</sup> day after surgery; Zusanli (ST 36), Shangjuxu (ST 37) and Xiajuxu (ST 39) and others points were selected, once a day for 10 days.

The Chinese medicine group was treated with Simo Decoction (composed of 4 elements such as *Fructus Aurantiis*, *Radix Aucklandiae*, *Semen Arecae* and *Radix Linderae*), 3 times daily for 10 days. The gastrointestinal function (time of the first bowel sound, exhaust and defecation), peripheral blood components and changes of T lymphocyte and NK cells in postoperative patients were observed. On the 10<sup>th</sup> day after surgery, the percentages of distribution of lymphocyte and neutrophil in the acupuncture and moxibustion group were better than in the Chinese medicine group and the routine treatment group (P<0.05). The acupuncture and moxibustion group was also superior both to the Chinese medicine group and to the routine treatment group in improving the subgroup of T lymphocyte, NK cells and the digestive system symptoms (P<0.05). The authors concluded that warming needle moxibustion has a good therapeutic effect on gastrointestinal function and can regulate bidirectionally peripheral blood lymphocyte and neutrophile granulocyte and improve the T lymphocyte subgroup and NK cells so as to promote the recovery of immune function in patients with colorectal cancer after operation.

Regarding the efficacy of acupuncture for postoperative ileus (POI) after intraperitoneal surgery for colon cancer, that prolongs hospitalization and increases risk of postoperative complications, 3 RCTs have been published with contrasting results. In 2 of them no significant differences were observed in the treatment of POI with acupuncture in comparison to the treatment of the control group with usual care (Meng 2010) or with sham acupuncture (Deng 2013). However, Ng et al. (2013) demonstrated that electroacupuncture was more effective than no or sham acupuncture in reducing postoperative analgesic requirement and time to ambulation and was associated with a shorter duration of postoperative ileus and hospital stay after the surgery.

**Single clinical studies on colon cancer patients (adults)**

<b>Type of study</b>	<b>Therapeutic protocol</b>	<b>N. patients and disease</b>	<b>Endpoint criteria</b>	<b>Results</b>	<b>Author, year</b>
RCT 1) electroacupuncture 2) usual care	1) electroacupuncture SJ6,GB34,ST36,ST37 bilaterally once a day starting on postoperative day 1 for 6 days 2) standard post operative care	n.137 eligible n.85 randomly assigned (44 group 1; 41 group 2)  patients with PPOI (postoperative ileus) after intraperitoneal surgery for colon cancer	measure of bowel motility (first flatus, first bowel movement, electrogastroenterograph)	no significant difference in PPOI on day 4 (P=0.71), on 5 day (P=0.69), on day 6 (P=0.88). No adverse events	Meng, 2010
RCT 3. acupuncture 4. sham	1) acupuncture ST36 PC6 LI4 SP6 SP9 ST25 Auricular shenmen bilaterally EA ST36 PC6 2) Same point; plastic guiding tube, without needle insertion and without electrical current  30 min. twice daily during the first 3 postoperative days follow up at weeks 9 and 12	n.90 enrolled n.81 completed treatment (39 group 1, 42 group 2)  patients with PPOI after intraperitoneal surgery for colon cancer	first tolerance of solid food and first passed flatus or bowel movement	no significant differences were found between groups (P=0.9)	Deng, 2013
RCT prospective study 1) electroacupuncture EA 2) sham SA 3) no acupuncture NA	1) EA ST36,SP6,LI4,TE6 2) SA shorter needles, placed 15 mm from acupoints less depth 3) NA	n.165 randomized (55 group 1, 55 group 2, 55 group 3)  Patients undergoing elective laparoscopic surgery for colonic and upper rectal cancer	first defecation, length of hospital stay	shorter time to defecation EA vs. NA (P < .001)and SA (P<0.007) and length of hospital stay (P < .007) EA vs. NA  No adverse events reported	Ng, 2013

## Conclusions of the literature and the authors

It is not possible to conclude whether or not acupuncture could improve the symptoms of patients with colon cancer. Therefore further studies and especially RTCs are strongly required.

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## Head and neck cancer

Until today a lot of papers have been published about the application of acupuncture in head and neck cancer (HNC), which are described in the paragraphs relating to the symptoms caused by surgery or chemoradiation such as xerostomia, lymphedema and pain (see Tab. 1).

Here we analyse the use of acupuncture in the treatment of dysphagia after chemoradiation therapy (CRT) in head and neck cancer patients.

Lu et al. (2010), in a retrospective case-series report, treated 10 patients (diagnosed with stage III/IV squamous cell carcinoma) with acupuncture for radiation-induced dysphagia and xerostomia.

Seven of 10 patients were percutaneous endoscopic gastrostomy (PEG) tube-dependent when they began acupuncture. Manual acupuncture (often used: ST36, SP6, LI2, LI11, GV20, Shenmen/ear, Sanjiao/ear, ST7, ST6, ST5, CV23, GB20, Yintang) and electroacupuncture (GV20 and Yintang with a frequency of 2–4 Hz) were used once a week for a median of 13.5 sessions (range 7-40).

Nine of 10 patients reported various degrees of subjective improvement in swallowing functions, xerostomia, pain and fatigue levels. Six (86%) of 7 PEG tube-dependent patients had their feeding tubes removed after acupuncture, with a median duration of 114 days (range 49-368) post CRT. Formal clinical trials are required to determine the effectiveness of acupuncture.

## Summary table

Symptoms/Paragraphs	Grading
Xerostomia (*)	1B
Lymphedema	2C (**)
Pain (*)	1A
Dysphagia (§)	

Tab.1. (\*) For detailed information, refer to the symptoms paragraph. (§) For detailed information, see head and neck cancer paragraph. (\*\*) In the absence of SIO grading, the grading was assigned by the authors.

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### *Kidney cancer*

In literature, only one systematic review and no RTCs were found about the effect of acupuncture on patients with kidney cancer.

In the systematic review, the authors evaluated the effectiveness of acupuncture for uremic pruritus in patients with end-stage renal disease (Kim KH. 2010). They consulted 16 electronic databases in the English, Korean, and Chinese languages that were searched from their inception to November 2009. A total of 464 articles were potentially relevant. Of these, 458 studies were excluded, the remaining 6 studies, were comprised of 3 RCTs, 2 uncontrolled observational studies and 1 non-randomized controlled clinical trial. The included RCTs had high risk of bias, assessed using the Cochrane classification, except 1 RCT that analyzed the use of acupuncture versus sham acupuncture in haemodialysis patients (Che-yi C. 2005).

In this paper, the authors described a randomized, controlled clinical trial to validate a single Quchi (LI11) acupoint for relieving uremic pruritus. In the study, 40 patients with refractory uremic pruritus were divided into 2 groups. In group 1 (n=20), acupuncture was applied unilaterally at the Quchi (LI11) acupoint 3 times weekly for 1 month. In group 2 (controls, n=20), acupuncture was applied at a non-acupoint 2 cm lateral to Quchi (LI11) 3 times weekly for 1 month. The effect of the treatment was evaluated with a pruritus score questionnaire given before and at the end of 1 and 3 months follow-up. The results of the pruritus scores were analysed statistically with a linear model to examine the effect of acupuncture on pruritus scores. The data show that in group 1, pruritus scores significantly decrease during three points of detection (respectively,  $38.3\pm 4.3$ ,  $17.3\pm 5.5$  and  $16.5\pm 4.9$ ), whereas in group 2 (controls) they were unchanged (respectively,  $38.3\pm 4.3$ ,  $37.5\pm 3.2$  and  $37.1\pm 5$ ).

Among the other RCTs, 2 did not report the methods and the running sequence, whereas the remaining RCTs revealed the use of invalid random sequence generation method.

In any case, only one RCT reported mild adverse events after acupuncture, such as elbow soreness, which spontaneously resolved after 1 day, and minimal bleeding.

The main finding of Kim's review is that there is inconclusive evidence to support the use of acupuncture for uremic pruritus because only 1 RCT was proved to have low risk of bias. Though this trial showed promising results for uremic pruritus, the data need to be confirmed on cancer patients with further well-designed RCTs.

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### *Liver cancer*

Until now, only a few papers have been published on the application of acupuncture in liver cancer, relating to the symptoms caused by surgery.

In this paragraph, we report 2 papers that investigated the effect of acupuncture in specific aspects of liver cancer; in particular a clinical study (Xin Y. 2001) and a more recent clinical trial (Sun BM. 2010).

In the first study, Xin YL. investigated the clinical effectiveness of electro-acupuncture therapy (EAT) in combination with liver artery intubation chemotherapy for primary massive liver cancer unsuitable for surgical operation. 106 patients with primary liver carcinoma were divided into 3 groups (Group A, patients underwent EAT in combination with invasive therapy; group B, patients received EAT alone; group C, patients underwent liver artery intubation chemotherapy). All the groups were matched for liver cancer size. In groups A and B, subcostal oblique incision was performed to expose liver cancer, and the electrodes were inserted into the tumor under direct vision and artery intubation was performed during the operation. In groups A and C, the liver artery intubation chemotherapy was performed by injecting drug through a cannula inserted into a skin femoral artery. The patients' examination, 6 months after the therapy, showed that the EAT in combination with liver artery intubation chemotherapy achieves best results (73.7% in group A) compared to EAT or artery intubation alone (respectively 55.6% and 28.1%) in the therapy for the reduction of liver cancer size. Clinical effectiveness was evaluated with ultrasonic examination, CT and ATP evaluation according to the standard evaluation of therapeutic effectiveness of the United International Cancer Committee.

The follow-up analysis of 106 patients suggests an increase in survival for patients treated with EAT in combination with artery intubation chemotherapy or alone. In particular, the average survival is 14.5 months. The data show that the group A, with combined therapy, has 1 year survival rate greater than the control group or EAT group (respectively 81.6%, 69.4%, and 53.1%); the 3 years survival rate is higher in EAT group (11.1%) compared to the others ( 5.3% in group A, and 3.1% in group C).

The second study evaluated the effects of acupuncture on postoperative gastroparesis syndrome (PGS) in patients after abdominal surgery. Sixty-three PGS patients, who had undergone abdominal surgery, were randomized into acupuncture group (32) and metoclopramide group (31). The first group was treated with acupuncture applied to ST36, RN12, PC6, and SP6 acupoints once a day, and the second was treated with 20 mg intramuscular of metoclopramide 3 times a day.

The results indicate that acupuncture and metoclopramide could significantly reduce gastric drainage volume. In the acupuncture group, the cure rate was 90.6% ( $p < 0.05$ ) and the number of treatments were  $6.58 \pm 4.26$  ( $P < 0.01$ ), while in metoclopramide group, the cure rate and the number of treatments were 32.3% and  $10.13 \pm 3.60$  respectively.

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## *Lung cancer and dyspnea*

The majority of studies that deal with lung cancer have been reported in the chapters that describe the symptoms which result from surgery, radiotherapy and/or chemotherapy. These symptoms are anxiety and depression, cancer-related fatigue, pain, nausea and vomiting and neuropathy. The same type of cancer is described in the chapter which refers to the quality of life.

We are reporting here the publications in the literature that refer to the symptom of dyspnea. This has not been considered among the general symptoms because it is predominantly related to lung tumours. Finally, the data referred to the literature on lung tumours in general, will be reviewed.

## Dyspnea

Few studies have been found in literature which report on the effectiveness of acupuncture for shortness of breath (dyspnea) in correlation to tumours and other pathologies of organs or systems.

The guidelines of Filshie and Hester (2006) indicate that advanced dyspnea correlated to cancer is a specific condition in which acupuncture can be considered.

In their review, Lu et al. (2008) evaluate 3 preliminary RCTs carried out in oncology. One RCT (Maa 2003) included 41 patients with chronic obstructive asthma (11 acupuncture plus standard care, 17 acupressure and standard care, 13 standard care alone); the result was a significant improvement in respiratory function in the patients treated with acupuncture ( $p = 0.02$ ) and with digital acupuncture ( $p = 0.05$ ). Another RCT (Maa 2007) included 35 patients with bronchiectasis (11 acupressure plus standard care, 11 sham acupuncture and standard care, 13 standard care alone). These were the results: self administered acupressure could be useful in reducing the effects of bronchiectasis on a patient's daily activities. The later RCT (Wu 2004) included 44 patients with chronic obstructive pulmonary diseases (true acupressure versus sham acupressure using different meridians improved significantly the pulmonary function and shortness of breath). The review concludes that acupuncture/acupressure seems to improve respiratory function and the quality of life in patients with asthma, bronchiectasis and chronic obstructive pulmonary disease.

The Cochrane review (Bausewein et al. 2008), referring to non-pharmaceutical intervention to treat respiratory difficulty in advanced stages of malignant and non-malignant disease, evaluates 5 studies, 3 on the use of acupuncture and 2 on acupressure (2). One RCT (Jobst 1986 - n.26) tested traditional Chinese acupuncture versus sham acupuncture (13 sessions over 3 weeks), in patients with chronic obstructive pulmonary diseases: acupuncture showed significantly greater benefits compared to the placebo. One study (Lewith 2004 - n.36, 6 sessions) with cross over design, evaluated acupuncture in lung disease followed by 2 indwelling studs into sternal points, versus TENS applied on the same points as placebo: there were no significant differences. A third study (Vickers 2005 - n.47) compared acupuncture and acupressure versus

placebo acupuncture and placebo acupressure in a single treatment in cancer patients. There were no differences between the groups. The review takes into consideration the studies on bronchiectasis and chronic obstructive pulmonary diseases described by Lu et al. (2008) and the only RCT conducted in cancer participants (Vickers 2005, see the table). The authors maintain that meta-analysis is not possible due to a variation in the interventions. Four studies were of high quality and showed significant improvement in shortness of breath. The review concludes that there is enough evidence to recommend the routine use of acupuncture/acupressure.

Ben-Aharon et al. (2008) analyzed the different treatments used in patients suffering from dyspnea in the terminal phase of the disease or in an advanced phase, sustaining the use of opiates for this problem. In reference to acupuncture, only one randomized and controlled trial is discussed (Vickers 2005). This trial was carried out on 47 patients with lung and breast tumours. The conclusions were that acupuncture was ineffective in treating dyspnea and should not be used.

According to the Guidelines for the Practice of Integrative Oncology (Deng et al. 2009) of the Society for Integrative Oncology (SIO), acupuncture is recommended for dyspnea correlated to cancer; the degree of recommendation is 2C, a weak recommendation, evidence of low quality.

Xue et al. (2010) analyzed different treatments in patients suffering from dyspnea in advanced stages of lung cancer. In reference to acupuncture, only one randomized controlled trial is discussed (Vickers 2005) which involved 47 patients with lung and breast tumours. The patients who were treated with acupuncture had a modest reduction in dyspnea in comparison to those treated with sham acupuncture. Therefore it was not possible to conclude that acupuncture was effective in reducing dyspnea.

### **Lung cancer**

Only one study has been found in the literature referring to the progression of the disease and treatment with TCM. This was a RCT by Zhang et al. (2013) in Chinese, which reported 80 cases with non-small cell lung cancer, randomized in 2 groups. The first group was treated with moxibustion directly on points Sihua, BL17 and BL 19 and chemotherapy, while the second group was only treated with chemotherapy. The authors concluded that direct moxibustion at Sihua points, in patients in chemotherapy for lung tumours could improve immune function, clinical efficacy and life quality.

According to the above quoted Guidelines for the Practice of Integrative Oncology published in 2007 and revised in 2009, for patients who do not stop smoking despite use of other options or those suffering from symptoms such as cancer-related dyspnea, cancer-related fatigue, chemotherapy-induced neuropathy, or post-thoracotomy pain, acupuncture may be helpful, but more clinical studies are necessary (Grade of recommendation: 2C weak recommendation, evidence of low quality).

Within the scope of the 3<sup>rd</sup> edition of guidelines for lung tumours, drafted by the American College of Chest Physicians (ACCP 2013), a multidisciplinary panel of experts in oncology and integrative medicine (Deng et al.) evaluated the evidence related to nausea and vomiting, pain and neuropathy in patients with lung cancer. The authors considered eligible 15 original articles, with one systemic review, which referred to nausea and vomiting from chemotherapy or radiation therapy in various tumours.

The recommendation given was: in patients suffering from nausea and vomiting from chemotherapy or radiation therapy, acupuncture or related techniques is suggested as an adjunct treatment option (Grade 2B, weak recommendation with evidence of moderate quality).

Regarding pain therapy, Deng et al. (2013) selected 19 studies, 12 of which RCT; the positive results cannot be considered sufficient to confirm the validity of acupuncture, given the problems in methodology. The recommendation was that in patients with cancer related pain and peripheral neuropathy, acupuncture is suggested as an adjunct treatment in patients with inadequate control of symptoms (Grade 2C).

### Single clinical studies on dyspnea and lung cancer (adults)

Type of Study	Therapeutic Protocol	N. patients and disease	Endpoints and criteria	Results	Author, year
pilot study randomized 1) true acupuncture and acupressure 2) sham acupuncture and sham acupressure in addition to dyspnea treatments	1) ST36, Ren17, Ren6, KI6, LU1, LU7  auricular points lung and kidney 2) no acupuncture points	n.47 randomized (25 group 1, 22 group 2)  lung or breast cancer	numerical rating scale (NRS 0 – 10)	patients in both groups improved, (p<0.003) but no important differences between groups emerged (means of 0.34, 95% C.I. --0.33, 1.02 and 0.56, 95% C.I. - -0.39, 1.51)	Vickers, 2005
randomized, parallel-group, placebo-controlled trial  1) traditional acupuncture 2) placebo acupuncture  patients, evaluators, and statistician were unaware of the random allocation	1) LU1, LU9, LI18, CV4, CV12, ST36, KI3, GB12, BL13, BL20, BL23  2) Park sham devices once a week for 12 weeks	n.68 randomized (34 group 1, 34 group 2) n.62 concluded treatment  Chronic Obstructive Pulmonary Disease (COPD)	modified Borg scale score  after the 6 minute walk test, after 12 weeks of treatment	significantly better in the real acupuncture group compared with the placebo acupuncture group (mean [SD] difference from baseline by analysis of covariance, -3.6 [1.9] vs. 0.4 [1.2]; mean difference between groups by analysis of covariance, -3.58; 95% CI, -4.27 to -2.90).	Suzuki, 2012
RCT 1) chemotherapy (Navelbine + Cisplatin ) + moxibustion 2) chemotherapy Navelbine + Cisplatin	moxibustion at Siha points (Master Tung Acupuncture: 4 Flower 77.08-77.09-77.10-77.11-77.13-77.14) + BL17 BL19	n.80 randomized (40 group 1, 40 group 2) non-small cell lung cancer  daily sessions 10 sessions	level: colony stimulating factor (CSF)  interleukin-2 (IL-2)  tumour necrosis factor (TNF)  Karnofsky scale (quality of life)	increase of CSF and IL-2 (p < 0.01)  decrease of TNF (p < 0.01)  decrease of Karnofsky score in the group 1 was higher (p < 0.01)	Zhang, 2013

### Summary table

Symptoms/Paragraphs	Grading
Dyspnea (§)	2C
Fatigue Related Cancer (*)	2C
Pain (*)	1A
Neuropathy	2C
Nausea and vomiting (*)	1A

Tab. 1. Symptoms studied in the treatment of lung cancer (\*) For detailed information, refer to the symptoms paragraph. (§) For detailed information, see lung cancer paragraph. (\*\*) In the absence of SIO grading, the grading was assigned by the authors.

### Conclusions of the literature and of the authors

Regarding dyspnea, the Filshie guidelines (2006) indicate that advanced dyspnea correlated to cancer is a specific condition which should be taken into consideration.

According to the Guidelines of the Society for Integrative Oncology (SIO) (Deng et al. 2009), it is not possible to conclude whether acupuncture could be used to improve the symptom of dyspnea in patients with cancer (Recommendation 2C: weak recommendation, evidence of low quality).

In the non-oncological field, the review of Lu (2008) concludes that acupuncture/acupression seem to improve respiratory function and the quality of life in patients with asthma, bronchiectasis and chronic obstructive pulmonary disease. The Cochrane review (Bausewein et al. 2008) reports one study with positive results relative to non-pharmaceutical interventions in patients with respiratory difficulty in non-malignant diseases.

we point out that the majority of studies are short term (the number of sessions are insufficient and at times only a single session) and in advanced stages of the disease, it is difficult to draw conclusions.

Overall, in reference to lung tumours Deng (2013) maintains that acupuncture is suggested as an adjunct treatment option in patients with chemotherapy or radiotherapy induced nausea and vomiting or cancer related pain that is poorly controlled by usual care, and as part of a comprehensive smoking cessation program.

The authors agree with these conclusions and point out that acupuncture can also be used in the treatment of dyspnea, insomnia, anxiety and depression. For fatigue the use of moxibustion is advised in order to obtain better results.

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*Prostate cancer*

The number of prostate cancer patients users of TCM has increased according to the last published studies: from 2.3% to 10.6% of patients with prostate cancer resort to Chinese medicine, among these from 72.8% to 78.8% use Chinese Herbal Medicine, and from 28.1% to 36.8% use acupuncture/traumatology manipulative therapies (Lin YH 2011). Most of these data have been reported in the corresponding paragraphs (see hot flashes, pain) as caused by surgery (see Tab. 1). Moreover, the use of acupuncture in prostate cancer has been described in the chapter on the quality of life. The database searches did not give any results about the action of acupuncture in the prostate cancer progression.

Here we report a study by Yang et al. (2010), in the Chinese language, which explored the effectiveness of electrical acupuncture stimulation therapy combined with pelvic floor muscle therapy (PFMT) in post prostatectomy incontinence. In this study, 109 patients were enrolled and divided into a study group (n=40) and a control group (n=69). The patients in the study group received electrical acupuncture stimulation therapy combined with PFMT 1 week after the removal of the catheter. The patients in the control group performed PFMT as the only treatment for post prostatectomy incontinence.

The results suggest the existence of a significant difference between the study group and the control group in the urinary control curve (p=0.029), and that the difference of continence between the 2 groups became greater from 4 weeks after surgery, with a peak at 6 weeks (p = 0.023). Then the difference became smaller, and there was no difference 16 weeks after surgery.

The results are promising, but it should be considered that so far the guidelines for the treatment of prostate cancer have not been identified. Therefore, other RTCs are needed.

**Summary table**

Symptoms/Paragraphs	Grading
Pain (*)	1A
Hot Flashes (*)	1B
Pelvic floor muscle therapy (§)	

Tab.1. (\*) For detailed information, refer to the symptom paragraph. (§) For detailed information, see lung cancer paragraph.

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## Herbal medicine

*Introduction: progression of the disease, primary and secondary prevention and substances of general type*

In the last decade, several *in vitro* studies have investigated the role of medicinal plants in the prevention and care of cancer. The active components of these plants act as chemopreventive, cytotoxic, immunostimulant (used to improve the response of the patient) and also inhibit the tumor growth.

The currently prevalent theory on cancer pathogenesis assumes that in addition to mutations accumulated by a single cell during its life, the microenvironment that participates in the progression in many ways providing cytokines, growth and survival factors is increasingly important; the creation of reactive oxygen species (ROS)-rich microenvironment could favour new mutations (Tafari M. 2013, 2011).

Within this context, numerous *in vitro* studies identified both medicinal plants and their main components as natural anti-inflammatory agents and anti-oxidants.

Epidemiological and clinical studies have suggested that cancer could be prevented or significantly reduced by anti-oxidant and anti-inflammatory drugs. Therefore, curcumin, the principal component of *Curcuma longa* (Basnet P. 2011), resveratrol, a natural phytoalexin derived from the skin of grapes and other plants (Jagdeo J. 2010, Jing Yu. 2011, Brisidelli F. 2009, Kundu JK. 2008, Udenigwe CC, 2008), lycopene, the most abundant carotenoid in tomatoes and other plants (Ilic D. 2012, van Breemen RB. 2008), polyphenols in different medicinal plants, and medicinal plants such as *Ruta chalepensis* (Acquaviva R, 2011), *Ganoderma lucidum* (Hsieh TC, 2011), and *Pinus morrisonicola* (Hsu TY 2005) with strong anti-oxidant and anti-inflammatory activities, can potentially be considered as an integration of cancer therapies or preventive treatment (fig. 1a).

It is known that the cellular transformation is characterized by loss control of proliferation and/or apoptosis, through the accumulation of mutations with gain-of-function (oncogenes) or loss-of-function (oncosuppressor genes) of specific gene families (Hanahan D. 2011; Larsson LG. 2011).

The proliferation of transformed cells can generate small tumors in the absence of neo-angiogenesis since the oxygen and nutrients can diffuse from normal tissue vessels over a radius of no more than 200  $\mu\text{m}$  (Brahimi-Horn et al., 2007). When the tumour reaches magnitudes greater than 400  $\mu\text{m}$ , it inevitably generates at its center a hypoxic microenvironment leading to cell death by necrosis and release of molecules that trigger a pro-inflammatory gene expression in various cell types. The most superficial cells activate the Hypoxic Inducible Factor (HIF) in response to low oxygen pressure leading to the activation of a survival pathway via NF- $\kappa$ B, cellular growth, and promoting a neo-angiogenic signal.

Recently, *in vitro* research has identified medicinal plants (or their compounds) able to inhibit the activation of HIF and the induction of hypoxia response. Among them, NG curcumin, salvianolic acid B, and guggulsterone, respectively studied in Hep3B liver and MCF-7 breast cancer cells (Ströfer M. 2011), in oral squamous carcinoma cells (Yang Y. 2011), and in neck squamous cell carcinoma (HNSCC) cell lines (Leeman-Neill RJ. 2009) (Fig.1b).

Similarly, other *in vitro* studies have shown that the action of plant extracts may interfere with the activation of NF- $\kappa$ B and consequently with both the pro-inflammatory response, the inhibition of cell death by apoptosis and with the production of molecules able to degrade the extracellular matrix promoting the acquisition of a metastatic phenotype. The medicinal plants that *in vitro* inhibit the activation of NF- $\kappa$ B are ginseng (Hwang JW, 2012), *Smallanthus sonchifolius* (Siriwan D. 2011), *Lindera obtusiloba* (Freise C, 2011), genus *Capsicum* with the main component capsaicin (Lin CH. 2013, Oyagbemi AA. 2010), *Silybum marianum* with the main component silibinin (Li L. 2010), and *Curcuma longa* with the main component curcumin (Shin HK. 2010) (Fig.1b).

Several studies focus on the ability of herbal medicines or their natural compounds to arrest cell cycle and induce apoptosis. Among these, *Scutellaria baicalensis* is able to inhibit cell cycle G1/S transition (Park KI. 2011), *Solanum nigrum* inhibits hepatocarcinoma cell growth by inducing G2/M phase arrest and apoptosis (Wang HC. 2011), *Punica granatum* inhibits androgen-independent prostate cancer growth through a NF- $\kappa$ B-dependent mechanism (Rettig MB 2008, Malik A, 2006), as well as single components like resveratrol which induce cell death in cervical cancer cells through apoptosis and autophagy (García-Zepeda SP. 2013, Tang Q. 2013, Delmas D. 2011, Udenigwe CC, 2008), and isoflavones (Li Y. 2011, Pavese JM. 2010) (Fig.1c).

Finally, the progression is characterized by the acquisition of the malignant phenotype that leads to a clinically significant tumor. Malignancy includes ability to grow above the limited dimensions conditioned by diffusion of oxygen and nutrients in the absence of newly formed vessels (neoangiogenesis), ability to extrude and/or inactivate entire families of molecules (resistance to drugs), invasion of adjacent tissues,

ability to detach from original tissue, to migrate in response to a chemoattractant, to homing in a specific site that will harbour the new tumor.

Medicinal plants have proved to be active also in inhibiting the motility of tumor cells and consequently metastasis. Recent *in vitro* studies show how *Rheum rhabarbarum*, *Punica granatum*, *Annona muricata*, *Vitis coignetiae*, *Curcuma longa*, and resveratrol inhibit the motility of cancer cells respectively in lung adenocarcinoma cells, in human breast cancer (Khan GN. 2009), in pancreatic cancer cells (Torres MP. 2012), in hepatocarcinoma cells (Shin DY. 2009), in squamous carcinoma cells (Shin HK, 2010) and in Lewis lung carcinoma in mice and rat (Busquets S. 2007) (Fig.1d).

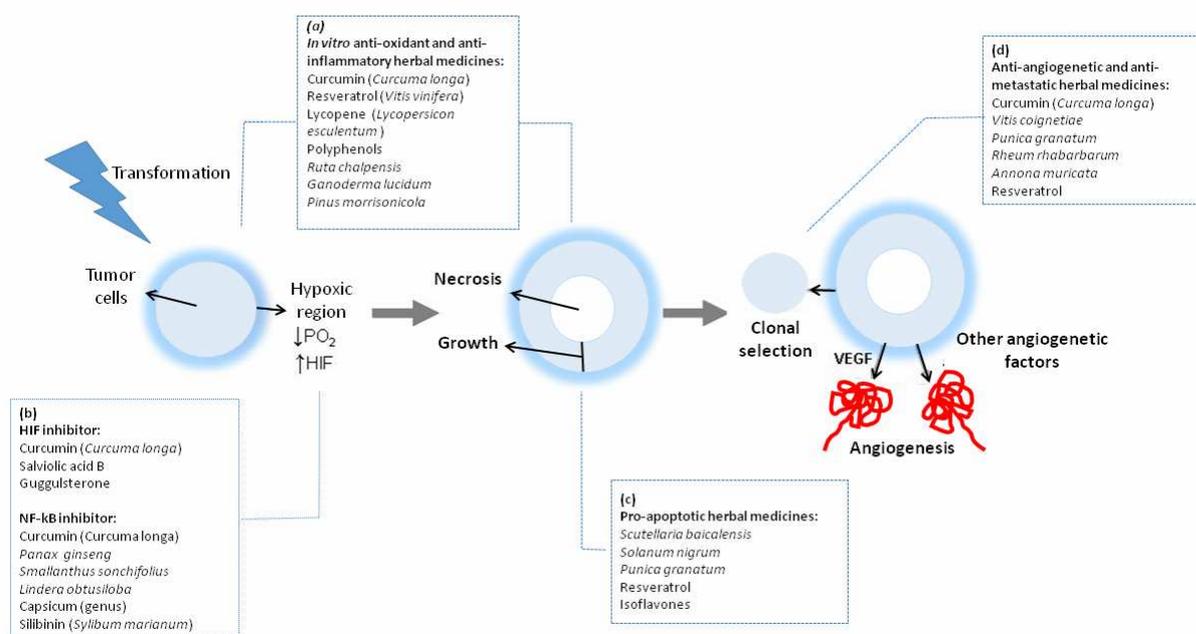


Fig.1. Herbal medicines active *in vitro* in different stages of tumor progression.

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### *Bladder cancer*

To date there are no publications on the treatment of bladder cancer with medicinal herbs. A single Cochrane Systematic Review (2012) on the effectiveness of cranberry products in preventing urinary tract infections (UTI) in susceptible populations shows the use of cranberry products in cancer patients.

The updated review includes 24 studies (6 cross-over studies, 11 parallel group studies with 2 arms; 5 with 3 arms, and 2 studies with a factorial design), with a total of 4,473 participants. Data included in the meta-analyses showed that, compared with placebo, water or non treatment, cranberry products did not significantly reduce the occurrence of symptomatic UTI overall (RR 0.86, 95% CI 0.71 to 1.04) or for any the subgroups including cancer patients (RR 1.15 95% CI 0.75 to 1.77).

Overall heterogeneity was moderate ( $I^2 = 55\%$ ). The effectiveness of cranberry was not significantly different from antibiotics in women (RR 1.31, 95% CI 0.85, 2.02) and children (RR 0.69 95% CI 0.32 to 1.51). There was no significant difference between gastrointestinal adverse effects from cranberry products compared to those of placebo/no treatment (RR 0.83, 95% CI 0.31 to 2.27). Many studies reported low compliance and high withdrawal/dropout problems, which they attributed to palatability/acceptability of the products, primarily the cranberry juice.

Given the inconsistent data due to large number of dropouts/withdrawals from studies (mainly attributed to the acceptability of consuming cranberry products over long periods) and the evidence that the benefit for preventing UTI is small, other preparations (such as powders) need to be quantified with standardised methods to ensure the potency and contain enough of the 'active' ingredient, before being evaluated in clinical studies or recommended for use.

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### *Blood cancer*

There is very little scientific evidence about the use of herbal medicines in haematological cancers . A recent review of data on efficacy, safety, and drug interactions was made by Ben-Arye E. et al. (2010). The authors focused on herbs commonly used by haemato-oncology patients and on those for which at least *in vitro* studies were available as well as the herbal medicines that could interact with drugs used in haemato-oncology (see Tab. 1). From the review of medicinal herbs that could be used in the treatment of haematological cancers, no definitive studies on the use of all medicinal plants are listed in this type of tumors: *Camellia sinensis*, *Crocus sativus*, *Zingiber officinalis*, *Laurus nobilis*, *Echinacea purpurea* and *Uncaria tomentosa*.

An interesting RCT (Ladas EJ, 2010) analyzes the use of *Silybum marianum* (SM) for the treatment of hepatotoxicity in childhood Acute Lymphoblastic Leukemia (ALL). In this double-blind study, 50 children with ALL and hepatic toxicity were randomized to capsules of SM or placebo orally for 28 days. The children were divided into 3 groups according to the following regimen: 15–20 kg = 80 mg/day; 21–40 kg= 160 mg/day; 41–60 kg= 240 mg/day; 61– 70 kg = 320 mg/day. The target dose of silibinin used for the doses was 5.1 mg/kg/day.

The data did not show any significant difference in the frequency of side effects, incidence and severity of toxicities or infections. There were no significant changes in mean amino alanine transferase (ALT), aspartate amino transferase (AST) or total bilirubin (TB) at day 28. At day 56, the MT group had a

significantly lower AST and ALT (respectively  $p=0.05$  and  $p=0.07$ ). In addition, no interactions with synthetic drugs were reported.

In conclusion, the data show that in children with ALL and liver toxicity, MT was associated with a trend toward significant reductions in liver toxicity but future studies are needed to determine the most effective dose and duration of SM and its effect on hepatotoxicity and leukemia-free survival.

Drugs used in haemato-oncology	Herbal medicines interactions
Cyclophosphamide, epipodophyllotoxins and vinca alkaloids	<i>Ginkgo biloba</i> and <i>Ginseng</i> spp (CYP3A4 and CYP2C19 inhibition) <i>Echinacea</i> spp, kava kava, and grape seed (CYP3A4 induction)
Dacarbazine	Garlic (CYP2E1 inhibition)
Alkylating agents	<i>Ginkgo biloba</i> or grape seed (free-radical scavenging)
Antitumor antibiotics	<i>Ginkgo biloba</i> or grape seed (free-radical scavenging)
Platinum analogs	<i>Ginkgo biloba</i> or grape seed (free-radical scavenging)
Cyclophosphamide	<i>Valeriana officinalis</i> (CYP2C19 inhibition)

Table 1. Herb-drug interactions in hemato-oncology. In addition to the plants listed, refer to the specific section for drug-drug interactions of *Hypericum perforatum*.

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## Brain cancer

To date, no RTCs, systematic reviews or meta-analyses have been published on the use of herbal medicines in the treatment of primary brain tumors with the exception of a recent article published by S. Kirste (2011). Here the authors analyze the *Boswellia serrata* effect on cerebral edema in patients irradiated for brain tumors (See Summary Table).

However, in literature some studies analyzed the effects of medicinal plants both *in vitro* and *in vivo* in mice that required randomized clinical trials of phase I, II and III before being specified in the integrated treatment of primary brain tumors.

## Summary table

Symptoms/Paragraphs	Herbal medicine in brain cancer
Edema (*)	<i>Boswellia serrata</i>

Table 1. Herbal medicines studied in the treatment of brain cancer symptoms. (\*) For the grading, doses and detailed information refer to the relevant paragraph.

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## Breast cancer

In addition to medicinal plants with evidence in the treatment of breast cancer already covered in the symptoms-related chapters (see Summary table), the action of *Scutellaria barbata* (SB) extract in the treatment of metastatic breast cancer has been recently analysed.

### ***Scutellaria barbata***

*In vitro* studies showed that the SB aqueous extract inhibited reproductive cancer growth in cell lines by regulating expression levels of key cell cycle components that differ with respect to the cancer cell phenotypes. Marconett CL et al. (2010) demonstrated that this extract exerts phenotype specific anti-proliferative gene expression responses in human breast (MCF7 and MDA-MB-231) and prostate (PC3 and LNCaP) cancer cells. Briefly, in early stage estrogen sensitive MCF7 cells, SB aqueous extract induced a G<sub>1</sub> cell cycle arrest and ablated expression of key G<sub>1</sub> cell cycle regulators Cyclin D1, CDK2 and CDK4, as well as growth factor stimulatory pathways and estrogens receptor- $\alpha$  expression. Similarly, it arrested the early stage androgen sensitive LNCaP cells in the G<sub>1</sub>/M phase with corresponding decreases in Cyclin B1, CDK1 and androgen receptor expression. In late stage hormone insensitive breast (MDA-MB-231) and prostate (PC3) cancer cells, SB aqueous extract induced an S phase arrest with corresponding ablations in Cyclin A2 and CDK2 expression. Later, Klawitter J et al. (2011) showed that the SB aqueous extract cytotoxicity toward cancer cells is primarily based on the inhibition of metabolic pathways that are preferentially activated in tumor cells, thus explaining its specificity for cancer cells.

Recently, *in vivo* studies have been conducted using SB in patients with metastatic breast cancer. Rugo H et al. (2008) performed a phase I clinical trial in 16 breast cancer patients, to evaluate safety, toxicity and tumor response. The treatment consisted of 350 ml/day of oral SB aqueous extract, administered as sole cancer therapy until disease progression. The data showed that there were no grade III or IV adverse events and that the most frequently grade I and II side effects were nausea (38%), diarrhea (24%), headache (19%) flatulence (14%), vomiting (10%), constipation (10%), and fatigue (10%). Moreover, 4/16 patients had stable disease (SD) for >90 days (25%), 3/16 had SD for >180 days (19%) and 5/16 patients reported an objective tumor regression.

Similarly, Perez AT et al. (2010) evaluated the safety and maximum tolerated dose (MTD) of SB aqueous extract in 27 women with metastatic breast cancer (MBC). Among them only 14 were evaluable according to the Response Evaluation Criteria in Solid Tumors with the following results: 3/14 patients with stable disease for >120 days (21%), 1/14 patient was on SB aqueous extract for 449 days and remained stable for 700 days and independent radiology review identified 3/14 patients with objective tumor regression (>0% and <30%). As the MTD was not reached, in this protocol it was defined as the maximum administered dose of 40 g/day.

The conclusion is that the oral administration of SB aqueous extract was safe, well tolerated, and showed promising clinical evidence of anticancer activity in this heavily pre-treated population of women with MBC; however larger studies are needed.

### **Summary table**

<b>Symptoms/Paragraphs</b>	<b>Herbal medicine in Breast Cancer</b>
Fatigue Related Cancer (*)	<i>Paullinia cupana</i>
Hot Flashes (*)	<i>Cimicifuga racemosa</i> <i>Trifolium pratense</i>
Radiodermatitis (*)	<i>Silybum marianum</i>
Pain (*)	<i>Cannabis sativa</i>
Mucositis (*)	<i>Rhodiola algida</i>
Tumor progression (§)	<i>Scutellaria barbata</i>

Table 1. Herbal medicines studied in the treatment of breast cancer symptoms. (\*) For the grading, doses and detailed information, refer to the relevant paragraph. (§) For detailed information, see the text.

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### *Colon cancer*

Three RTCs report the use of Aged Garlic Extract (AGE) in the treatment of colon cancer. The first, published by Tanaka S et al. (2004), was a double-blinded randomized trial in 51 patients with colorectal adenomas, using high-AGE (AGE 2.4 ml/day) and low-AGE (AGE 0.16 ml/day) doses for 0, 6 and 12 months. The data showed that in 37 patients, 47.4% (9/19) in the high-AGE and 66.7% (12/18) in the low-AGE group there was at least one new adenoma for the first and second interval (0 to 12 months after intake), and its relative risk was 0.71.

The decrease rate of at least one adenoma was 50.0% (7/14) in the high-AGE group for the second interval (6 to 12 months after intake), whereas there was no decrease in subjects in the low-AGE group ( $p=0.02$ ). Therefore, the paper concludes that there is a base-line total size increase in the low-AGE group and decrease in the high-AGE group for the second interval ( $p=0.03$ ). In a second RCT the authors (2006), using AGE therapy in cancer colon patients, confirm the data published in the first RCT.

In the third RTC, Ishikawa H. et al. (2006) analyzed the action of AGE in inoperable colorectal, liver, or pancreatic cancer evaluating, as primary endpoint, the Quality of Life (QOL) with a questionnaire based on the Functional Assessment of Cancer Therapy. A sub-endpoint was the change in the natural-killer (NK) cell activity and the salivary cortisol level before and after administering AGE. The authors enrolled 42 patients with liver cancer (84%), 7 with pancreatic cancer (14%), and 1 patient with colon cancer (2%) and conclude that, although no difference was observed in QOL, both the number of NK cells and the NK cell activity increased significantly in the AGE group.

The evidence show a potentially role of AGE in cancer colon treatment, but major studies are required to confirm efficacy, safety and toxicity.

In a dose-escalation study to explore the pharmacology of curcumin in humans, Garcea G et al. (2004) analysed 15 patients with advanced colorectal cancer refractory to standard chemotherapies who took capsules (containing 500 mg of curcuminoids) compatible with curcumin doses between 0.45 and 3.6 g daily for up to 4 months.

Levels of curcumin and its metabolites in plasma, urine, and faeces were analyzed by high pressure liquid chromatography and mass spectrometry. The data showed that curcumin and its glucuronide and sulphate metabolites were detected in plasma in the 10 nmol/L range and in urine. A daily dose of 3.6 g of curcumin was well tolerated at dose levels, and induced a decrease in inducible PGE2 production in blood samples taken 1 hour after the dose on days 1 and 29, respectively, compared with levels observed immediately before the dose ( $P < 0.05$ ).

The same authors (Sharma RA 2001) had observed that 29 days of treatment for 2-4 months in cancer patients may lead to radiologically stable disease.

Two types of adverse events, both gastrointestinal, were possibly related to curcuma consumption: nausea during the first month of treatment, which resolved spontaneously despite the continuation of treatment, and diarrhea.

These studies are the first clinical evaluation of a standardized Curcuma extract as potential cancer chemopreventive agent in patients with colon cancer and provide information that might help to optimize the design of the future clinical evaluation of curcumin.

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### *Liver cancer*

Drug resistance, either innate or acquired and especially in its multiple form (multidrug resistance, MDR), remains a major problem in the therapy of many cancer types. This process has previously been interpreted mainly in a “pharmacological” manner focused on the ability of tumor cells to extrude or inactivate the cytotoxic agents or modify their targets of action. Much attention has been drawn to the over-expression of multidrug efflux transporters such as P-glycoprotein (P-gp), Multidrug Resistance Related Proteins (MRPs) and others (Notarbartolo M. 2005, Nishikawa T. 2006, D’Alessandro N. 2006). Overall, it would appear that the presence of high P-gp levels in HCC correlates with a poorer response to chemotherapy.

To date there are no studies about the use of medicinal plants in the treatment of liver cancer but in a review D’Alessandro N. et al. (2007) support the possible use of natural multi-targeted agents like the polyphenols (resveratrol, curcumin and epigallocatechin-3-gallate), alone or in combination with conventional chemotherapeutic agents, in the treatment of hepatocellular carcinoma (HCC) (D’Alessandro N. 2007, Nishikawa T. 2006).

In particular, the authors observed that in human hepatocellular carcinoma cells (HA22T/VGH cells), curcumin exerted cell growth inhibitory and apoptotic effects, related, at least in part, to free radical generation and mainly dependent on caspase-9 and -3 activation. Curcumin sensitized the cells to the antitumor effects of cisplatin, while the results were only additive in combination with doxorubicin.

As reported in similar settings, curcumin reduced (only modestly) the basal levels of nuclear activated NF- $\kappa$ B (p65 subunit), but when combined with cisplatin or doxorubicin, it blunted their increases induced from the two drugs, which were slight for cisplatin and very remarkable for doxorubicin (D’Alessandro N. 2006).

However, one of the main limitations to the *in vivo* use of such compounds is their low oral bioavailability; in addition, free curcumin is highly hydrophobic and difficult to be administered systemically.

Different polyphenols are undergoing clinical trials, which ultimately will confirm or not the expectations regarding the efficacy and safety of their use in advanced cancers, including HCC.

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### *Lung cancer*

In the last 10 years not many RTCs, meta-analyses or systematic reviews have been conducted on the use of medicinal plants in the treatment of lung cancer.

In a randomized, double-blind, placebo-controlled trial, Yu HM et al. (2008) investigated the effects of rhubarb extract on radiation induced lung toxicity (RILT), pulmonary function (PF), transforming growth factor-beta-1 (TGF-beta1), and interleukin-6 (IL-6) in lung cancer patients treated with radiotherapy.

The authors randomized 80 patients in 2 groups; the trial group received three-dimensional conformal radiation therapy (3D-CRT) plus rhubarb (20 mg/kg once a day) for 6 weeks. The control group received 3D-CRT plus a placebo containing starch for 6 weeks.

The data show significantly lower levels than in the control group during and after the treatment of: plasma TGF-beta1 ( $p < 0.05$  or  $0.01$ ), serum IL-6 levels ( $p < 0.01$ ), forced vital capacity and forced expiratory volume ( $p < 0.05$  or  $0.01$ ).

The authors concluded that the rhubarb extract significantly attenuated RILT and improved PF, probably by decreasing the level of TGF-beta1 and IL-6. These results may be of value for the prophylaxis of RILT, but more studies are necessary to evaluate the mechanism of action, safety of use, adverse effects and drug interactions.

Moreover, two meta-analyses were conducted in order to identify the preventive actions of soy intake on lung cancer in epidemiologic studies. Both the studies identified an inverse relationship between soy food intake and the relative risk of developing lung cancer in non-smoking women.

Yang WS et al. (2012) evaluated 11 epidemiologic studies that consisted of 8 case-control and 3 prospective cohort studies. A significantly inverse association was shown between soy intake and lung cancer with an overall RR of 0.77 (95% CI: 0.65, 0.92). The trend was also confirmed when analyses were restricted to 5 high-quality studies confirming, thus, a statistically significant protective effect of soy consumption in women (RR: 0.79; 95% CI: 0.67, 0.93), non-smokers (RR: 0.62; 95% CI: 0.51, 0.76), and Asian populations (RR: 0.86; 95% CI: 0.74, 0.98).

Similarly, Yang G et al. (2012) included 71,550 women recruited into the Shanghai Women's Health Study (Shanghai, China) in 1997-2000. The authors showed that soy food intake was inversely associated with subsequent risk of lung cancer ( $p$  (trend) = 0.004); this inverse association was prevalent among women who reached later the menopause ( $p$ (interaction) = 0.01) and for aggressive lung cancer, as defined by the length of survival (<12 months vs.  $\geq 12$  months;  $p$ (heterogeneity) = 0.057). Furthermore, a meta-analysis of 7 studies conducted among non-smokers found a summary relative risk of 0.59 (95% confidence interval: 0.49, 0.71) for the highest categories of soy or isoflavone intake versus the lowest.

However, because of different methods used to assess soy consumption across the studies, well designed cohort studies or intervention studies that use unified measures of soy intake are necessary to fully characterize such an association.

### Summary table

Symptoms/Paragraphs	Herbal medicine in Lung Cancer
Pain (*)	<i>Cannabis sativa</i>

Table 1. Herbal medicines studied in the treatment of lung cancer symptoms. (\*) For the grading, doses and detailed information refer to the relevant paragraph.

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### Prostate cancer

Over the last decade, the activity of isoflavones and (-)epigallocatechin-3-O-gallate (EGCG) in prostate cancer (PCa) has been explored.

### Isoflavones

The action of isoflavones on hot flashes was already addressed in the corresponding section; here we report 4 RCTs on the use of isoflavones in PCa treatment.

In the first, the authors studied the effects of diets rich in soy and linseed compared with a control diet on biochemical markers of PCa in 29 men diagnosed with PCa and scheduled to undergo a radical

prostatectomy. They were randomized into 3 groups: soy (high content of phytoestrogens), soy and linseed (high content of phytoestrogens), or wheat (low phytoestrogen).

Bread was specially manufactured to incorporate 50 g of heat-treated (HT) soy grits or 50 g of HT soy grits and 20 g of linseed as part of the study participant's daily diet. The daily isoflavone levels achieved through 4 slices of the high phytoestrogen bread were 117 mg in genistein, daidzein, and glycitein in aglycone. The data showed a statistically significant differences between the HT soy grits group and the control wheat group for the percentage of change in total PSA (-12.7% versus 40%,  $P = 0.02$ ) and the percentage of change in free/total PSA ratio (27.4% versus -15.6%,  $P = 0.01$ ); and between the HT soy grits group and the HT soy grits and linseed group for the percentage of change in free androgen index (16.4% versus -15.5%,  $P = 0.04$ ) and the percentage of change in free/total PSA ratio (27.4% versus -10%,  $P = 0.007$ ).

The data indicate that a daily diet containing bread rich in HT soy grits favorably influences the PSA level and the free/total PSA ratio in patients with PCa. In particular, there are statistically significant differences between the HT soy grits group and the control wheat group for the percentage of change in total PSA (-12.7% versus 40%,  $P = 0.02$ ) and that of change in free/total PSA ratio (27.4% versus -15.6%,  $P = 0.01$ ). The variation between the HT soy grits group and the HT soy grits and linseed group for the percentage of change in free androgen index (16.4% versus -15.5%,  $P = 0.04$ ) and the percentage of change in free/total PSA ratio (27.4% versus -10%,  $P = 0.007$ ) (Dalais FS, 2004) are also significant.

Rannikko A et al. (2006) have evaluated how oral phytoestrogen supplementation influences the phytoestrogen concentrations in prostate tissue. In a RCT, 40 men assigned for radical prostatectomy, received 240 mg of clover phytoestrogens or placebo daily for 2 weeks before their operation. The authors detected that the oral supplementation with phytoestrogens induced a statistically significant ( $P < 0.001$ ) 23- and 7-fold increase in prostate tissue concentrations of the phytoestrogens genistein and daidzein, respectively. Moreover, the prostate tissue genistein and daidzein concentrations were over twofold higher than their plasma, concluding that prostate tissue can concentrate genistein and daidzein.

The effects of a high dose, aglycone-rich soy extract on prostate-specific antigen (PSA) and serum isoflavone concentrations were studied by deVere White RW et al. (2010). In the study 53 men with PCa were enrolled; the treatment group consumed 450 mg of genistein, 300 mg of daidzein, and other isoflavones daily for 6 months. PSA and serum concentrations of genistein, daidzein were measured in both groups at baseline, 3 months, and 6 months. The authors concluded that dietary supplements alone did not lower PSA levels in men with low-volume PCa.

These data are inconsistent with those obtained by Lazarevic B. et al. (2011) who concluded that genistein at a dose of a diet rich in soy reduces the level of serum PSA in patients with localized PCa, without any effects on hormones.

In this study 54 subjects were recruited and randomized to treatment with genistein or placebo for 3 to 6 weeks prior to prostatectomy. The authors reported few and mild adverse events and 7.8% PSA serum decrease in the genistein arm compared to the increase by 4.4% in the placebo arm ( $P = 0.051$ ). Plasma concentrations of total genistein were on average 100-fold higher in the genistein arm after treatment ( $P < 0.001$ ). Moreover, the total cholesterol was significantly lower in the genistein arm ( $P = 0.013$ ) and no significant effects on thyroid or sex hormones were reported.

### ***Camellia sinensis***

*Camellia sinensis* non fermentatum, folium (green tea leaf) consists of whole or cut young, unfermented, rapidly hot dried leaf of *Camellia sinensis* (L.) and its cultivated varieties. It contains mainly EGCG and not less than 2% of caffeine. Traditionally, this herbal medicine is used in the treatment of migraine, nausea, diarrhoea (Gruenwald 2004).

The herbal preparations in use are: comminuted herbal substance for herbal teas, powdered herbal substance and dry extract (purified corresponding to 55-72% EGCG and decaffeinated that contains not less than 60% of polyphenols, calculated as EGCG, not less than 40% of EGCG, and not more than 0.1% of caffeine, calculated on the anhydrous basis) (EMA. 2012).

The adult dosage, based on information received from a Member State (France) and the literature (Gruenwald 2004), is 0.8-2.2 g / 3-5 times daily of whole or comminuted herbal substance in 100-150 ml of boiling water as a herbal infusion, and 390 mg 3-5 times daily of powdered herbal substance. The use in children and adolescents under 18 years of age is not recommended.

Overdose, quantities corresponding to more than 300 mg caffeine or 5 cups of tea as a beverage, can lead to restlessness, tremor, and elevated reflex excitability. The first signs of poisoning are vomiting and abdominal spasm (Gruenwald 2004).

Great interest has been shown in recent years regarding the preventive action of *Camellia sinensis* extract in several tumors, among which PCa. However to date, there are no RTCs consistent about its action and its main component EGCG, in cancer prevention. Also the meta-analyses report conflicting data.

Briefly, Seely D. (2005) in a meta-analysis concluded that the consumption of 5 or more cups of green tea a day showed a non-statistically significant trend towards the prevention of breast cancer development. A more recent meta-analysis of 22 studies (Tang N 2009) provided data on the consumption of green tea or black tea or both related to lung cancer risk and concluded that high intake or an increase in the consumption of green tea, but not black tea, may be related to the reduction of lung cancer risk. Finally, Ogunleye AA (2010) analyzed 5,617 cases of breast cancer divided in 2 studies of breast cancer recurrence and 7 studies of breast cancer incidence (case-control studies, cohort studies and epidemiologic evidence). The data analysis shows a summary relative risk (RR) between 0.73 and 0.81 confirming that the association between green tea consumption and breast cancer incidence is unclear.

The conclusions of systematic reviews and the analysis of epidemiological data do not show definitive data about the preventive role of *Camellia sinensis* and its main component (see tab. 1).

Type of study	Results	Author, year
Systematic review and meta-analyses of observational studies from systematic searches of 8 electronic data sources and contact with authors	Epidemiological data indicate that consumption of 5 or more cups of green tea a day shows a non-statistically significant trend towards the prevention of breast cancer development	Seely D. 2005
Systematic review of interventional and observational studies (Western countries and China), published between 1989 and December 2007	Ten qualified studies with various outcomes were chosen. Eight of them showed a significant protective role of green tea against various liver diseases, as determined by relative risk/odds ratio or P-value. Among them, 4 studies showed a positive correlation between green tea intake and attenuation of liver disease. The other 2 studies also presented a protective tendency of green tea against liver disease	Jin X. 2008
Review of peer-reviewed articles on observational and interventional studies on green tea, its extract or its purified polyphenol EGCG	Observational studies on the benefits of green tea in the prevention of most cancers are inconclusive. There are trends towards prevention in breast and prostate cancers. Interventional studies demonstrated a reduction in relapses after surgical resection in colorectal adenomas and increased survival rates in epithelial ovarian cancer	Clement Y. 2009
Systematic review of literature on tea intake and risk of ovarian and endometrial cancers	The data support a protective role of green tea on risk of ovarian and endometrial cancers. Observational data are needed to evaluate whether green tea reduces the risk of human papillomavirus-related cancers	Butler LM. 2011
Systematic review about the effects of green tea or green tea components on the prevention and progression of epithelial ovarian cancer	Green tea and its components have been shown to downregulate the expression of proteins involved in inflammation, cell signalization, cell motility and angiogenesis. Green tea and its components would induce apoptosis and could potentiate the effects of cisplatin. In human observational studies, significant associations between green tea intake and both decreased ovarian cancer occurrence and better prognosis were reported	Trudel D. 2012

Tab.1. Reviews on *Camellia sinensis* use in cancer. Legend: EGCG (epigallocatechin gallate). Other studies are in progress to investigate the effects of herbal medicines or their components in PCa treatment.

### Other medicinal plants

In an interesting RCT (Lukasewycz S 2010), the authors assessed the action of belladonna and opium suppositories to improve postoperative pain following robotic assisted laparoscopic radical prostatectomy. Ninety-nine patients were included and randomized in two groups: the treated group showed both a significant improvement in postoperative pain during the first two postoperative hours and a decrease in 24-hour morphine consumption.

A recent RTC phase II study of Paller CJ et al. (2013) analyzed the effect of *Punica granatum* extract (PG) in men with rising PSA following initial therapy for localized PCa. 104 patients with a rising PSA and without metastases were randomized, in a period of 18 months, to receive 1 (low-dose) or 3 g (high-dose) of PG, to detect a 6-month on-study increase in PSA doubling time (PSADT) from baseline in each arm. The

results showed a median PSADT lengthened from 11.9 months at baseline to 18.5 months after treatment ( $P < 0.001$ ). PSADT lengthened in the low-dose group from 11.9 to 18.8 months and 12.2 to 17.5 months in the high-dose group, with no significant difference between dose groups ( $P = 0.554$ ). These preliminary data need confirmation through placebo-controlled studies in this patient population.

In a systematic review on the CAM integration in the treatment of PCa, Von Löw EC (2007) et al. also analysed, in addition to medicinal plants already evaluated, the effect of polyphenol in medicinal plants like diferuloylmethane (*Curcuma longa*), epigallocatechin-3-gallate (*Camellia sinensis*), and resveratrol (grapes, peanuts and types of berries). The authors analyzed both *in vitro* and *in vivo* studies in literature; there is little and inconsistent evidence in term of clinical trials.

Etminan M. et al. (2004) investigated the effect of lycopene's diet in the prevention of PCa in a meta-analysis. Eleven case-control studies and 10 cohort studies or case-control studies on the use of tomato, tomato products, or lycopene according to the inclusion criteria were analyzed. Compared with non frequent users of tomato products (1st quartile of intake), the Relative Risk (RR) of PCa among consumers of high amounts of raw tomato (5th quintile of intake) was 0.89 (95% CI 0.80-1.00). For high intake of cooked tomato products, this RR was 0.81 (95% CI 0.71-0.92). The RR of PCa related to an intake of one serving/day of raw tomato (200 g) was 0.97 (95% CI 0.85-1.10) for the case-control studies and 0.78 (95% CI 0.66-0.92) for cohort studies. These results show that tomato products may play a role in the prevention of prostate cancer. In a systematic review on the use of lycopene for the prevention and treatment of benign prostatic hyperplasia (BPH) and PCa, Ilic D. et al. (2012) concluded that the scarce number of RCTs published and the varying quality of the studies do not allow to support or refute the use of lycopene for preventing or treating BPH or PCa.

#### Summary table

Symptoms/Paragraphs	Herbal medicine in prostate cancer
Pain (*)	<i>Cannabis sativa</i>
Cancer progression (§)	<i>Camellia sinensis</i>

Herbal medicines studied in the treatment of prostate cancer symptoms. (\*) For the grading, doses and detailed information refer to the relevant paragraph. (§) For detailed information, see the text.

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## Homeopathy

### *Introduction*

In Western countries, homeopathy is a complementary therapy to conventional cancer therapy, used to counter its adverse effects.

Homeopathic treatment for different types of tumors has not been validated by randomized clinical trials and there are only few observational studies. It is the clinical experience of more than 2 centuries that defines the possibility of a complementary homeopathic treatment to integrate conventional cancer treatment.

The only data available, however lacking, were published in peer-reviewed journals and are about the application of the so-called “Banerji Protocol”, generally reported also in the introduction.

The "Banerji Protocol" in India is a new method of using ultradiluted natural substances classically used in homeopathy through prescribing specific remedies for specific diseases.

As previously mentioned, in 2008 a clinical report from India on 14 patients treated apparently successfully with homeopathic remedies as part of a unique National Cancer Institute (NCI) program concluded that homeopathy could have positive effects on cancer care (Banerji P, 2008).

Later on, the PBHRF (Banerji Foundation Kolkata, India) documented a group of 21,888 patients with malignant tumors, monitored at PBHRF between 1990 and 2005 (see fig. 1 and 2). These patients used the Banerji Protocol without being subjected to any additional method of conventional care. 941 of them had breast cancer. The clinic's physicians reported that in 19% of the cases, the malignant tumors completely regressed, and in another 21% they were static or improved after treatment. For patients with static tumors, the follow-up continued for at least 2 years, and for some, for 10 years.

For detailed information, see chapter 3 “CAM in Integrative Oncology/Homeopathy”.

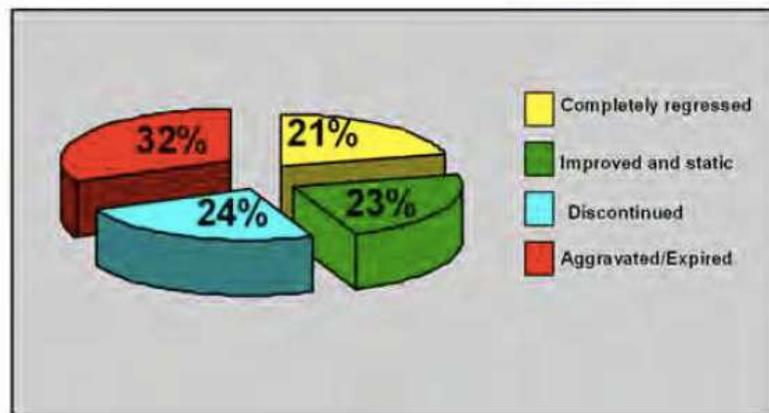


Fig. 1. Results of Treatment of 30,288 Malignant Tumor Cases (1990 – 2008)

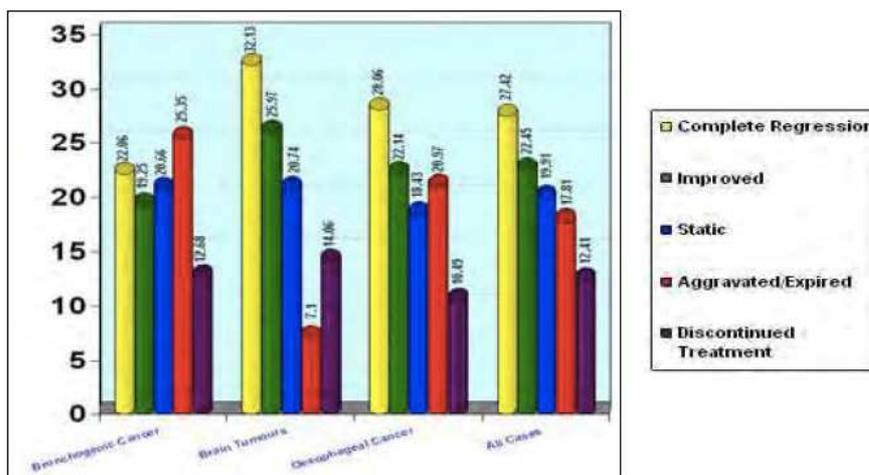


Fig. 2. Results of treatment of 1132 cases of lung, brain and esophageal cancers, August 2006-August 2007

### Bladder cancer

Following the Banerji Protocol, for bladder cancer use Thuja 30CH 3 times a day.

For the related symptoms

If there is high hematuria, use GeraniumTM: 10 drops 2-3 times a day.

### Blood cancers

#### Hodgkin Lymphoma

Following the Banerji Protocol, use Thuja 30 CH, 2 times a day and Kalium muriaticum 3DH and Ferrum phosphoricum 3DH, 2 times a day. Then Carcinosinum 30 CH every 48 hours to ameliorate the immunological system.

#### Mieloid Leukemia

Following the Banerji Protocol, use Natrum mur. 30 CH - 1 dose a day and Kalium mur. 3DH plus Ferrum phosp. 3DH 2 times a day. In acute cases it is necessary to increase the frequency of the doses.

For the related symptoms

If there is fever: Chininum sulfuricum 3DH every 3 hours with the other remedies.

If the spleen rates are high: Ceanothus TM. 5 drops twice a day.

If there are sweatings during the night: Carbo veg. 200CH for the night.

#### Lymphoid Leukemia

Following the Banerji Protocol, use Thuja 30 CH 2 times a day. Natrum mur. is not given when the spleen is affected.

Add if altered blood analysis: Kalium mur. 3DH plus Ferrum phos. 3DH twice a day.

If there is anemia, add China off. 3DH 5 drops twice a day.

#### Acute linfoblastic leukemia

Following the Banerji Protocol use Natrum mur. 30 CH once a day.

Kalium mur. 6 DH and Ferrum phosph. 6 CH

For the related symptoms

If there is fever, add Eupatorium Perfoliatum 30 CH.

If there is pneumonia, Hepar sulfur 6DH twice a day.

### *Bone cancer*

Following the Banerji Protocol use *Symphytum 200C* and *Calcarea phos. 3DH*, every 3 hours alternately, and *Carcinosinum 30CH* on alternate nights. When ameliorated, use *Symphytum 200CH* twice a day and *Calcarea phos. 3DH* twice a day.

The second line of intervention includes *Ruta graveolens 200CH*, in place of *Symphytum*; the other remedies remain the same.

### *Brain cancer*

#### Clinical studies

In an Indian study (Garg, 1998) 122 patients with various forms of brain tumor were taken into consideration. 70 of these patients (57.4 %) were included in the study. The criteria for inclusion and exclusion were defined based on the duration of treatment and patients treated for less than 6 weeks were excluded.

When each case was being diagnosed, the overall clinical picture was studied in detail with CT and Functional Magnetic Resonance Imaging (FIRM). The examination included a neurological consultation. The remedies were selected taking into account the totality of the symptoms, the clinical evaluation, the cause and nature of the disease. In the Indian clinic, the following frequency of the different types of brain tumor had been detected: glioma 17.2%, astrocytoma, 43.4%, 9.8% meningioma, pituitary adenoma 9 %, other 20.6%. The ratio between male and female patients was 4:3 for glioma, 2:1 for astrocytoma, 1:2 in meningioma, pituitary adenoma 1:1 and 2:1 in other types of tumors.

The majority of patients undergoing homeopathic treatment were in an advanced stage of the disease, had complications or had been declared incurable by other therapeutic systems. It was reported that 5 patients (2 cases of glioma, 2 of pituitary adenoma and 1 medulloblastoma) fully responded to homeopathic treatment and the lesions had completely resolved as demonstrated by the diagnostic tests performed in a second phase. Following the Banerji Protocol, the first line treatment includes *Ruta graveolens 6CH* and *Calcarea phos. 3DH* both twice daily.

Second line: add *Thuja 1000CH*, once a week.

Third line: add *Conium maculatum 1000CH*, once a week.

For the related symptoms

Seizures, headache: *Arnica montana 3CH* plus *Cuprum metallicum 6CH*.

Confusion: *Helleborus 30CH* twice a day.

Cerebral oedema: *Lycopodium 30CH* twice a day.

Hemoptysis: *Ferrum phos. 3DH* for 5 times in case of need.

Pleural effusion: *Lycopodium 30CH* 3 times a day.

### *Breast cancer*

#### Clinical studies

The use of complementary therapies appears to be widespread among women with breast cancer (Yap KP, 2004; Thompson et al., 2008) especially to control the effects of iatrogenic menopause.

As we have previously mentioned, in 2008 a clinical report from India on 14 patients treated apparently effectively with homeopathic remedies as part of a unique National Cancer Institute (NCI) program drew the conclusion that homeopathy might have effects on cancer care (Banerji P, 2008).

Later on, the PBHRF documented a group of 21,888 patients with malignant tumors, monitored at PBHRF between 1990 and 2005. This group of patients used the Banerji Protocol without being subjected to any additional method of conventional care.

Of these, 941 patients had breast cancer. The clinic's physicians reported that in 19% of the cases, the malignant tumors completely regressed, and in another 21% of cases, the tumors were static or improved after treatment. For patients with static tumors, the follow-up continued for at least 2 years, and for some of them for 10 years.

#### Laboratory findings

American researchers at the M.D. Anderson Cancer Center, University of Texas have confirmed the clinical results obtained by the PBHRF; they have demonstrated plausible biological mechanisms for the antitumor

effects of the homeopathic medicines tested. The studies reported 4 homeopathic remedies used for treating breast cancer against two human breast adenocarcinoma cell lines (MCF-7 and MDA-MB-231) and a cell line derived from immortalized normal human mammary epithelial cells. The remedies exerted preferential cytotoxic effects against the two breast cancer cell lines, causing cell cycle delay/arrest and apoptosis. These effects were accompanied by altered expression of the cell cycle regulatory proteins, including down regulation of phosphorylated Rb and up regulation of the CDK inhibitor p27, which were likely responsible for the cell cycle delay/arrest as well as induction of the apoptotic cascade that manifested in the activation of caspase 7 and cleavage of PARP in the treated cells (Frenkel et al., 2010).

Following the Banerji Protocol for breast cancer, the first line treatment includes a series of remedies, *Phytolacca decandra* 200CH twice a day, *Carcinosinum* 30CH every alternate day.

The second line protocol includes *Phytolacca* 200CH twice a day; *Carcinosinum* 30C, on alternate night plus *Conium maculatum* 30CH twice a day.

A third line protocol includes *Thuja occ.* 30CH twice daily and *Carcinosinum* 30CH once a day.

For the related symptoms

If there are ulcers, use *Nitricum acidum* 30CH 2 times a day.

In aggressive open ulcers with offensive discharge, use *Psorinum* 1000CH on alternate morning and *Antimonium crudum* 200CH plus *Arsenicum album* 200CH 4 doses a day.

In order to prevent recurrences use *Phytolacca* 200 CH twice a week.

#### *Colon-rectum cancer*

Following the Banerji Protocol for the colon cancer use *Nitric acidum* 3 DH alternated to *Hydrastis TM.* 5 drops twice a day or 200CH, one dose twice a day. In acute cases use both remedies every 3 hours. Then *Conium* 30CH instead of *Nitric acidum*, as a second line of treatment.

The third line protocol includes *Carbo animalis* 200CH, 4 times a day, *Ferrum phos.* 3DH plus *Calcarea fluorica* 3DH twice a day.

For the related symptoms

If there is bleeding per rectum, use *Hamamelis virginica* Q after every bleeding.

If there is obstruction, use *Staphysagria* 200CH every 12 hours.

If there is bleeding, use *Hamamelis TM* 5 drops 3 times a day. If it is not enough use *Geranium TM* three times a day.

If there are metastases on the liver, add *Chelidonium* 6DH.

If there are metastases on the lung: *Kali carbonicum* 200CH.

Following the Banerji Protocol, for rectum cancer use *Nitric acidum* 3CH, 3 drops every 3 hours. This is the first remedy for this type of cancer. The remedy can be repeated 6 times a day, when there is bleeding until 15 times a day.

The second line includes *Hydrastis* 200CH and *Mercurius solubilis* 200CH, every 3 hours alternately and, third line: *Thuja occ.* 30C twice a day.

For the related symptoms

If there is proctitis, use *Hamamelis T.M.* 5 drops. If *Hamamelis* does not work, *Geranium T.M.*, 10 drops 2-3 times a day can be used.

For the treatment of involuntary stool use *Veratrum album* 200CH every 3 hours.

Following the Spinedi Protocol, for rectum cancer *Ruta* DH1 – DH3 is used. *Ruta* has a strong organotrophic action on the rectum, characterized by inflammation, severe pain when sitting at the slightest touch the pain often radiating to the bladder and to urethra.

*Arsenicum* DH10, as well. has an organotrophic action in cancer of the rectum treating the general symptoms of:

- Restlessness and fear
- Cachexia

- Burning pain in the rectum enhanced by warm applications
- Excoriating diarrhea with tenesmus, burning and fetid.

#### *Kidney cancer*

Following the Banerji Protocol for kidney cancer use Thuja 30 CH 2 times a day and Hydrastis TM. twice a day.

The second line of intervention includes Conium 30CH every 3 hours plus Hydrastis T.M 3 times a day. If there is amelioration, it is possible to diminish the frequency of the doses.

#### *Liver cancer*

Following the Banerji Protocol for the liver cancer, use Hydrastis Q (mother tincture) twice daily, Chelidonium Majus 6DH twice daily, Carcininum 30CH every alternate morning.

Following the update of the Banerji Protocol, Hydrastis canadensis Q and Chelidonium majus 6DH will be used every 3 hours alternately and Conium maculatum 30CH twice a day.

The second line includes Myrica TM and Hydrastis canadensis TM every 3 hours, alternately, and Carduus marianus TM twice a day.

In acute pain: Belladonna 3 CH one dose every 10 minutes alternately with Cardus marianus TM till relief.

#### *Lung cancer*

##### Clinical Studies

In a reported study of Banerji (2008): “a male, 47 years old, came to the clinic on 30<sup>th</sup> November 1994. He was suffering from chest pain with severe cough along with loss of weight for the last three months. On examination restricted respiratory movement on the left side with few localized crepitations were present in the upper part of the left chest. Chest X-ray dated the 18<sup>th</sup> of November 1994 showed well-defined large soft tissue density mediastinal mass in the left upper mediastinum. C.T. Scan of chest dated 19<sup>th</sup> November 1994 shows “an 8.0 cm x 6.4 cm well defined soft tissue mass in upper mediastinum in left side with air space consolidation of adjacent left upper lobe. Guided FNAC of mediastinal mass dated 24<sup>th</sup> of November 1994 showed “malignant tumor”. After undergoing treatment with the medicines Kali carbonicum 200CH two drops thrice a week and Ferrum phosphoricum 3DH 2 tablets twice daily, patient became asymptomatic. X-ray dated 31<sup>st</sup> of January 1995 showed “considerable shrinkage in the mediastinal mass”. X-ray dated 5<sup>th</sup> of July 1995 showed “Gradual and excellent regression of the mediastinal mass since original X-ray of 18 November 1994.” X-ray dated 9<sup>th</sup> January 1996 described only a “small residual opacity still present. At the National Cancer Institute it was described as a diagnosed case of malignant neoplasm. According to TNM classification of the tumor in this case, the growth was T2, N1, M0 – Stage II; if it was a case of metastasis from an unknown primary, then it would be staged at Stage IV. Additional chest X-rays were done on several occasions. The last was on 7<sup>th</sup> of January 1999, which showed complete resolution of the mediastinal tumor. There were no complications during treatment. We are still reviewing the case off and on but there has been no recurrence”.

Following the Banerji Protocol, the first line treatment for the lung cancer includes Kali carb. 200CH every alternate morning, Thuja occ. 30CH twice daily, Kali muriaticum 3DH and Ferrum phos. 3DH twice daily.

Second line: Carbo animalis 200CH, twice daily, Bryonia alba 30CH and Aconitum napellus 200CH, twice daily

For the related symptoms

In case of cough Bryonia 30CH, Aconitus 200CH taken together with Kali carb., Thuja and Ferrum phos.

#### *Prostate cancer*

Following the Banerji Protocol the first line treatment is Thuja occ. 30CH 4 times a day and Carcininum 30CH on alternate night.

The second line protocol includes Medorrhinum 200C twice a day and Cantharis 200CH twice a day.

The third line protocol includes Conium mac. 1000CH, once a week and Sabal serrulata TM, twice a day and

Carcinosinum 30CH on alternate days.

For the related symptoms

If there is hematuria, use *Geranium maculatum* TM, 3 times a day. If this remedy fails, use *Hamamelis virginica* TM, four times a day.

### Conclusions

Homeopathy has a long tradition in the treatment of tumors and more recently it has also been applied in oncological prevention. However, today it is used as unique treatment for cancer patients only in the Southern countries of the world and especially in India. In this country there is a long homeopathic tradition and the socio-economic conditions of the population do not allow patients to access conventional cancer treatments. In Western countries homeopathic remedies are mainly focused on the treatment of the adverse effects of chemo- and radiotherapy.

Specific high quality studies on the treatment of the tumor with homeopathy have not yet been published in peer reviewed journals. As previously stated, generally speaking, there are two types of homeopathic treatments for cancer patients: the first one is an individualized approach and the other follows fixed protocols.

According with these two modalities there are also reported data, case reports and series of cases in which homeopathy seems to have stopped the progression of the tumor and/or caused its regression.

We can conclude that so far, even if there are no evidence in the literature and therefore it is impossible to provide recommendations (in spite of some interesting researches *in vitro* and with tumoral cell lines); at the same time there are no contraindications to the use of homeopathic treatments to ameliorate the quality of life of cancer patients. In fact, it should be emphasized that homeopathy does not interfere with cancer therapy and its rare adverse effects are mild.

The results of our evaluation of the literature suggest that homeopathic treatment may be indicated to reduce the adverse effects of chemo- and radiotherapy and integrate conventional treatment in cancer patients.

Therefore, it is desirable to conduct more studies to evaluate the efficacy of the homeopathic treatment not only in improving the quality of life but also in reducing the tumor progression, survival of patients.

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## Anthroposophic medicine

### *Bladder cancer*

*Viscum album* L. extracts (VAE) appear in the list of possible immunomodulatory drugs in the management of non-muscle invasive bladder cancer (NMIBC) in a number of reviews on this topic (Brassel et al. 2006; Smaldone et al. 2010; Tomaszewski et al. 2010; Suttman et al. 2012).

It is listed as potentially active, safe and well tolerated (Tomaszewski et al. 2010; Smaldone et al. 2010ab) and is described as an attractive alternative to BCG (*Bacillus Calmette-Guerin*) in selected patients (Elsaesser-Beile et al. 2005ab; Smaldone et al. 2010a). BCG is mostly the treatment of choice after tumor resection and is known to delay the time to first recurrence, but its use can be limited by its side effect profile (Tomaszewski et al. 2010). Intravesical application of VAE, well known in real-life clinical practice, seems to be promising. While further investigation is needed, VAE might be a better-tolerated option in some patients (Smaldone et al. 2010a) and in BCG-refractory disease (Smaldone et al. 2010b). A beneficial effect of mistletoe therapy is supported by preclinical research. Favourable courses of disease, with the routinary subcutaneous use of anthroposophic mistletoe therapy, have been described in casuistics (Leroi et al. 1959).

The intravesical use of VAE has suscitated recent attention in research. VAE have been investigated in few trials concerning intravesical application, in the adjuvant setting, after transurethral resection.

Eisenbraun et al. (2011) performed a dose-escalation-trial with an anthroposophic VAE administered intravesically, preliminary to a planned randomised, confirmatory, phase III study. Two centres in Germany and Egypt were involved. Patients had been previously treated with TUR-B for superficial bladder cancer Ta G1/G2 and T1 G1/G2. High dosages of VAE (Abnoba viscum® Fraxini ) up to 45 x 20 mg given intravesically have shown good tolerability and have given initial proof of a tumor response comparable to mitomycin C, verified with a re-TUR after 12 weeks (Eisenbraun 2011). A previous casuistic had also described dose finding and safety (Schaefermeyer 1999).

An Egyptian trial concerning predictive models for recurrence and progression in resected NMIBC compared a cohort of 1,019 patients, treated after resection with different schedules and combinations of intravesical chemotherapeutic/immunomodulating agents (Ali-El-Dein et al. 2013). The authors could not draw conclusions concerning mistletoe, as only 8 patients were treated with BCG and VAE (Abnoba Viscum® fraxini) and an arm with mistletoe alone was not present. As an isolated factor in the analysis, all adjuvants added to TURBT decreased recurrence rate at 12 and 60 months, with mistletoe working best. Side effects of the combination of BCG with VAE were observed, discouraging concomitant treatment. The only comparison between BCG and VAE alone in a randomised trial has been found in a congress abstract and showed a lower recurrence rate with BCG (Hekal et al. 2008, Kienle et al. 2011).

Phytotherapeutic mistletoe extracts have been studied in two trials and showed that the recurrence rate for VAE was similar to BCG, but VAE were better tolerated. In adjuvant setting, a lectin-titrated aqueous mistletoe extract (Plenosol®), administered intravesically, has proven to be safe and beneficial (Elsaesser-Beile et al. 2005ab). The prospective phase I/II trial was performed in 30 patients with superficial bladder cancer, treated with complete transurethral resection. 23/30 were male and median age was 70 years (35 – 80 years). The patients were diagnosed as pTa G1 (6/30), pTa G2 (14/30) and pT1 G2 (10/30). The 30 patients received 6 intravesical instillations of mistletoe extract, starting 2-7 weeks after the resection, once weekly, with escalating dose (10 ng/ml of mistletoe lectin to 5000 ng/ml), retaining the extract for 2 hrs. Follow up was 12 months. The recurrence rate was comparable to the recurrence rate of 18 patients of an historical group treated with BCG. In contrast to BCG, tolerability was very good at all applied concentrations, with no local or systemic side effects. Concerning subcutaneous administration, a prospective randomised phase II trial (Goebell et al. 2002) compared a mistletoe phythoterapeutic extract (Eurixor®) to no treatment in 45 patients with complete resection for NMIBC pTa G1-2, N0 M0. No difference in outcome was observed. However, the treatment arm had received low dose and very short duration of treatment (Rostock 2003).

Preclinical research has shown that mistletoe and its components have antiproliferative activity against urothelial carcinoma in cell-line cultures (Urech et al. 2006; Hunziker-Basler et al. 2007; Simoes-Wust 2007) and in animal xenografts (Menges et al. 2000). They increase in vitro PMBC-killing of bladder tumoral cell lines (Schwarz et al. 1998). In animal models, the isolated mistletoe lectines used intravesically prevented chemically induced tumor development (Elsaesser-Beile et al. (2001), without effects by subcutaneous application (Kunze et al. 1998; Kunze et al. 2002). Lectin-poor VAP-A revealed a cytotoxic effect comparable to, or even stronger than, that of the lectin-rich VAP-Qu, on all tested bladder and breast

carcinoma cell lines, suggesting that other components of mistletoe are also active (Eggenschwiler et al. 2007). VAE reduce urotoxicity caused by cyclophosphamide (Serekoglu et al. 2011).

Non-muscle-invasive bladder cancer comprises 75% of bladder transitional cell carcinomas (Ali-El-Dein 2013) and is classified into risk categories. First choice adjuvant treatment after transurethral resection for high grade NMIBC is usually intravesical BCG. But often the choice has to be devolved to patient-physician discussion, due to the development of new approaches and the management of various conditions: recurrence/progression, BCG use-limiting side effects in some patients, BCG refractory disease and patients unsuitable for or refusing cystectomy (Smaldone et al. 2010ab). VAE are considered among the alternatives in the immunological treatment of non-muscle-invasive bladder cancer. They are proven to be safe, have clinical efficacy with intravesical application and do not show the side effects of BCG. Preclinical efficacy on bladder cancer cell has been proven. Further evaluations in patients with bladder cancer are needed, both for subcutaneous and/or intravesical application, together with a better definition of treatment schedules and patients selection (Sylvester et al. 2006; Ali-El-Dein et al. 2013). With further investigation of their clinical activity, VAE can have an effective role in non-muscle-invasive bladder cancer.

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#### *Bone and other sarcomas*

Sarcomas are rare tumor entities and data about mistletoe treatment refer to small numbers of patients. A randomised trial (Cesari et al. 2012) conducted in 20 patients with osteosarcoma, observed a prolonged disease free survival after the second relapse, compared to etoposide chemotherapy, with a median follow up of 16,4 months (up to 39 months). The median post-relapse survival of the local historical group was 11,8 months. In a casuistic of 6 patients with various sarcoma entities favourable disease courses were also described (Kirsch et al. 2011).

Osteosarcoma is a highly aggressive bone cancer, which accounts for 45% of all primitive bone sarcomas and affects mostly adolescents (median age at diagnosis is 18 years). Osteosarcoma is treated with surgery ± chemotherapy. After the second relapse, the relapse-free survival after 12 months is < 20%, there is no standard therapy and the median post-relapse disease free survival (PRDFS) is of 11,8 months, according to the historical control group of the institute (620 patients). The randomised trial with an anthroposophic *Viscum album L.* extract (VAE) was conducted at the Istituto Ortopedico Rizzoli, Bologna (I), center of excellence for research and treatment of orthopedic diseases, in pediatric and adult age (Longhi et al. 2009 – 2012; Cesari et al. 2012).

A pilot study of 5 patients treated after the second relapse with VAE alone (*Viscum album* ferm. Pini) over 12 months showed an average PRDFS of 18 months and a safety profile. Therefore a randomised trial was planned to compare the efficacy of an adjuvant treatment with VAE (*Viscum album* ferm. Pini, escalating dose 0,01 – 20 mg sc. or best tolerated dose, 3 times weekly, for 12 months) towards adjuvant oral etoposide (50 mg/kg/day, 1-21 q28). The study has been amended, due to slow recruitment rate, and the 20 patients originally planned for interim analysis were evaluated as final analysis (Cesari et al. 2012). The 20 patients had a diagnosis of histologically confirmed osteosarcoma / spindle-cell sarcoma of the bone and were free from disease after their second relapse. Nine were allocated in the VAE arm and 11 in the etoposide arm, with a median follow-up of 16,4 months (2-39). Median age was 33,9 years (11-65); 11 M and 9 F.

In 2012, Cesari et al. calculated a median DFS of 27,7 months in the VAE arm (2-57) and of 10 months in the etoposide arm (2-39). The VAE arm showed a longer PRDFS, a better trend in QOL for global health,

pain, fatigue and insomnia, measured by EORTC QLQ-C30, and a lower toxicity profile than the etoposide arm, with lower costs. The authors consider VAE as a promising adjuvant treatment in prolonging DFS after a second relapse and suggest further evaluation and comparison with an immunostimulant drug currently approved in osteosarcoma (IFN ad L-MTP-PE). Cost-effectiveness was also in favour of VAE.

Kirsch et al. (2011) describe a cohort of 6 patients treated with standardised VAE (Iscador®), sc., twice weekly, at a dose of 0,75-1 ng/kl mistletoe lectin. The case reports show favourable disease courses, with complete and partial remissions, and durable stabilisations of disease, in patients with angiosarcoma, metastatic liposarcoma, endometrial stromal sarcoma. A first patient had a diagnosis of lung and mediastinum metastases 21 months after surgery for primary liposarcoma, refused conventional treatments and was treated only with VAE. Due to discontinuations of VAE therapy, it was possible to observe progression of metastases during the interruptions and partial/complete regressions during treatment periods, with an overall survival of 21 years at the reporting time. The other cases added VAE to surgery alone or to chemotherapy or hormone therapy and earlier and longer responses than expected are described. Preclinical research shows that VAE and mistletoe components (lectins, triterpenes) can inhibit the growth of chemically induced fibrosarcoma in Swiss albino mice (Kuttan et al. 1996) and leiomyosarcoma xenograft in nude mice (Steinberg et al. 1992) and inhibit proliferation and induce apoptosis in paediatric osteosarcoma and Ewing's sarcoma cell models in vitro (Kauczor et al. 2012; Dejewski et al. 2013; Kauczor et al. 2013), associated with induction of immunomodulation in cell cultures and in animals (Steinberg et al. 1992; Hajto et al. 2011).

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### Brain cancer

Few studies describe *Viscum album* L. extract (VAE) application in brain cancer; however Heese et al. (2010) reported an extensive use of complementary therapies, among which mistletoe, in patients with glioma. Main reasons were “To do something for the treatment by myself”, “To build up body resistance”, “To support the conventional therapy”, “To have tried everything possible”. Almost 20% of patients declared to have used mistletoe.

Only one randomised prospective study in the 1990s investigated the effects of a phytotherapeutic VAE (Eurixor®, subcutaneous, twice weekly for 3 months) after surgery and during radiotherapy in 35 glioma patients in stage III/IV. Endpoints were immune parameters and quality of life (Spitzer’s test) related to radiotherapy induced immunosuppression. An improvement of both was observed in the VAE group (Lenartz et al. 1996, 2000). In 2000, Lenartz et al. published a reanalysis of the group, this time including 38 patients, to evaluate as endpoint disease free survival and overall survival, suggesting an increase of both in the VAE treated arm.

In vitro, VAE induce apoptosis in C6 rat glioma cells (Uçar et al. 2012). Mistletoe lectin is cytotoxic in vitro towards anaplastic glioma cell line F-98 and induces at low dose a tumor response in vivo in mouse (Lenartz et al. 1997, 1998). Lectin rich VAE (Iscador®M, Iscador® Qu, significantly enforce the NK-mediated glioblastoma cell lysis and reduces their migratory and invasive potential (Podlech et al. 2012).

According to anthroposophic medicine, a potential use of *Helleborus niger* injectable extracts has been described by Debus (2010), in combination with whole brain radiotherapy, for the antioedema properties of the plant (GAÄD 2008).

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### Breast cancer

Women with breast cancer seem to be the most relevant population in cancer patients treated with anthroposophic medicine. Their proportion is higher in the anthroposophic medicine cancer register than in other cancer registers, indicating in patients with breast cancer a relevant demand for integrative oncological treatment. The main group is represented by women with early disease and young women under 40, with a median age 11 years younger compared to other registers (Schad et al. 2013). As in other cancer entities, the declared reasons are the desire to improve quality of life (QOL), reduce side effects during conventional treatments, prevent recurrences and reduce treatment related-symptoms during follow up and

in survivorship (fatigue, menopause, depression etc.), and more generally to be active, promote own resources and experience self development throughout the treatments (Heusser et al 2006; Kienle 2013; Schad et al. 2013).

The majority of women with breast cancer, asking for complementary treatment with anthroposophic medicine, benefit from the whole system and from single therapies, especially mistletoe, eurythmy therapy, art therapy and other NPIs, and show a good compliance. (Ben Arye et al. 2013; Schad et al. 2013). Combination with chemotherapy is safe and side effects are reduced (Piao et al. 2004; Tröger 2012; Kienle et al. 2009; Kienle 2013). Women with breast cancer seek integrative oncology, combining anthroposophic medicine and conventional treatments, provided by dual trained conventional/complementary physicians, in anthroposophic institutions, (Schad et al. 2013), as well as in conventional oncology services offering integrated complementary medicine consultations and treatment (Ben Arye et al. 2013). The anthroposophic medicine treatments are provided outside institutions to patients with breast cancer, in medical practices and therapeutic centers.

Breast cancer is also the major tumor entity studied in clinical trials concerning anthroposophic medicine. The published studies have examined early and advanced stages and considered both the anthroposophic medicine whole system (Heusser et al. 2006; Carlsson et al. 2001-2006; Kröz et al. 2013) and the single treatments with mistletoe or NPIs. Improvement of QOL and reduction of side effects of conventional treatments were the major evidence (Mahfouz et al. 1998; Borrelli 2001; Carlsson et al. 2001-2006; Grossarth-Maticek et al. 2001; Piao et al. 2004; Heusser et al. 2006; Büssing et al. 2008; Tröger et al. 2009, 2010, 2012; Kienle et al. 2010; Eisenbraun et al. 2011; Kröz et al. 2013). An impact of *Viscum album L.* extracts (VAEs) on overall survival (OS) has been reported in epidemiological research (Grossarth-Maticek et al. 2001, 2006ab). Tumor shrinking with mistletoe is rare but has been described in casuistics and with off-label applications, such as high dosages and/or intratumoral application of VAEs, or in mistletoe pleurodesis for metastatic effusions (Werner et al. 1999; Kienle et al. 2007, 2010; Orange et al. 2010).

#### Anthroposophic mistletoe treatment

Most of the trials in breast cancer concern mistletoe alone. In 2009 Kienle et al. published a systematic review of clinical and preclinical research concerning breast and gynaecologic cancer and concluded that there existed a clinical benefit of *Viscum album L.* extracts (VAE) treatment in QOL, better toleration of conventional treatments and a possible increase in OS. Nineteen randomized (RCT), 16 non randomized (non RCT) controlled studies and 11 single arm cohort studies were identified that investigated VAE treatment, including altogether respectively 2420, 6599 and 1130 patients (8 RCTs and 8 non-RCTs were embedded in the same large epidemiological cohort study, first published by Grossarth et al. in 2001). Among the prospective controlled studies, 12 of the 22 assessing survival reported a statistically significant benefit, the others a trend or no difference. Of the 24 studies (15 RCTs and 9 non-RCTs) concerning quality of life (QOL) and tolerability of conventional treatments, 21 reported a statistically significant positive result. Methodological quality of the studies differed substantially. Few studies show no difference for the mistletoe arm. Tumour remission was observed after high dosage and local application. Preclinical research *in vitro* showed cytotoxic activity of mistletoe or its compounds and in animal models (34 animal experiments) safety, increase of survival and tumor response (Kienle et al. 2009; Simoes Wüst et al. 2011).

#### Overall survival

An increase in overall survival (OS) related to mistletoe treatment has been reported in epidemiological studies (Ostermann et al. 2012; Grossarth et al. 2001, 2006ab). Further studies are needed for more conclusive results. Evaluations of OS need a long follow up and the assumption of classifications in subgroups related to risk. Furthermore, the compliance to randomisation in central Europe is low, as VAE are popular among cancer patients.

In a large epidemiological cohort study, which had involved 35,814 participants over a 27 years period, 10,226 were cancer patients and 1,668 were treated with VAEs (Iscador®) (Grossarth et al. 2001). Patients were evaluated in differentiated analyses in general and according to tumor entities, including prospective matched-pair randomised and non randomised studies, nested in the larger study. Concerning breast cancer, 17 matched-pair in early stage were included in a randomised trial and 3 groups of 42, 55 and 83 pairs in all stages were enrolled in a non randomised trial. A clinically relevant effect on breast cancer survival and time to relapse was seen, with an HR and 95% confidence interval 0,43 (0,27-0,68). In the early stage pairs T1-3N0M0, the mistletoe groups had a better survival (RCT  $p < 0,02$  and non RCT  $< 0,0002$ ) and lower

progression (respectively  $p < 0,012$  and  $< 0,0001$ ) (Grossarth et al. 2006ab). A 5 year survival benefit has been suggested also by Gutsch et al. (1988) in early disease.

#### Quality of life and control of side effects of conventional treatments

Quality of life and control of side effects of conventional treatments actually represent the major evidence of mistletoe treatment for breast cancer (Kienle 2013). QOL has been evaluated in 11 RCTs (5 placebo-controlled): 7 investigated the impact on QOL of VAE combined to chemotherapy (Heiny 1991; Piao et al. 2004; Semiglasov et al. 2004, 2006; Auerbach 2005; Tröger et al. 2009, 2012) and 4 of VAE independently (Borrelli 2001; Grossarth et al. 2001, 2006a, 2006b). All studies showed better QOL in the VAE-treated groups except a very small group (Auerbach 2005), where no differences were seen. Some trials investigated early disease (Auerbach et al. 2005; Tröger et al. 2009, 2010, 2012; Semiglasov 2004, 2006), others advanced disease (Heiny 1991; Borrelli 2001) or all stages (Piao 2004; Grossarth et al. 2006). Most trials were conducted with anthroposophic VAEs; few with other phytotherapeutic VAEs (Heiny 1991; Semiglasov et al. 2004, 2006). Among the QOL issues, fatigue has been specially studied with, relevant positive results (Wode et al. 2009; Kröz et al. 2013).

Tröger et al. (2009, 2010, 2012) in a pilot study randomised in 3 groups 95 patients with breast cancer T1-3 N0-2 M0 undergoing 6 cycles of FAC chemotherapy and evaluated for QOL (EORTC-QLQ-C30) and hematological parameters. 1 received FAC alone, 2 groups added a VAE to FAC (respectively Iscador® M spez. sc. 0,01-5 mg or Helixor®) only during the 6 cycles. The QLQ-C30 showed better results in all 15 QOL scores in the Iscador group, significant ( $p < 0,02$ ) in 12/15 scores. Major advantage for the Iscador group was found for role function, social function, pain, and insomnia (Tröger 2009). Similar results were described after chemotherapy also in the Helixor group (Tröger 2010). A trend towards less neutropenia ( $p = 0,182$ ) was also observed in the Iscador group (Tröger 2009). The 5 year follow up after the end of mistletoe and chemotherapy showed a similar incidence of relapses, suggesting that the combination with VAE had not affected chemotherapy benefit (Tröger 2012).

In a RCT conducted in China, 68 patients with breast cancer, among other tumor entities, were randomised to receive in addition to standard chemotherapy mistletoe with CAF or CAP (Helixor® A sc., escalating dose 1 – 200 mg) versus Lentinan (i.m. 4 mg). QOL was evaluated with FLIC, TCM Index and Karnovsky Index. The group treated with VAE had significantly higher QOL scores for FLIC ( $p < 0,014$ ), TCM Index ( $p < 0,0007$ ) and KI ( $p = 0,002$ ), especially for nausea and pain, and less incidence of adverse events. (Piao et al. 2004).

Semiglasov et al. (2006) randomised 352 patients with breast cancer T1-3 N-/± M0 to 2 groups receiving a phytotherapeutic VAE (Lektinol®) or placebo combined to adjuvant CMF. A previous dose-finding trial had enrolled 272 patients with similar design and results. Together with immune parameters improvement, QOL was significantly increased in the VAE group, measured by GLQ-3, specific for CMF side effects ( $p < 0,0007$ ), Spitzer's uniscale and FACT-G ( $p < 0,0001$ ) and regarded fatigue, nausea/vomiting, depression. Improvement in QOL with anthroposophic VAE in metastatic disease was also described in one RCT evaluating with Spitzer's test mistletoe (Iscador®) versus placebo (Borrelli 2001).

A significant and clinically relevant reduction of adverse events related to conventional therapy was also described by Bock et al. (2004) and Matthes et al. (2012). According to the retrospective evaluation of 1,442 patients (710 treated also with VAE and 732 controls) with long-term VAE therapy (median 52 months) and follow up (67 months), adverse events related to conventional treatments were significantly lower ( $p < 0,001$ ) in the VAE group (16,3%) than in control (54,1%) (Bock et al. 2004).

Eisenbraun et al. (2011) performed a non-interventional, prospective clinical investigation concerning the longitudinal course of QOL (EORTC QLQ- C30 and QLQ-BR23) of 270 breast cancer patients during adjuvant chemotherapy and mistletoe therapy with Abnobaviscum® Mali, under conditions of daily practice. VAE produced a relevant stabilisation of Health Related Quality of Life during various chemotherapy regimes (CMF, FEC, EC, AC, FAC, paclitaxel), possibly due to a reduction of chemotherapy caused side effects with an excellent tolerability of the mistletoe therapy. After an initial deterioration, the average range of all obtained QLQ-C30 function scales ( $n = 262$ , 48.9–71.5) remained stable even at the last chemotherapy cycle and improved significantly ( $p < 0,0001$ ) to 66.9–80.7 4 weeks later, compared to the initial visit. As well, the QLQ-BR23 function scales significantly improved ( $p < 0,0001$ ) 4 weeks later. Tolerability of the therapy, judged by physicians, was rated as good or very good for 91% of the patients and efficacy was rated as good or very good for 94%. 89% of the patients reported about a good or very good benefit.

Similarly, Büssing et al. (2008) randomised 65 breast cancer patients to adjuvant (F)EC chemotherapy+VA-E (32 pats) or (F)EC alone (33 pats), mean age 54.7 years (26–77 years). This time, VAE were given i.v. (1-5 mg). The intravenous application of VA-E during chemotherapy was safe and tolerable, had no significant effect on granulocyte function and gave significant beneficial effects with respect to chemotherapy-related side effects.

A specific perspective considered in anthroposophic medicine and more generally connected to QOL, is self regulation, a theme that in cancer patients is related to coping, resilience and personal growth. Grossarth et al. (2001, 2006a, 2006b) observed a connection between self regulation and more favourable course of disease. Self regulation might be an independent prognostic factor for the survival of breast cancer patients (Kröz et al. 2011). The 2 prospective studies concerning breast cancer patients described a significant improvement in psychosomatic self-regulation (Grossarth et al. 2006a, 2006b; Ziegler et al. 2010). Alteration of circadian rhythms are also altered in patients with breast cancer (Bettermann et al. 2001) and may benefit from treatment.

#### Tumor shrinking

Tumor shrinking has been described in case reports and small cohorts. It is usually related to selected off-label administration protocols (intratumoral, high dosages, combination of various administration routes) (Mahfouz et al. 1999; Kröz et al. 2002; Orange et al. 2010). With high dosage VAE (Abnbaviscum @ Fraxini 2mg), Mahfouz et al. (1999) obtained 62% response rate (8% CR and 54%PR) in 26 patients with advanced breast cancer and the 2 case reports (Kröz et al. 2002; Orange et al. 2010) described a complete response with intratumoral VAE.

#### Immune enhancement

With VAE, a general enhancement in the immune system is observed. Preoperative i.v. infusions with VAE significantly reduce immune suppression induced by surgery for breast cancer ( $p < 0,001$ ). With the usual subcutaneous administration, a reduced chemotherapy-related neutropenia (Heiny 1991; Semiglasov 2006; Tröger et al. 2009), positive effect on NK cells (Auerbach 2005, Hajto et al. 1986; Braedel-Ruoff et al. 2010), increase in CD4+ and CD4+/CD8+ ratio (Semiglasov et al. 2004) and other immune parameters and release of beta endorphins (Heiny et al. 1998, Son et al. 2010) have been described.

#### Safety

As well as in the general mistletoe reviews, the listed breast cancer studies confirm safety and low rate of adverse events related to mistletoe treatment (Kienle et al. 2009). The combination with the common chemotherapy agents used for breast cancer seem to be safe and may in future be understood as leading to positive synergies. No disadvantage has been seen combining various chemotherapeutic agents with VAE in clinical studies (Gutsch 1988; Bock et al. 2004; Piao et al. 2004; Tröger 2012). No negative interaction of VAE or mistletoe lectins has been seen until now in animal experiments and *in vitro*, nor with gemcitabine in humans (Mansky et al. 2013).

#### Anthroposophic medicine whole system

A relevant clinical benefit in breast cancer can be obtained with mistletoe treatment alone, nevertheless the affected patients seem to have a definite interest for a more comprehensive approach. Long duration of chronic disease, long-term conventional treatments, survivorship, symptoms related to disease and to treatments, unmet needs are presumably associated to the desire for interventions coming from various directions and encouraging the active involvement and empowerment of patients. The majority of cancer patients recurring to anthroposophic medicine have breast cancer (Heusser et al. 2006; Schad et al. 2013). An over proportional amount of cancer patients recorded in the Network Oncology database are breast cancer patients (3.312 of total 10.405). The median age is 11 years younger, compared to the official German epidemiological data. A great majority had early disease and 335 were young women < 40 years (Happe 2013). Mistletoe treatments continue to be used by survivors (Templeton et al. 2013). The impact of subgroups classification (Gorman et al. 2010; Goldhirsch et al. 2011) is not known but can be found in the recent trials. Epidemiological and treatment patterns have been recently described by Schad et al. (2013). More than half of the patients have been treated with anthroposophic medicine as whole system. The non pharmacological interventions (NPIs) of anthroposophic medicine have a role in a comprehensive treatment.

Some research groups have investigated the patterns and the outcome of the whole system of anthroposophic medicine in patients with breast cancer. Heusser et al. (2006a, 2006b) described the patterns of treatment and improvements in QOL in patients with advanced disease including breast cancer during and after hospitalisation in a Swiss anthroposophic medicine oncological clinic (Lukas Klinik, Arlesheim, CH).

The Swedish group of Carlsson et al. (2001, 2004, 2005, 2006), at the Uppsala University, specifically studied patients with breast cancer. Trials investigated QOL and coping in 60 breast cancer patients comparing a group treated with mistletoe, anthroposophic medications and NPIs in an anthroposophic clinic (Vidarkliniken, Järna, SE) and the university clinic group. However, the anthroposophic medicine group was initially disadvantaged for QOL level and emotional state. In the first year, the patients treated with anthroposophic medicine showed a significant improvement in QOL, while the control patients showed no difference. Improvements in EORTC QLQ-C30, Life Satisfaction Questionnaire were statistically significant in the VAE group and, in regard to coping, the same group showed a decrease in passive and anxious behaviour and greater fighting spirit.

More recently the anthroposophic medicine whole system has been studied in relationship to fatigue, alteration of circadian rhythms, of autonomous regulation and of self regulation. These parameters are known to be altered in breast cancer patients at diagnose, in adjuvant time and in survivors. The anthroposophic medicine multimodal approach including mistletoe, art therapy, eurythmy therapy and psychoeducational interventions significantly improved sleep, fatigue and autonomic regulation (Kröz et al. 2000, 2013) and self regulation (Ziegler et al. 2008).

Studies have proved that also NPIs alone can be helpful in cancer related conditions, such as disease and symptom scores improved by eurythmy (Hamre et al. 2007), depression improved by art therapy (Bar-Sela et al. 2007) and fatigue improved by eurythmy therapy (Kanitz et al. 2012; Seifert et al. 2013) and art therapy (Bar-Sela et al. 2007).

## Conclusions

The published literature shows a clinical benefit in different issues of QOL, in support to conventional treatment and possibly in OS. Further investigations concerning high dosages and intratumoral use for tumor shrinking are needed. Data reveal a high demand existing in women with breast cancer for integrative cancer treatment with anthroposophic medicine: they seem to be interested in coping strategies and in integration, both with mistletoe and with the anthroposophic medicine whole system approach. They have needs concerning long lasting symptomatic load after the initial phase of disease (fatigue, depression, menopause, reproductive concerns). Compliance is high and both pharmacological and non pharmacological interventions are requested. Integration is good with mainstream medicine and traditional medicines (Ben Arye et al. 2012ab). Lifestyle interventions, biodynamic nutrition and exercise coaching, in relationship to the well known risk factors for disease relapse have been included since the beginning in anthroposophic medicine. Some subgroups at high risk, young women, survivors with symptoms burden might especially profit from the offer of anthroposophic oncology and represent specific research issues, together with early and advanced disease. More studies would be interesting to further define the clinical impact of integration with anthroposophic medicine and to meet the differentiated needs of patients in anthroposophic medicine facilities, to help counsel and design comprehensive treatment strategies.

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### *Colorectal cancer*

Retrospective research suggests that combination of *Viscum album L.* extract (VAE) to standard treatments in patients with colorectal cancer might prolong disease free survival (DSF) and overall survival (OS) in adjuvant and advanced disease, but further prospective trials are needed for these endpoints. Evidence of improvement in quality of life (QOL) and reduction of side effects of conventional treatments is clearer. Neoadjuvant and perioperative administration might be beneficial, and need specific investigation. In advanced disease, intraperitoneal treatment of ascites can prolong the time between punctions.

The combination of VAE with conventional treatments in adjuvant setting for colorectal cancer has been studied in a retrospective study on 804 patients and suggests a possible effect on prolonged metastasis free survival and possibly of overall *survival*, together with a significant improvement in side effects of standard treatments (Zaenker et al. 2012).

A pharmacoepidemiological, retrospective, observational (“retrospective”) cohort study investigated the impact of best supportive care with VAE (Iscador® Qu) in patients with colorectal carcinoma (stage I-III), treated with adjuvant standard therapy after R0 surgery. A group of 429 patients who added VAE was compared to a group of 375 without VAE (Bock et al. 2007; Friedel et al. 2007, 2009). The endpoints (therapy-induced adverse effects, disease symptoms and disease free survival (DSF) were significantly improved in the group treated with VAE. A confirmatory analysis was published in 2012 (Zaenker et al. 2012), selecting the host specificity of VAE (106 patients treated with Iscador® Qu). This group showed a significant improvement in conventional treatment side effects, a significant delay in metastatic relapse and longer DSF, compared to patients receiving standard treatments (212). The metastasis-free survival was 133 months in the Iscador Qu versus 94 months in the control (p=0,002), corresponding to a HR of 0.31. Side effects of conventional treatments, like nausea and vomiting, loss of appetite, fatigue, depression, sleep disturbances and mucositis, were significantly less (p<0,001) in the group treated with VAE. Major efficacy was shown on loss of appetite, fatigue, mucositis and depression.

The casuistics concerning colorectal cancer of two German anthroposophic public hospitals (Gemeinschaftskrankenhaus Havelhöhe and Gemeinschaftskrankenhaus Herdecke) have been described in two publications. Schad et al. (2005) evaluated the stratification of 481 patients in all stages of disease, treated between 1996 and 2002. 67% had received sc or i.v mistletoe treatment. Low incidence of side effects and high satisfaction (91% “positive”, 70% “helpful”, 95% “further recommended”) were reported. Stumpf et al. (2007) described a population of 1354 patients with colorectal cancer in all stages, treated between 1981 and 2001. 476 (70,2%) had also received treatment with VAE for  $22,8 \pm 26,2$  months. The comparison with the regional cancer register suggests a prolonged survival in the VAE treated group. Similar results have been described in a previous retrospective study (Salzer et al. 1992).

Few prospective studies have investigated VAE in colorectal cancer (Douwes et al. 1986, 1988; Grossarth et al. 2001; Cazacu et al. 2002), respectively with 60, 130 and 64 patients, mostly with advanced disease. They all studied the combination of VAE to standard chemotherapy and suggest an increase in overall survival in the arm treated also with VAE. Another study investigated tumor response in a small group of patients with metastatic colorectal cancer beyond chemotherapy lines (Bar-Sela et al. 2004). With VAE (Abnobaviscum® Qu, 0,2-20mg) no tumor response was observed, but symptomatic relief was reported in 40% of patients and stable disease for 2,5 months (1-7 months).

Some different administration modalities of VAE have been described for specific conditions. Metastatic disease with ascites can be beneficially influenced by intraperitoneal instillation of VAE (Iscador® M, 10 mg), increasing the interval between instillations, without toxicity. In 23 patients, following the first instillation, the median time between injections increased from 7 to 12 days, reaching 13 days after the third injection. (Bar-Sela et al. 2006) Perioperative i.v. administration of VAE attenuates the immunosuppressive effects of surgery (Enesel et al. 2005; Schink et al. 2007). Neoadjuvant intralesional VAE application has been described in a cohort of 14 patients. The procedure was well tolerated, induced tumor shrinking and led to surgery. A local immunostimulation was observed at histology (Matthes et al. 2005).

Regarding quality of life in colorectal cancer, the mentioned studies described a benefit from VAE in relation to side effects of conventional treatments.

Relevant issues in colorectal cancer are also cancer related fatigue and alterations of circadian rhythms, connected to the index of self regulation. The latter appears to be an independent prognostic factor for survival of patients with colon carcinoma (Kröz et al. 2011) and seems to be enhanced by mistletoe therapy (Grossarth et al. 2001) and more generally by AM whole system approach.

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#### *Gastric cancer*

Some randomised trials (Günczler et al., 1968; Salzer et al, 1979; Salzer et al, 1983, Kim et al., 2012) and an epidemiologic cohort study (Grossarth-Maticek et al. 2001) showed a trend to improvement in overall survival (OS) and in quality of life (QOL) of patients with gastric cancer, globally and in adjuvant stage, using anthroposophic mistletoe extracts. An immunoprotective effect of *Viscum album* L. extracts (VAE) in relation to surgery has been described.

A randomised controlled pilot study was conducted in Korea in 32 patients after radical surgery (stage Ib or II). Gastric cancer is the most frequent cancer in Korea, and the second most common worldwide: Patients were randomised in 2 groups to investigate implementation of VAE (Abnoba *Viscum*® Qu, sc 3 times weekly, dose escalating, 7 days after surgery to week 24) to oral chemotherapy (doxifluridine). The aim of the trial was the evaluation of quality of life (QOL), immune modulation and safety of VAE in adjuvant setting. Safety of VAE and a significant improvement in QOL, measured by EORTC QLQ-C30 and –STO22, an increase of WBC and eosinophils, stable NK and a lower frequency of diarrhea have been observed (Kim et al. 2012; Eisenbraun 2012).

Concerning survival, a randomised controlled trial, conducted in Vienna in 137 patients, allocated patients after surgery in 2 groups. The aim of the trial was to compare an adjuvant treatment with *Viscum album* L. extracts (VAE) (Iscador® sc.) versus no treatment. 72 were lymph node-positive. The VAE treatment group had a significantly higher survival: respectively 749 days (LN+)/ 1661 days (LN-) versus 540 days (LN+)/ 1364 days (LN-) (Salzer et al. 1983).

In 1990, Salzer et al. also published their retrospective comparative study of all the casuistic of gastric cancer treated in the Ludwig Boltzmann Institute in Vienna. The 421 evaluable patients in stadium I-IV LN -/+ were divided in three groups having received VAE or chemotherapy or no treatment. Survival was longer in the 2 treated groups than in control (median OS respectively 55 and 57 months versus 27, in node-negative, and 26 and 29 months versus 15, in node positive).

A prospective matched-pair study on gastric cancer, all stages (85 pairs, 44 strictly matched), was embedded in the Grossarth Maticek study (2001a; 2001b). Mean survival time was higher in the VAE group (Iscador®) versus control: respectively 1,92 years versus 1,32 and 2,06 versus 1,41.

VAE (Isorel®, dose escalating) have been used in preoperative application in a randomised trial in order to evaluate surgical immunosuppression and stress in patients with gastrointestinal cancers, including gastric cancer. In one of the arms, VAE were added to surgery and were administered in 60 mg/ml 3 times weekly in the 2 weeks before and the 2 weeks after surgery. In the treated group less immunosuppression, less anxiety (analogic scale of anxiety) and a better Karnovsky Index had been observed after 60 days (Enesel et al. 2005).

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## Kidney cancer

Like melanoma, renal cell carcinoma is classed as an immunogenic tumor, based on its response rate to immunotherapy, the incidence of spontaneous regression, and the high level of tumor T cell infiltration (Itsumi et al. 2010). Immunological approaches are currently investigated as new promising offers (McDermott et al. 2013).

Despite this fact, no major investigation about anthroposophic *Viscum album L.* extracts (VAE) in kidney cancer treatment has been found. The only clinical study performed with VAE in renal adenocarcinoma is a small single arm retrospective cohort phase II study, including 14 patients with stage IV renal carcinoma and clearly measurable lung metastases, where no clear effects were shown. VAE were administered at escalating dose (Iscador® Qu/M 0,1 – 50 mg every second day, in individualised schedule, median duration 13/47 weeks). Treatment and course varied in patients and no objective response was observed. Quality of life (VAS scale) and survival time appeared to be comparable with data of patients included in a parallel phase II trial with high dose MPA (Kjaer 1989).

In the preclinical setting, the aqueous mistletoe extract Lektinol® i.p. or s.c. showed to have antiproliferative efficacy similar to adriamycin against Renca renal cell carcinoma in a murine model (Burger et al. 2001).

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### *Liver cancer*

Treatment options for hepatocellular carcinoma (HCC) are mainly surgical or locally ablative therapies. Targeted therapy has high costs and side effects (Borovicka et al. 2011). HCC shares with other cancers some characteristics that render it a potential target for immunotherapy. Among immunotherapy attractive approaches to HCC management there are immunomodulatory drugs and anthroposophic *Viscum album* L. extracts (VAE) have proven to be beneficial. (Palmer et al. 2005). A tumor response was observed in HCC with high dosage VAE, given subcutaneously and in small casuistics which evaluated the intralesional/intraarterial off-label administration in liver metastases. A possible preventive role can be seen in treating patients with HCV infection.

The potential of a positive effect of VAE in patients with primary liver cancer, treated with VAE alone, has been clearly shown by 2 clinical trials conducted in Egypt, in chemotherapy-naïve patients with advanced disease (Mabed et al. 2004, Ebrahim et al. 2010). Some evidence of beneficial effect have been described also for liver metastases and for less frequent off-label application modalities for VAE, such as intralesional application.

In 23 patients with unresectable HCC, treated with high dosage VAE (Abnoba *Viscum Fraxini* 2®, 40 mg once weekly), for a median time of 14 weeks, a complete response was observed in 3 patients (13,1%) and a partial response in 2 (8,1%), with a low toxicity profile (fever and local reaction) and a survival range of 8 to 38 months in the responders (Mabed et al. 2004).

Ebrahim et al. (2010) studied a far greater number of patients. In a two stage-design trial, 120 patients with advanced chemotherapy-naïve HCC were treated with the same VAE schedule (*Viscum Fraxini* 2, 40 mg, subcutaneously, once weekly) and a similar safety profile. Twenty-four patients (20%) achieved RECIST objective response (including 2 CR) and 40 patients (33,3%) achieved stable disease. The median survival in the patients with objective response was 16 months (8 months for all patients) (Ebrahim et al. 2010).

In a retrospective cohort study, Matthes (1997, 2001) described the intratumoral application of VAE in liver, evaluating the intralesional treatment with Helixor M® (dose escalating, 100-2500 mg, median 7 interventions, 1-3 times weekly) in a cohort of 6 patients with primary HCC and 21 patients with *hepatic metastases* from colorectal cancer (Kienle et al. 2003). After the intralesional application, 52% of the patients with liver metastases had a reduction of the initial diameter (1 >75%, 4 >50%, 6 > 25%) and of tumor markers, with an average need of 7 injections and few concomitant side effects. In the 6 patients with HCC, 5/6 displayed a reduction in the lesion diameter (1 >75%, 2 >50%, 1 >25%) and reduction of AFP.

Six further patients with liver metastases from colorectal cancer, with no response to intra-arterial chemotherapy, were treated intra-arterially (via port in hepatic artery) with VAE (Helixor ® M 1000 mg or Abnoba *Viscum* ® Qu 100 mg). All 6 experienced better general condition and 3/6 had a 25-50% reduction of metastases. The treatment was well tolerated; 3 patients had post-treatment fever.

Hajto et al. (2013) describes a case report series of 8 patients showing complete/partial remission of hepatic metastases from melanoma, breast, ovary and colorectal cancer, after treatment with VAE standardised for lectin content (Iscador®, 0,5 – 1 ng/kg lectin, sc., twice weekly) combined with a heteropolysaccharide rice bran preparation standardized for arabinoside (12-45mg/kg MGN-3/BiobranR twice a week) and wheat germ extract (WGE). Accordingly, the effect of mistletoe cannot be isolated.

HCC is strongly related to HCV chronic infection. The beneficial effect on clinical parameters and symptoms in patients with HCV hepatitis suggests that application of AM regimens including VAE could find a role also in HCC and cirrhosis prevention in HCV positive hepatopathic patients (Matthes et al. 1998; Matthes et al. 1999; Tusenius et al., 2001, 2005).

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### *Lung cancer*

Both anthroposophic mistletoe extracts and non pharmacological interventions (NPI) seem to meet some needs of patients with lung cancer. In centers offering integration between conventional oncology and the comprehensive system of anthroposophic medicine, half of lung cancer patients profit from the opportunity to receive *Viscum album* L. extracts (VAE), other anthroposophic medications and NPIs (Schad et al. 2012). A few trials have been published concerning VAE in non small cell lung cancer (NSCLC). Endpoints were survival and quality of life, mainly in advanced stage. For patients treated with VAE, one trial indicates a prolonged survival (Grossarth et al. 2001), two trials observed a better quality of life and/or a reduction of conventional treatments side effects (Piao et al. 2004; Grah et al. 2011) and one trial described a minor frequency of chemotherapy dose reductions, severe non-haematological side-effects and hospitalisations (Bar-Sela et al. 2013). Recent advances in the understanding of immune response in lung cancer raise hope for the development of different kinds of novel immunotherapeutic agents, cancer vaccination and immunomodulation (Declerck 2013), with renewed interest for immunomodulating approaches, starting also in earlier stages of disease. Studies with VAE in a larger number of patients are needed.

In the epidemiological study published by Grossarth et al. (2001) two prospective matched-pair studies concerning treatment with VAE (Iscador®) in NSCLC (109 pairs) and in microcitoma (25 pairs) were included. For NSCLC, the increase in mean *survival* in the mistletoe-treated was highly significant: 3,41 years versus 2,78 years ( $p=0,002$ ). With the strict criteria, 52 pairs were identified, with a significant ( $p=0,05$ ) advantage in survival for the patients treated with mistletoe. For microcitoma, the mean survival in the mistletoe-treated was as well significantly longer: 1,87 years versus 1,43 years. ( $p=0,03$ ). 21 pairs matched the strict criteria and the results in survival for the mistletoe-treated patients were 1,99 vs. 1,44 years ( $p=0,02$ ).

Concerning quality of life, in a prospective randomized controlled clinical trial, Piao et al. (2004) described a beneficial effect of VAE addition to conventional treatment in NSCLC (all stages). In this multicentric randomized open prospective clinical trial 233 patients were enrolled, among which 94 patients with NSCLC. The trial compared VAE (Helixor A®, escalating dose 1–200 mg 3 times weekly) and a polysaccharide extract from *Lentinula edodes* (shiitake) as complementary agents to improve QOL during standard cancer treatments. Quality of life (QOL) was measured with FLIC (Functional Living Index-Cancer), TCM (Traditional Chinese Medicine Index) and Karnovsky Index. The VAE arm showed a significant improvement in QOL and reduced chemotherapy side effects. (Piao et al. 2004).

Recently, Bar Sela et al. (2013) enrolled 72 patients with NSCLC (non-operable St IIIA/B-IV; 65% stage IV, 63% squamous histology) in a randomised phase II trial. One arm added VAE (Iscador® Qu 10 mg, every 2nd day, after induction) to standard chemotherapy (carboplatin combined with gemcitabine or pemetrexed). In both groups the median overall survival was 11 months. Median time to progression (TTP) was 6 months in the Iscador arm versus 4.8 months for the controls. Chemotherapy dose-reduction (13% vs. 44%), severe grade 3-4 non hematological chemotherapy toxicities (16% vs. 41%) and hospitalisations (24% vs 54%) were less frequent in the VAE group. The difference in favour of VAE was significant for chemotherapy induced neuropathy. Differences in grade 3-4 haematological toxicity were not significant.

Though survival time was similar in both groups, time to progression was prolonged in the VAE arm and the reduction of chemotherapy side effects led to a better global treatment performance.

Grah et al. (2011) documented safety and good tolerance of VAE (Iscador® Qu) combined with cisplatin/docetaxel chemotherapy, given for NSCLC (stage IIIb/IV), in an open-phase II, monocentric, randomised study of 50 patients. Combination with VAE resulted in improved tolerance of chemotherapy. No significant superiority in survival of the VAE arm was shown towards chemotherapy alone, but a trend towards prolonged survival and time to progression was described. In the VAE arm, the survival in the first quartile was 259 days versus 170, and the time to progression 272 days versus 190, without significant difference in QOL (EORTC-C30 and EORTC-LC13).

Two randomised studies showing some methodological problems were conducted with VAE versus no treatment, in postoperative adjuvant condition (Salzer et al. 1991) and versus placebo, in advanced stage (Dold et al. 1991), without statistically significant results (Kienle et al. 2003).

The off-label intralesional use of VAE has shown effectiveness in obstructive conditions. A safe and tumor shrinking effect of endoscopic intralesional VAE instillation was described in a cohort of patients with endobronchial obstructive localisations of bronchial carcinoma. The endobronchial reduction was performed in specialistic palliative setting and was accompanied by induction of apoptosis. (Grah et al. 2005; Grah et al. 2007).

In advanced NSCLC cancer, the relevance of best supportive care has been clearly described by Temel et al. (2010), in a nonblinded, randomized, controlled trial. Early palliative care was superior in survival to conventional treatment, with a median OS of 11 months (0,97 years), versus 8,9 months. Comprehensive supportive approaches might therefore have a relevant role in the treatment of advanced lung cancer, as alternative or as complementary options. The Network Oncology group has described the patterns of treatment and survival of patients with advanced NSCLC in observational study recorded in the cancer register (Schad et al. 2013). The multimodal approach of anthroposophic medicine was offered, in addition to the required standard treatments, to 441 patients with NSCLC stage IV, having had at least one of the following therapies: mistletoe, rhythmical massage, eurythmy therapy, art therapy or other NPIs and hyperthermia. Median age was 64 yrs. (32-92). 84% of the patients received chemotherapy, 55% radiation and 40% surgery. Most frequent additional therapies were *Viscum album* (72%), embrocation (43%), therapeutic unction (42%), eurythmy therapy and physiotherapy (both 27%). Patients used combinations of up to 9 different additional therapies. Median length of VAE therapy was 6.4 months. Compliance was good. Median OS was 1.05 yr. (95% CI: 0.83 - 1.32), 2 and the 3-years survival was 31 % and 20%, respectively. Patients with lung cancer turned to the anthroposophic hospital with a consistent interest for integrative oncology.

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### *Pancreatic cancer*

Pancreatic cancer is often diagnosed in advanced condition and prognosis is often severe. Chemotherapeutic regimens have side effects and it is not always easy to keep to the chemotherapy schedules. The combination of VAE can allow better toleration and higher dosages of gemcitabine, the most frequently used (Mansky et al. 2013). If their general condition is bad and after standard therapies have failed, patients with locally advanced or metastatic pancreatic cancer have few therapeutic options. Relief to symptom burden and help for side effects of conventional treatments become relevant questions. The promising results of a recent randomised phase III trial (Tröger et al. 2013) showed a significant and clinically relevant improvement in overall survival after treatment with *Viscum album* L. extracts (VAE), complementary to standard therapy. The disease-related symptoms were improved as well, especially weight-loss, lack of energy, pain and nausea/vomiting.

A prospective, parallel, open label, monocentre, group-sequential, randomised phase III study had enrolled at the interim analysis 220 patients, with locally advanced or metastatic pancreatic cancer (Tröger et al. 2013, Galun et al. 2012ab). After randomisation, one group was treated with VAE subcutaneously (Iscador Qu spezial®, dose escalating, 0,01 mg to 5 mg) and best supportive care versus best supportive care alone. The mistletoe-treated group showed a significant and clinically relevant prolongation of overall survival and a significant improvement of disease-related symptoms, such as weight loss, pain, loss of energy, nausea/vomiting, diarrhea, anxiety. Median overall survival (OS) was 4,8 months in the VAE group versus 2,7 in control group. Patients were stratified into two groups regarding their expected prognosis. In the 'poor prognosis' subgroup (UICC IV, age  $\geq 65$  or ECOG  $\geq 2$ ) median OS was respectively of 3,4 and 2 months ( $p = 0.0031$ ). In the 'good prognosis' subgroup the median OS was 6,6 vs. 3,2 months ( $p < 0.0001$ ). Due to the results of clear efficacy, the study was stopped after the first planned interim analysis of 220 patients by the Independent Data Committee, proposing to put on VAE the remaining 220 patients (Tröger et al. 2013). In the VAE group, the frequency and severity of post-baseline disease-related symptoms was significantly lower for: pain, weight loss, loss of energy, nausea/emesis ( $p < 0.0001$  for all parameters), diarrhea ( $p = 0.0033$ ) and anxiety ( $p = 0.046$ ). A more detailed examination of quality of life parameters and of symptom burden is currently undergoing further evaluation. The authors concluded that VAE represent a non-toxic and effective second-line therapy, that offers a prolongation of survival, as well as less disease-related symptoms for patients with locally advanced or metastatic pancreatic cancer.

Gemcitabine in mono- or in polychemotherapy is the most used chemotherapy agent in pancreas cancer. In a phase I study (44 patients with advanced solid tumors) the combination of VAE (Helixor A®, dose escalating, s.c.) with gemcitabine (GEM) showed clinical activity, was safe and well tolerated, allowing for a 30% higher gemcitabine dose than recommended in single agent treatment (Mansky et al. 2010, 2013). Gemcitabine 1380 mg/m<sup>2</sup> and mistletoe 250 mg combined were the maximum tolerated dose. 6% of

patients showed partial response, 42% stable disease. Median survival was 200 days. Compliance was high. Gemcitabine hematologic toxicity appeared to be reduced by implementation with VAE. Pharmacokinetics of gemcitabine was not affected. No botanical/drug interactions were observed. Absolute neutrophil count showed a trend to increase between baseline and cycle 2 in stage I dose escalation. Clinical response was similar to gemcitabine alone.

VAE implementation in pancreas cancer treatment seem to reduce gemcitabine toxicity and need for hospitalisation during standard treatments, therefore contributing to better compliance and more adequate dosages and timing of chemotherapy schedules. A retrospective evaluation of 396 patients from 17 centres, treated after surgery with chemotherapy alone or chemotherapy+VAE (Iscador®) showed remarkable reduction of tumor associated symptoms and chemotherapy-related adverse reactions (13,7% vs. 48,9%) in the group treated also with VAE, as well as better quality of life, better Karnovsky Index and reduction of hospitalisation needs (Matthes et al. 2007-2010; Ostermann et al. 2012).

A retrospective analysis of the survival of 292 patients with advanced pancreatic cancer, treated with VAE (Iscador®m 2-3 x weekly, sc., 1-30mg) at the Lukas Clinic Arlesheim, Switzerland, between 1986 and 1996, was published by Schaefermeyer et al. (1998). One year survival rate was 26.3%. Median survival time was calculated for all stages. It was 6.58, months for the complete group, 16.69 months for 29 patients who had undergone resection, and 5.6 months for 161 stage IV cases.

Tumor shrinking by intratumoral application of VAE has been observed in animal models (Rostock et al. 2005) and casuistics of inoperable patients treated intralesionally (Matthes et al. 2007a). Intratumoral VAE were given with a schedule of 3 initial instillations every 2-3 days, then every 3-4 weeks (Helixor® M 200-300 mg, escalating dose up to 900 mg, or Abnoba® Fraxini St 2) to 7 inoperable patients (AJCC stage IIA-IV), combined with subcutaneous VAE and gemcitabine. Locoregional control without progression was obtained in all patients for a median of 6 months (up to 11 and 13 months), with an improvement of Karnovsky Index and quality of life in 5/7 (Matthes et al. 2007a).

In a retrospective analysis (Schad et al. 2013) of 39 patients with advanced, inoperable pancreatic cancer, who received in total 223 intratumoral applications of mistletoe, no severe procedure-related events were observed. This interesting off-label use needs further validation. Patients received standard first- and second-line chemotherapy and palliative surgery, as well as additive subcutaneous and partly intravenous mistletoe application. A median survival of 11 months was observed for all patients (11.8 and 8.3 months for stages III and IV, respectively). Due to the multimodal therapeutic approach and the lack of a control group, the effect of intratumoral mistletoe administration alone remains unclear, but the analysis suggests that intratumoral-applied mistletoe is feasible and safe, might contribute to improve survival of patients with pancreatic cancer and deserves further evaluation in a randomized controlled trial.

The safety and the results obtained in advanced setting suggest a need for the evaluation of VAE also in earlier stages of disease, in adjuvant setting and in combination with the more recent polichemotherapy / targeted therapy/radiotherapy regimens.

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### Prostate cancer

Casuistics report clinical response to *Viscum album* L. extracts (VAE) in prostate cancer, but we lack decisive and specific studies. No prospective clinical trials have been published. Mistletoe is mentioned among CAM and dietary approaches for prostate cancer. The latter are described in connection with improvement of general condition and a possible use in chemoprevention, together with advocating collaboration with urologists (Auerbach 2006, Perabo FGE 2009).

Episodial favourable courses, with pain improvement, have been described by Boie (1977) and complete/partial responses have been reported by Kempenich (2009). The two authors published small case series of patients treated in clinical practice with VAE in combination with conventional (Boie 1977) or anthroposophic medicine (Kempenich 2009) therapies.

Boie (1977) describes 12 patients with advanced prostate cancer, having had long survival, improvement of pain and better general condition, under treatment with VAE (Helixor®) together with hormone therapy, Pain improvement was correlated to use of VAE (Kienle et al. 2003).

The 3 case reports published by Kempenich (2009) concern patients with prostate cancer stage I-III, who had refused conventional treatments and had therefore been offered treatment with VAE (Iscucin® Populi, escalating dose, D13 to 5%), combined with an individual complex of anthroposophic medications. 2 patients had complete response (T1bN0M0 Gleason 3+3, T3aN0M0 Gleason 3+4) and 1 (T1cN0M0 Gleason 2+3) had partial response.

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### Pediatric oncology

Mortality rates have been reduced by more than 50% over the past 3 decades and the 5-year survival rate has increased to approximately 80% in conventional pediatric oncology (Pui et al. 2011). Further issues, such as quality of life during treatment and long-term effects in survivors, are taken in account. Supportive/palliative care starting at diagnosis should be seen as an essential part of management of

children with cancer, together with survival. Central Europe data confirm a relevant use of anthroposophic medicine by children with cancer. Families recommend it to other parents. Safety, in combination with conventional treatments, is described by retrospective studies and casuistics. The same publications also suggest a potential clinical efficacy and reduction of side effects of standard treatments, but we still lack for published prospective trials concerning efficacy and have to wait for the results of the ongoing ones. A role for anthroposophic mistletoe extracts is suggested also by the reduction of recurrent infections in immunodepressed children and by effectiveness *in vitro* against pediatric cancer cell lines.

Families having children with cancer seek anthroposophic medicine and other complementary approaches. The use of complementary and alternative medicine (CAM) in children with cancer is common and probably increasing (Göttschling et al. 2006). In the surveys, the main reasons for use are to reduce therapy-related side effects, to strengthen the immune system, to achieve physical stabilization and to increase healing chances. In a population-based survey over a 1 year period with 497 participants (322 children and 135 adolescents) 31% reported CAM use from the diagnosis. A majority of CAM users (97%) would recommend CAM use. Side effects were rarely reported (5%), and were minor and self-limiting (Göttschling et al. 2013). In a retrospective survey on CAM use in pediatric oncology (1,063 evaluable questionnaires), 35% of the children had used CAM. Homeopathy and anthroposophic medicine, included mistletoe treatment, were used by 72% and 89% of the users would recommend CAM to other parents. (Längler et al. 2008). The high prevalence rates seem to represent the parental or patients needs for an additional treatment, perceived as successful and devoid of side-effects (Göttschling et al. 2013).

As anthroposophic medicine and mistletoe treatment are not always differentiated from homeopathy by families, or they are used together, specific data for anthroposophic medicine are not so clearly defined (Längler et al. 2008). 27% of the parents using CAM in pediatric oncology use anthroposophic medicine, which stands out as being characterized by a particularly long duration of use (median 619 days for anthroposophic medicine and 225 days for other CAM treatments) and a high level of patient satisfaction and physician loyalty (Längler et al. 2010).

A survey on attitudes and beliefs of paediatric oncologists regarding complementary and alternative therapies in Germany showed that the majority of the responding physicians was open towards continuing medical education on CAM, especially younger doctors and manifest interest in becoming more competent to advise their patients. Nevertheless the majority currently tended not to actively bring up the topic in the consultations (only 41% did it) and seemed to be worried about CAM use by their patients because of possible interactions (76%) or side-effects (65.7%), additional costs (75.4%) (Längler et al. 2013). Contrary to an Italian experience (Clerici et al. 2009), in the German survey most users (78%) had informed physicians about CAM use (Göttschling et al. 2013).

From the clinical perspective, only few publications are present to date. A retrospective-matched pair analysis investigated the safety and efficacy of anthroposophic medicine supportive therapy combined with conventional treatments in children with brain neoplasms, but it was not possible to retrospectively explore a difference in disease free survival or overall survival (Seifert et al. 2011). Case reports and casuistics (Lenard 1998; Kameda et al. 2011; Seifert et al. 2011) have described the safety of the combination of *Viscum album L.* extract (VAE) with conventional treatments in children respectively with fibrillary astrocytoma, anaplastic lymphoma and medulloblastoma, suggesting a possible tumor response to VAE. We have to wait for prospective studies in order to evaluate efficacy on survival parameters and on side effects, beyond the real life observations.

A large prospective multicentric study is currently ongoing in Germany. The preliminary studies and the real life clinical practice in pediatric oncology have led to a protocol of recommendations for the treatment of children with cancer and of side effects of conventional therapies. The recommended anthroposophic medications and non pharmacological therapies have been reviewed, according to indications, by Längler et al. (2012).

The anthroposophic *Helleborus niger L.* extracts also find an indication in clinical practice in pediatric oncology (GAÄD 2013). *In vitro* *Helleborus niger* extracts are cytotoxic in neuroblastoma cell line NXS2 (Delebinski et al. 2012b), in Burkitt-like lymphoma cell line BJAB, in the leukemia cell lines NALM-6, Sup-B-15 and REH (Jesse et al. 2008, 2009), with apoptosis induction. A significant apoptosis was also induced in primary leukemia cells *ex vivo*, from children with ALL or AML, which were partly poor responding to the anthracyclines doxorubicin and daunorubicin. In NALM-6 cells resistant to vincristine and paclitaxel, apoptosis induction by *H. niger* was as high in the control than in the resistant cell line, so that drug resistance against these two compounds was overcome *in vitro* (Jesse et al. 2008).

Actually the only pediatric oncological center worldwide, which systematically treats children conventionally, according to current guidelines, in combination with anthroposophic treatment procedures is the Gemeinschaftskrankenhaus Herdecke, in Germany. However, integration is applied in other oncological settings and several physicians in Europe offer anthroposophic medicine for children with cancer in the outpatient setting. The main medication is subcutaneous mistletoe therapy (Längler et al. 2012). In addition, typical anthroposophic medicaments are recommended in daily practice to reduce the side effects of conventional treatments (lack of appetite, pain, fever, neutropenia, mucositis, nausea, steroid related symptoms, insomnia, anxiety, restlessness) (Längler et al. 2012).

NPIs are also regularly applied, such as oil applications, rhythmic massage, art therapy (music, painting), eurythmy therapy (Längler et al. 2012). In a pilot study, eurythmy therapy has shown a rehabilitative effect with good adherence and improvements in cognitive and neuromotor functioning in 7 children, survivors after posterior fossa tumours, presenting an extensive burden of neurologic, emotional, behavioral and mental impairments (Kanitz et al. 2013b). Eurythmy therapy and most of mind-body therapies are of low risk and are accessible for patients and their families in nearly all stages of cancer therapy. Positive results included increased self-confidence and a more optimistic view in coping with the illness (Kanitz et al. 2013a).

Preclinical research shows a therapeutic efficacy of VAE or its components *in vitro* or in animal models against the most common cell lines related to pediatric oncology (induction of apoptosis and inhibition of proliferation): neuroblastoma (Delebinsky et al. 2011b), medulloblastoma (Zusak et al. 2006), Ewing's Sarcoma (Dejewska et al. 2013), osteosarcoma (Kauczor et al. 2012, 2013) acute lymphoblastic leukemia (Delebinsky et al. 2011a, 2012a), acute myeloid leukemia (Delebinsky et al. 2013).

Finally, 75% of survivors have late-effects and this issue also represents an important topic in the strategy of further investigation with anthroposophic medicine and other CAMs. The number of survivors is high (over 300,000 in the US). Major long term effects in primary care are immune, neurocognitive, endocrine impairments and second malignancies. (Seehusen et al. 2010).

A suggestion concerning mistletoe administration to immunodepressed children comes from a group of studies performed in a peculiar condition: the studies described the efficacy of an anthroposophic VAE against immune impairment and recurrent infections in children of areas exposed to the radioactive fallout from Chernobyl. Exposed children were known to suffer from an immune and neuroendocrine deficiency, leading to recurrent infections and probably contributing to the rising incidence of malignancies in the same area. Observations were made in an uncontrolled prospective study on 30 children, aged 8-15 years, treated with Iscador® M (Chernyshov et al. 1997), in a placebo controlled crossover trial, in 56 children, 7-14 years, treated with Iscador® M/P (Loukyanova et al. 1998) and in a later evaluation of 92 children, aged 5-14 years (Chernyshov et al. 2000). VAE at low dose were effective in reducing infection rates, ameliorating general well-being and improving immune parameters (Chernyshov et al. 1997, 2000; Loukyanova et al. 1998). Infection rates one year after the treatment were reduced by 78-73% (Chernyshov et al. 2000).

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## Chapter 6

### CAM and quality of life of cancer patients

#### Quality of life and acupuncture/TCM

Many clinical studies have analyzed the efficacy of acupuncture in reducing cancer symptoms and simultaneously improving the quality of life (QoL) of cancer patients. Only 2 RCTs indicate as research aims, the evaluation of the action of acupuncture in improving the QoL of patients, while most of the other RCTs indicate the QoL among the criteria used for the evaluation of results.

In a small single-blinded RCT, Cho JH et al. (2008) investigated the effects of manual acupuncture to improve the QoL in head and neck cancer patients with radiation-induced xerostomia. Twelve patients were randomized into 2 groups (real or sham acupuncture). Acupuncture was conducted twice weekly for 6 weeks in a single-blind setting. The results were evaluated by measuring whole salivary flow rates (stimulated and unstimulated) and a questionnaire-based on QoL pre- and post-treatment (3 and 6 weeks after acupuncture treatment). The data demonstrated that acupuncture markedly increases unstimulated salivary flow rates, improves the score for dry mouth (by 2.33 to 0.33) and significantly ameliorates the subjective sensation of xerostomia closely associated with QoL in patients with head and neck cancer.

Hervik J and Mjåland O (2010) analysed the QoL of breast cancer patients medicated with estrogen antagonists, 2 years after the acupuncture treatment for hot flashes. A total of 82 women (41 women from the true acupuncture treatment group and 41 women from the sham acupuncture control group; mean age 51.3), who had 2 years previously received a course of 15 acupuncture treatments over a period of 10 weeks, were asked to answer an open question about their breast cancer diagnosis and treatments. According to the data, most women (more than 50%) were troubled by two or more side effects due to anti-estrogen medication, negatively affecting their life quality. Symptoms included hot flashes, sleep problems, muscle and joint pain, arm oedema, fatigue, weight gain, depression, and lack of sexual desire. Women previously treated with sham acupuncture complained that hot flashes were still problematic, while those previously treated with traditional Chinese acupuncture found them less of a problem and generally had a more positive outlook on life.

Similarly, Frisk J et al. (2012) evaluated the effects of electro-acupuncture (EA) and hormone therapy (HT) on health-related quality of life (HRQoL) and sleep in breast cancer survivors with vasomotor symptoms. In this RCT, 45 patients were randomized in the EA group (n=27) for 12 weeks or in the HT group (n=18) for 24 months. Distress caused by hot flashes, hours slept and times woken up/night, Psychological and General Well-being Index (PGWB) and Women's Health Questionnaire (WHQ) were registered before and during treatment and at 6, 9, 12, 18 and 24 months after starting the treatment. Results indicate that both EA and HT groups increased HRQoL and sleep, probably through decreasing numbers of and distress by hot flashes. The data show that after 12 weeks in EA group (n=19), WHQ improved from 0.32 at baseline to 0.24 ( $p < 0.001$ ) and PGWB from 78 to 79 ( $p = 0.002$ ). All sleep parameters improved and Hot Flash Score (HFS) decreased by 80%. At 12 months, WHQ, PGWB and all sleep parameters remained significantly improved (n=14) and HFS decreased by 65%. After 12 weeks of treatment in HT group (n=18), WHQ improved from 0.29 at baseline to 0.15 ( $p = 0.001$ ), PGWB from 75 to 90 ( $p = 0.102$ ) and 3 of 5 sleep parameters improved.

Moreover, in a pragmatic, randomized controlled trial aimed at evaluating the effectiveness of acupuncture for cancer-related fatigue (CRF) in patients with breast cancer, Molassiotis A et al. (2012) have assigned 75 patients to usual care and 227 patients to acupuncture plus usual care (random assignment of 1:3 respectively) with minimization controlling for baseline general fatigue and maintenance treatment. Treatment was effected by acupuncturists once a week for 6 weeks through 3 pairs of acupoints and a secondary outcome of QoL was measured with Hospital Anxiety and Depression Scale, Functional Assessment of Cancer Therapy-General quality-of-life scale, and expectation of acupuncture effect. The data show that acupuncture effectively improves the QoL, reducing CRF and improving Physical Fatigue and Mental Fatigue ( $p < .001$ ), anxiety and depression ( $p < .001$ ), and quality of life (Physical Well-Being effect, 3.30; Functional Well-Being effect, 3.57; both at  $P < .001$ ; Emotional Well-Being effect, 1.93;  $P = .001$ ; and Social Functioning Well-Being effect, 1.05;  $p < .05$ ).

Mao et al. (2012) conducted open-ended, semi-structured interviews with 25 women in stage I–III of breast cancer who had finished primary cancer treatments (surgery, chemotherapy, radiation) and were currently

experiencing daily hot flashes. The interview was developed using the Theory of Planned Behaviour (TPB) model already applied in numerous research settings in order to understand the decisions about specific health behaviours such as CAM research. This study was among the first to explore demographic differences in treatment decisions related to hot flashes by breast cancer survivors. African Americans appear to be much more willing to accept the empirical evidence from historical use as a rationale for their willingness to try acupuncture. While all African American and most Caucasian patients endorsed acupuncture as a natural alternative, they arrived at this idea from different paths. The results show that perceptions about the attributes of acupuncture are likely to vary according to racial group and symptom burden. These data play a critical role in decision support for cancer survivors, in assisting patients to choose therapeutic options that are acceptable and lead to symptom reduction and better quality of life.

In the same group of breast cancer patients, after integration of acupuncture to conventional treatment, even other authors identified improvement in the QoL. In particular, Walker EM et al. (2010) identified an improvement in QoL testing using acupuncture to reduce vasomotor symptoms and produce lower adverse effects than venlafaxine.

Crew KD et al. (2007) showed how acupuncture reduced aromatase inhibitors-related joint symptoms and improved functional ability. The 21 women enrolled in the RCT reported a significant improvement in the QoL ( $p=0.04$ ) in addition to a reduction of pain.

As well, when acupuncture is applied in the treatment of xerostomia, a significant improvement in QoL was found. In addition to the study already described of Cho JH et al., we recall the RCTs of Meng Z et al. (2012 –b), Wong RK et al. (2012), and Simcock R et al. (2013). Meng Z et al., in 2 RTCs with low number of patients, showed how acupuncture, integrated in nasopharyngeal cancer treatment to prevent xerostomia, improves the QoL of head and neck patients undergoing radiotherapy. The patients in the studies were randomized in 2 groups (acupuncture group versus sham group) and treated 3 times/week during radiotherapy. The QoL was measured using MD Anderson Symptom Inventory for Head and Neck Cancer (MDASI-HN) that measures, on a 0–10 numeric rating scale, both the severity of symptoms and interference with patients' daily activities. The data show that the acupuncture was statistically significant in improving the MDASI-HN scores in week 1–11 for general cancer Symptom Severity, Interference, and the Head/Neck subscales, and there was a significant main effect of time ( $p<0.001$  for all 3 subscales).

Wong RK et al. (2012), in a phase 2/3 randomized trial, analyzed the efficacy of acupuncture-like transcutaneous electrical nerve stimulation (ALTENS) in reducing radiation-induced xerostomia. The results obtained from the treatment of 47 patients were evaluated for a secondary outcome using University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS). Six-month XeQOLS scores were available for only 35 patients and indicated that 30 of them (86%) improved QoL with a mean  $\pm$  standard deviation reduction of  $35.9\% \pm 36.1\%$ . Five patients developed grade 1 or 2 gastrointestinal toxicity, and 1 had a grade 1 pain event.

Moreover, in a randomised crossover clinical trial of Simcock R et al. (2013), 145 patients with chronic radiation-induced xerostomia were enrolled to receive 2 group sessions of oral care education and 8 of acupuncture with standardised methods. The primary outcome and the QoL were evaluated by the patient-reported outcome (PROs) measures at baseline and weeks 5, 9, 13, 17, and 21. The statistically significant data show that the 8 sessions of weekly group acupuncture compared with group oral care education provide significant reductions in dry mouth, sticky saliva, needing to sip fluids to swallow food, and in waking up at night to drink (respectively  $p = 0.031$ ,  $p = 0.048$ ,  $p = 0.011$ , and  $p = 0.013$ ).

Lu W. et al. (2012), in a randomized, sham-controlled trial, analyzed as secondary outcomes, the positive impact on the QoL of acupuncture in 42 head and neck cancer patients with dysphagia. The patients receiving platinum-based CRT were randomised in 12 sessions of active acupuncture or sham acupuncture. The outcomes were assessed at baseline, 20 weeks post-CRT (end of acupuncture), and 12 months after baseline (6-month follow-up) with a multidimensional quality of life instrument specifically designed for cancer patients (Functional Assessment of Cancer Therapy-Head and Neck Scale. FACT-H&N). The data provide preliminary evidence regarding the value of acupuncture for dysphagia treatment in improving the QoL of head and neck cancer patients.

More generally, Feng Y et al. (2010) studied the effect of acupuncture on depression and insomnia in malignant tumor patients. Eighty patients with cancer related depression and sleep disorders were randomized into 2 groups (acupuncture group  $n=40$  and Fluoxetine group  $n = 40$ ), and all patients were assessed by Self-rating Depression Scale (SDS), Hamilton Depression Rating Scale (HAMD) and Pittsburgh Sleep Quality Index (PSQI) after treatment for 30 days. The data showed a statistical significant

decrease of SDS (from 64.12 +/- 5.34 to 43.64 +/- 5.28) and HAMD score (from 20.92 +/- 2.38 to 9.88 +/- 1.27) compared to the control group, and a consequent improvement in the QoL.

Recently, Bao T et al. (2013) conducted a RCT to evaluate the efficacy of magnetic acupressure in reducing pain in cancer patients undergoing bone marrow aspiration and biopsy (BMAB). Seventy-seven cancer patients without previous acupuncture or acupressure experience were stratified by the number of prior BMAB and randomized to having magnetic acupressure delivered to the LI4 acupoint or a sham site. Though there was no significant difference between the median pain scores of patients treated at the LI4 site and the sham site ( $P=0.87$ ), the data show a QoL improvement in the LI4 group considering that the severe pain ( $VAS \geq 7$ ) was reported in only one patient (2.7%) treated at the LI4 site compared with 8 patients (20%) at the sham site ( $p=0.03$ ).

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## Quality of life and herbal medicine

Palliative care is largely used to improve quality of life and reduce psychological distress in cancer patients, and also herbal medicines are similarly used for this purpose.

In addition to the herbal remedies dealt with in symptoms paragraphs and summarized in Table 1, in this chapter the action of aromatherapy massage on quality of life of cancer patients is analysed.

The beneficial effects of massages with essential oils (EO) in cancer care have been studied for many years and here the researches from 2003 until today are reported.

Soden K. et al. (2004) studied the effect of massages with essential oils in a hospice setting. Forty-two patients were randomly allocated to receive weekly massages with lavender essential oil and inert carrier oil, inert carrier oil only or no intervention. During the treatment the following scales were used: Visual Analogue Scale (VAS) of pain intensity, the Verran and Snyder-Halpern (VSH) sleep scale, the Hospital Anxiety and Depression (HAD) scale and the Rotterdam Symptom Checklist (RSCL). The data show that aromatherapy massages can statistically improve sleep scores in both the massage and the combined massage (aromatherapy and massage) groups and reduce the depression scores in the massage group with a better response to therapies (Soden K. 2004).

Similarly but with inconsistent results, Wilcock A. et al. (2004), conducted a randomised controlled pilot study to examine the effects of adjunctive aromatherapy massage on mood, quality of life and physical symptoms in patients with cancer attending a specialist unit. Forty-six patients were randomized to conventional day care alone or day care plus weekly aromatherapy massage using a standardised blend of oils for 4 weeks. The authors did not identify any statistically significant difference between groups; that could be explained by the large number of withdrawals, 48% in the aromatherapy group and 78% in the control group.

In the same year a Cochrane Systematic Review investigated whether aromatherapy and/or massage decreases psychological morbidity, lessens symptom distress and/or improves the quality of life in patients with a diagnosis of cancer. The search strategy retrieved 1,322 references. Ten reports met the inclusion criteria, 8 RCTs including 357 patients. The most consistent effect of massage or aromatherapy massage seems to be on anxiety. Four trials (207 patients) measuring anxiety detected a reduction post intervention, with benefits of 19-32% reported. Other papers analysed symptoms such as depression, fatigue, anger, hostility, communication and digestive problems but further evidence need to be produced in order to evaluate the action. Aromatherapy massage seems to confer short term benefits on psychological wellbeing (Fellowes D. 2004).

A systematic review (Wilkinson S. 2008) evaluated the effectiveness of massage for patients with cancer in reducing physical or psychological symptoms, improving quality of life, or producing unwanted side effects. Ten trials were selected among 1,325 papers; the data confirm that massage might reduce anxiety in patients with cancer in the short term. Moreover, aromatherapy massage may have a beneficial effect on physical symptoms of cancer, such as pain and nausea.

An interesting RTC (Wilkinson SM. 2007) quantified the period of aromatherapy massage action. Two hundred eighty-eight cancer patients, referred to complementary therapy services with clinical anxiety and/or depression, were randomised to a course of aromatherapy massage or usual supportive care alone.

The results show that aromatherapy massage group had no significant improvement in clinical anxiety and/or depression compared with control at 10 weeks post randomization, but did at 6 weeks post-randomization ( $p = .01$ ).

Stringer J. et al. (2008) evaluated whether single massage sessions (20 min.) were safe and effective in reducing stress levels of isolated hematological oncology patients through measures of both cortisol, prolactin plasma levels, and quality of life interviews. The results show a significant difference between the arms in cortisol ( $p=0.002$ ) and prolactin ( $p=0.031$ ) levels from baseline to 30 min post-session, as well as a significant improvement in the quality of life.

Finally, Lai TK et al. (2011) showed that aromatherapy massage significantly improves the quality of life in physical of advanced cancer patients with constipation. In this RCT, the degree of constipation was statistically measured using a constipation assessment scale, severity level of constipation and the frequency of bowel movements. The conclusions suggest that aromatherapy massage can help to relieve constipation in patients with advanced cancer.

The difficulty in evaluating the effectiveness of this type of massage also depends on the heterogeneity of essential oils used as well as on the intrinsic variability of a single type of essential oil.

<b>Symptoms / Paragraphs</b>	<b>Herbal medicine and Quality of Life</b>	<b>Author, year</b>
Constipation (§)	Aromatherapy massage	Lai TK, 2011
Insomnia (*)	<i>Valeriana officinalis</i>	Morin CM, 2005
Mucositis (*)	<i>Aloe vera</i>	Su CK, 2004
Nausea and vomiting (*)	<i>Cannabis sativa (THC)</i>	CICSG, 2006 Johnson JR, 2010
Pain (*)	<i>Cannabis sativa</i>	Johnson JR., 2010 Portenoy RK, 2012

Herbal medicines studied to ameliorate the quality of life in cancer patients. (\*) For the grading, doses and detailed information, refer to the relevant paragraph. (§) For detailed information see the text.

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## Quality of life and homeopathy

In 2009 Frass et al. selected 90 patients with breast (35), colorectal (10), renal (7), cerebral (7), and pancreatic (6) cancer; sarcoma (5), bronchial (4) cancer, lymphoma (4), pharyngeal (3) cancer and others (9). The patients underwent an elaborate medical history including questions relating to social and private circumstances. Symptoms given by patients were correlated with the signs of homeopathic evaluation of remedies as recorded in repertories (Zandvoort, Complete Repertory; MacRepertory®).

Patients were requested to complete visual analogue scales as well as a specially developed form evaluating subjective existential orientation and, finally, EORTC QLQ-C30 form version 3.0. With respect to the latter, the mean QoL improved by 0.31 points ( $4.33 \pm 1.54$  before vs.  $4.64 \pm 1.59$  after additive homeopathic therapy;  $p=0.008$ , Student's-*t*-test for paired data) between first and last registered consultation which were distanced by a mean of 24 weeks. Similar results were found for the specially developed form: the visual analogue scale showed a difference of 0.71 ( $5.60 \pm 2.06$  before vs.  $6.31 \pm 2.3$  at the third consultation,  $p=0.043$ ; corresponding to an improvement of 16.1% in a 10 part-series), and a difference of 0.59 ( $5.56 \pm 2.15$  vs.  $6.15 \pm 2.31$ ,  $p=0.007$ ; 13.3% improvement in a 10 part-series) between the first and last consultation.

Following the fourth consultation, analysis in 45 participants revealed that 80% ( $n=36$ ) felt an improvement of the general condition, while 20% ( $n=9$ ) experienced no effect. In total 24.4% ( $n=11$ ) felt the improvement mainly physically; 51.1% ( $n=23$ ) physically as well as psychologically; 2.2% ( $n=1$ ) only psychologically; the remaining one patient did not comment. Improvement was ascribed to a combination of homeopathy and conventional therapy by 23/36 (63.9%) of the improved patients; 10 (27.8%) ascribed improvement to homeopathic treatment only, 1 patient (2.8%) to oncologic therapy only, 1 to the season, 1 patient remained without comment. All patients were interested in continuing homeopathic treatment.

In a study by Thompson EA et al. (2003) conducted on 45 women with breast cancer, 40 had a significant improvement in symptoms of anxiety and depression ( $p < 0.001$ ) and more generally in the quality of life.

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## Quality of life and anthroposophic medicine

Quality of life during conventional treatment, in the follow up and in long-term survivors is a major issue in anthroposophic medicine, as well as in other CAM approaches. What contributes a clinically significant change or difference in perceived quality of life has objective aspects, but keeps being highly individual. Common targets for quality of life are disease-related symptoms and side effects of conventional treatments. Furthermore, quality of life for anthroposophic medicine is strongly connected with the motives of salutogenesis, coping, resilience, with spiritual issues and self development. Anthroposophic medicine interventions for patients with cancer aim to design a tailored multimodal treatment, inspired by a broader whole-person concept of quality of life, and anamnesis and consultations include specific questions and deepenings.

Most of the studies conducted on the anthroposophic medicine whole system or mistletoe therapy alone or non pharmacological interventions include measures of quality of life and described positive effects. Measurements were made with the usual instruments for quality of life and health-related quality of life (KI, EORTC QLQ-C30, Spitzer's test, SF-36, POQOL, and other disease-or age-specific questionnaires etc.) or with validated inventories applied to clinical practice, that have been adapted or developed in the anthroposophic medicine context, wishing to include in the evaluation some anthroposophic medicine perspectives (SRQ Self-Regulation Scale, HLQ Herdecke Quality of Life questionnaire, ICS Internal Coherence Scale, SNQ Spiritual Needs Questionnaire etc.). (Grossarth-Maticek et al. 2001; Grossarth-Maticek 2002; Kröz et al. 2008, 2009, 2011, Büssing et al. 2009, 2010). The most relevant benefits seen in clinical trials (anthroposophic medicine whole system, mistletoe therapy, art therapy, eurythmy therapy and other NPIS) concern an improvement in the positive issues of appetite/weight, vitality, energy, coping, emotional and functional well-being, ability to work, and a reduction of the burden of fatigue, exhaustion, nausea/vomiting, anxiety and depression. Hope is itself a variable that positively contributes to the experience of quality of life (Rustøen 1995). Hopelessness negatively affects cancer patients' quality of life, and hope and quality of life questions are among the reasons that patients cite for using CAM therapy (Gross et al. 2013). The added and more active and subject-related possibilities of treatment offered by anthroposophic medicine and other CAMs contribute to hope in cancer patients and in their care-givers.

In the published works, anthroposophic medicine showed to be beneficial in reducing disease related symptoms and side effects of conventional treatment. Improvement of cancer related weight loss and in fatigue are relevant examples, as well as better coping with chemotherapy regimens for various cancers. In the course of disease and in survivors, use of anthroposophic medicine has also been associated with improvement in self regulation. Mistletoe therapy, medications and NPIs alone, as well as anthroposophic medicine whole system can improve QOL in patients with cancer.

### *Disease related symptoms and side effects of conventional treatment*

A systematic review of controlled clinical studies was conducted by Kienle et al. (2010) on the efficacy and effectiveness of *Viscum album L. extracts* (VAE) regarding quality of life in cancer patients. VAEs seemed to have an impact on QOL and the reduction of the side effects of conventional therapies (chemotherapy, radiation) in experimental trials as well as in routine daily application. 26 randomized controlled trials (RCTs, total 3058 patients) and 10 non-RCTs (total 4996 patients) that investigated the influence of VAEs on QOL in malignant diseases were identified, with varying degrees of methodological quality. The cancer sites were breast, ovary, endometrium, cervical, gastrointestinal, colorectal, pancreas, lung, head and neck, melanoma, glioma, osteosarcoma. 26 studies included assessment of patient-reported QOL. Half of the studies investigated VAEs concomitant with chemotherapy, radiotherapy, or surgery. 22 of the 26 RCTs and all the non-RCTs reported a benefit in QOL. In 3 RCTs no difference was observed.

Of the studies with higher methodological quality, most reported a benefit. Major improvements were observed in regard to coping, fatigue, sleep, exhaustion, energy, nausea, vomiting, appetite, depression, anxiety, ability to work, and emotional and functional well-being in general. Data for pain and diarrhea varied in the different studies.

Evidence of a benefit on QOL had been already stated in a Cochrane review dedicated to mistletoe therapy in oncology in 2008. Fourteen of the considered 16 studies investigated the efficacy of mistletoe extracts for either improving QOL, psychological measures, performance index, symptom scales or the reduction of adverse effects of chemotherapy (Horneber et al. 2008).

A relevant example of improvement of QOL with VAE versus best supportive care alone is given in a recent RCT conducted by Tröger et al. (2013) on patients with locally advanced or metastatic pancreatic cancer.

The improvement in QOL parameters in the VAE arm was significant. The frequency and severity of post-baseline disease-related symptoms was significantly lower for pain, weight loss, loss of energy, nausea/emesis ( $p < 0.0001$  for all parameters), diarrhea ( $p = 0.0033$ ) and anxiety ( $p = 0.046$ ). Especially weight loss is an important parameter related to QOL and prognosis in patients with pancreas cancer and other cancers. Weight decreased as expected in control patients, but increased in mistletoe-treated patients.

Fatigue is another important parameter for QOL during the conventional treatments and up to long term. A relevant efficacy of VAE on fatigue has been described by Wode et al. (2009). Some RCTs and retrolective studies on VAE in cancer and studies on the anthroposophic medicine whole system assessed fatigue as a subscale of QOL with positive outcomes (Carlsson et al. 2001, 2004; Heusser et al. 2006; Wode et al. 2009). Better toleration of chemotherapy side effects has been described in several studies, in combination with different chemotherapy and for different tumor entities. Examples of the different aspects of benefits are taken from some recent pilot studies: improved QOL during chemotherapy, reduced neutropenia and/or other hematological parameters, minor chemotherapy dose reductions and less duration of hospitalisation.

A combination of VAE with CAF for early breast cancer was studied in prospective randomized open label pilot study with 95 patients for QOL (EORTC QLQ-C30), including fatigue, and neutropenia (neutrophils count  $< 1000/\mu\text{l}$ ). All 15 scores of the EORTC-QLQ-C30 showed better quality of life in the VAE-group compared to the control group, significant in 12 ( $p < 0,02$ ), and 9 scores showed a clinically relevant and significant difference of at least 5 points. Neutropenia occurred in 3/30 IMS patients and in 8/31 control patients ( $p = 0.182$ ). (Tröger et al. 2009).

The combination of VAE with chemotherapy (carboplatin-gemcitabine/pemetrexed) for advanced breast cancer in a randomised phase II study on 72 patients was reported. The EORTC QLQ-C30 results were not different in the 2 arms and differences in grade 3-4 haematological toxicity were not significant, but more control patients had chemotherapy dose reductions (44(X) versus 13%,  $p = 0.005$ ), grade 3-4 non-haematological toxicities (41% versus 16%,  $p = 0.043$ ) and hospitalisations (54% versus 24°/u,  $p = 0.016$ ). VAE in combination allowed a better performance of chemotherapy (Bar Sela et al. 2013).

A relevant stabilisation of Health Related Quality of Life (QLQ- C30 and QLQ-BR23) during various chemotherapy regimens for breast cancer and a significant improvement 4 weeks after the end ( $p < 0.0001$ ) has been described in patients treated with VAE (Eisenbraun e al. 2011).

Less adverse events form chemotherapy and less hospitalisation were also described in a retrolective study on 270 patients with pancreatic cancer. In the VAE arm the adjuvant therapy induced adverse events were significantly less than in the control arm: 8,3% vs. 43,7% ( $p < 0,001$ ) and the need for hospitalisation was lower (Matthes et al. 2010; Stauder et al. 2012). Similar results come from 3 other retrolective studies concerning breast cancer, melanoma and colorectal cancer (Augustin et al. 2005; Friedel et al. 2009; Bock et al. 2004).

### *Self regulation*

Adaptive characteristics such as sense of coherence or self-regulation could be more appropriate as a prognostic tool than classical HRQL (Kröz et al. 2011). Self regulation was defined as the “ability to actively achieve well-being, inner equilibrium, and a sense of being able to control stressful situations” and its regulation improvements have been associated with prognosis and with mistletoe therapy (Grossarth-Maticsek et al. 2001). A possible impact of self-regulation on survival has been observed in breast and colorectal cancer patients in a prospective outcome study on 146 cancer patients and 120 healthy subjects (Kröz et al. 2011). Improvement in self regulation is also related to the improvement of disease related symptoms, such as fatigue, and distress (Kröz et al. 2013).

### *The medical system of anthroposophic medicine*

Improvements in QOL have also been described in relationship to the anthroposophic medicine medical system as a whole, in out- and in-patients with different cancer entities, measuring EORTC QLQ-C30, HADS and SELT-M (Heusser et al. 2006), MAC, EORTC QLQ-C30, LSQ, (Carlsson et al. 2001-2005); CFS-D and PSQI (Kröz et al. 2013).

Anthroposophic medicine therapies, as therapies activating patients self-healing resources, have a role in the benefit obtained in QOL. Art therapy was found to improve depression and fatigue in cancer patients in chemotherapy (Bar Sela et al. 2007). The beneficial effect of eurythmy therapy on stress coping strategies, health-related quality of life and heart rate variability has been to date observed in healthy, moderately stressed adults and in patients with fatigue (Kanitz et al. 2011; Seifert et al. 2013). A 4 year prospective cohort study described improved outcome with eurythmy therapy in chronic diseases, including patients

with cancer (Hamre et al. 2007). A regular practice of NPIs is also commonly used as self-development and as prevention of burn out for the health professionals in oncology.

Concluding, quality of life (QOL) is one of the major issues in cancer treatment together with survival and tumor response. It is seen by anthroposophic medicine as extended health-related quality of life along all the course of disease, conventional treatments, recovery and long-term follow up, and contributes to opening a broad view, that includes the dimensions of body, soul-spirit, biography and social life. The salutogenetic concept and self regulation are central in defining the treatment offers and influence choices directed to coping with conventional treatments in the initial, chronic and end-of life care, but also directed to obtaining a higher level of potential individual health in the follow up and in survivors. Perception of health-related quality of life is shared between patient and caregiver and influences the strategy of therapeutic interventions. On the individual level, this includes all health perceptions and their social correlates. Evaluation of QOL with common and anthroposophic inventories is therefore seen as an instrument not only for research, but also for the design and the effectiveness of the individual treatment in patients with cancer.

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## Chapter 7

### Conclusions

Many researches published in the literature show that patients with cancer very frequently use complementary medicines both to treat the cancer-related symptoms and to improve their quality of life.

So far, there is not enough evidence on the treatment of the cancer progression as the studies in this area are quantitatively limited and not always of good quality. However, in herbal medicine the research is trying to identify natural compounds which can interfere with the progression of the cancer itself; for instance, experimental protocols have introduced the use of *Curcuma longa* and *Camellia sinensis* respectively in the treatment of colon and prostate cancer.

In acupuncture and predominantly in Chinese herbal medicine, initial studies have been conducted on the increase of organism defences and also on the progression of the disease. However, the use of Chinese herbs has not been reported in this publication due to the problems already described in the introduction.

In homeopathy as well, interesting experiences have been conducted on cancer patients especially in India and Switzerland with promising therapeutic approaches. Finally, *Viscum album* formulations are diffusely used in anthroposophic medicine to improve the defences of the organism.

This trend of the research is progressively increasing the confidence in the possibility of creating an integrated therapy for cancer patients.

As to the use of acupuncture and TCM in the treatment of symptoms correlated to anti-cancer therapy, the literature has demonstrated a good level of evidence in the following cases: nausea and vomiting, pain, hot flashes and xerostomia, taking also in account the absence of relevant adverse effects and interactions.

The herbal medicines which can be used with a sufficient level of confidence and safety are: *Crocus sativus*, *Hypericum perforatum* and *Lavender* spp for the treatment of anxiety and depression; *Panax* spp, *Paullinia cupana* and *Rhodiola rosea* for CRF; *Boswellia serrata* in the case of perifocal edema in brain tumours; *Glycine max* to reduce the discomfort of hot flashes; *Aloe barbadensis* to alleviate the mucositis related to anti-cancer therapy; *Zingiber officinalis* to contrast nausea and vomiting after anti-cancer therapies and finally *Cannabis sativa* (THC) both to alleviate vomiting and cancer-related pain. It is however important to keep in mind that herbs can give rise to interactions and interferences with anti-cancer therapies as fully described in a specific paragraph of this publication.

Based on the literature, homeopathy and homotoxicology can be recommended in the treatment of hot flashes, radiodermatitis and mucositis, taking also in account the absence of relevant adverse effects and interactions.

The results of our work have shown that in some cases complementary medicines may be effective on cancer patients. As a consequence, it is the right of these patients to have information and access to these therapies.

It is also of primary importance that the medical staff taking care of cancer patients and mainly the oncologists, are correctly informed about the potential benefits of CAM improving in this way the relationships between conventional practitioners and CAM therapists.

It is crucial to remember that patients should be treated with a multidisciplinary approach always choosing the best treatment for each patient in the perspective of true comprehensive cancer care.