Indian herbs for the treatment of chemo- and radiotherapy Side-effects in cancer patients: a systematic review.

MSc in Ayurvedic Medicine

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Abstract:

Background: The incidence of cancer has gradually been increasing over the last decades. A considerable amount of patients has to go through distressing treatments like chemo- and radiotherapy. These treatments can produce very severe side effects like bone marrow depression with low peripheral count of erythrocytes, thrombocytes and neutrophiles, low appetite, weight loss, mucositis, fatigue, nausea, vomiting and diarrhoea. With conventional medical treatment it isn't always possible to prevent and treat chemo- and radiotherapy side effects sufficiently. Therefore the aim of this dissertation was to find evidence if ayurvedic herbal remedies might be a suitable and safe alternative and/or addition to conventional drugs.

Methods: I approached this question by doing a systematic literature review. Some of the major medical databases were searched for randomised controlled clinical trials, which investigated the use of ayurvedic herbal remedies in patients receiving chemo-and radiotherapy. Thirteen trials were included in the systematic review and were analysed by applying the Jadad's scale and the RCT appraisal guidelines from Oxford Centre of Evidence Based Medicine.

Results: A majority of high quality trials presented encouraging results about the successful use of ginger for prevention of chemotherapy induced nausea and vomiting. Another included trial, which was also of high quality showed that the use of amrit kalash can have beneficial effects when used during chemotherapy. Some trials, which investigated the used of garlic, Tinospora cordifolia, Brahma Rasayana and Rasayana Avaleha showed promising tendencies, but would need further large scale trials to confirm the results.

Conclusion: There seems to be extensive information available about some ayurvedic herbal remedies. Based on these information/trials, a more widespread use of these herbs can be justified.

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Working Title:

The title of my dissertation is: “Indian herbs for the treatment of chemo- and radiotherapy side effects in cancer patients: a systematic review”.

Introduction:

The incidence of cancer contributes considerably towards the global burden of disease (Kamangar *et al.*, 2006; Weir *et al*., 2003). Conventional treatments of cancer, like surgery, chemotherapy and radiotherapy as the most important ones lead to an improved survival rate of cancer patients in some European countries and the USA over the last years (Brenner, 2002; Verdecchia *et al*., 2007). But chemotherapy and radiotherapy can cause considerable side effects like diarrhoea (Griffin et al., 1996), nausea and vomiting (Schwartzberg, 2006; Partridge *et al.,* 2001; Molassiotis *et al*., 2008), mucositis (Partridge *et al*., 2001; Duncan *et al*., 2003; Raber *et al*., 2010), low appetite (Griffin et al., 1996) , weight loss (Griffin et al., 1996), fatigue (Ahlberg *et al*., 2003, Partridge *et al.,* 2001) and bone marrow depression (Partridge *et al*., 2001; Gill *et al*., 2010) with anaemia (Gill *et al*., 2010), thrombocytopenia (Gill *et al*., 2010) and neutropenia (Crawford *et al*., 2003; Gill *et al*., 2010; Lyman *et al*., 2005). Bone marrow depression can have further severe consequences like infections (Gill *et al*., 2010), septicaemia, sepsis and/or severe bleeding (Gill *et al*., 2010).
Considering that cancer is very common in Europe and USA and therefore its treatments are frequently used, a considerable number of patients will need to go through very stressful treatments with above mentioned side effects. These side effects can reduce quality of life and survival (Montazeri, 2009) .
With conventional treatment it isn’t always possible to offer sufficient relief for chemotherapy and radiotherapy side effects. This might be the reason why quite a few cancer patients are looking for help in the complementary health sector (Richardson et al., 2000; Cassileth et al., 1984). Diverse studies show a varying percentage of cancer patients using complementary medicine. Numbers varied depending on the area where the studies were performed, type of cancer, education level and wealth (Lerner et al., 1992).
In this dissertation, the aim is to find out if there is enough evidence to suggest that supportive treatment with ayurvedic herbal remedies during chemotherapy and radiotherapy can prevent or reduce side effects like nausea, vomiting, diarrhoea, low appetite, weight loss, fatigue, mucositis and bone marrow depression and in that way improve quality of life. I will also have a good look at

unwanted adverse events, which could possibly occur during the treatment with herbal remedies. I will approach the subject by doing a systematic literature review.

Ayurvedic background:

Cancer has already been mentioned in the ancient ayurvedic literature. In 800 BC Charaka Samitha mentioned different types of gulma/ abdominal swellings (Sharma *et al.,* 2009, Nidanasthana, chapter III, verses 10,11, Sutrasthana, chapter XVIII, verses 19-36). In Charaka Samhita there is a specific description of a kaphaja type of gulma and associated symptoms: "fever associated with feelings of cold, prostration, anorexia, nausea, cough, heaviness, affected part of body is hard to touch, is also elevated, has less pain and is cold to touch" (Sharma et al. 2009). In this description it is very likely that a malignant abdominal tumor has been described. Furthermore the term arbuda (malignant) tumor has been shortly mentioned in Charaka samhita in the chapter about different types of swellings.
In 550-600 AD Vagbhata mentioned granthis/ benign tumors and arbudas/ malignant tumors (Murthy, 2008, Uttara sthana, chapter XXX, subchapter granthi, verses 1-7 and subchapter arbudas, verses 1-3).
In 800 AD arbuda has again been mentioned in Madhava Nidanam (Murthy, 2005). In this scripture malignant tumors are described invading muscles and blood, that some types of arbudas can produce anaemia and that a second arbuda developing concurrently with the first one being incurable (Murthy, 2005, Chapter 38, verses 18-26).
In Ayurveda, tumors in general are distinguished depending on their clinical features (Sharma et al., 2009). Depending on the clinical features the tumors are put in different groups, which consequently get a different treatment (Sharma et al.,2009, Chikitsasthana, chapter V). For example a tumor which is painless or only provokes mild pain, is stony, large in size and grows slowly (mamsaja arbuda) would be treated differently than a tumor which presents as elevated fleshy growth, is discharging blood and grows rapidly (raktaja arbuda).
As we can see, cancer treatments practised in ayurvedic medicine have been quite different than nowadays cancer treatments. Chemotherapy and Radiotherapy didn't exist and therefore the side effects provoked by these treatments have been unknown. Using ayurvedic herbal remedies to treat these side effects is a new approach, which is an attempt to help those patients whose side effects can't be sufficiently prevented or treated by modern medicine. Quite a few trials have been published about how ayurvedic herbal remedies can be used to treat radiotherapy and

chemotherapy side effects. During the course of this dissertation we will look into these trials in more detail.

Methods:

Inclusion and Exclusion Criteria:

All randomised controlled clinical trials (RCT), which compared the effects and/or adverse effects of conventional cancer treatment (chemotherapy, radiotherapy and surgery) with conventional cancer treatment plus ayurvedic medicine were included into the systematic review.
Eligible studies investigated patients with histologically confirmed cancer. Any type of cancer, treated with either one or the combination of the following treatments was included in the review: chemotherapy, radiotherapy and surgery. One reason not to make a tighter selection regarding types of cancer and cancer treatments is that a relatively low amount of research has been done in ayurvedic medicine and that I didn't expect to find a large amount of studies. Additionally this systematic review is looking into the improvement of treatment side effects and quality of life and not into a cure of a specific type of cancer
Regarding the medicinal preparations, trials, which used whole herbs in form of powders, capsules, pastes, decoctions and infusions and which are described in ayurvedic literature, have been included (Pole, 2006, Part I, chapter III). Also trials where herbal extracts have been used, have been included in the review. A herbal extract is a more modern type of herbal preparation, which allows to standardise and if necessary potentiate the ingredients of a plant, whilst at the same time the qualities of the whole herb can be preserved (Tierra, 1999).
Studies, where single molecules from plants have been tested, have been excluded, because this wouldn't be at all compatible with the principles of ayurvedic medicine: In Ayurveda the beneficial effects of a plant are considered to be caused by taste/rasa, twenty qualities/gunas (heavy, lighty, oily, dry, soft, hard, clear, sticky etc), postdigestive taste/vipaka and potency/veerya (Gogte, 2000, chapters IV-VII). Therefore, if just single molecules would be extracted from a plant all these qualities would be lost.
Only studies which investigated preparations for oral intake where included in the review. Preparations for topical, intravenous and subcutaneous application haven't been included.

The species of herbs with accepted use in ayurvedic medicine are documented accordingly in the old reference books like Charaka Samhita (Sharma *et al*., 2009), Sushruta Samhita (Bhishagratna, 2006) and Astanga Hrdayam (Murthy, 2008). My decision which herbs can be qualified as "ayurvedic" herbs, was based on these scriptures. Only RCTs, which used these "ayurvedic" herbs were included in the review.

At this point I also need to mention that herbs used in ayurvedic medicine, which originated from India can grow in other parts of the asian continent as well, for example in Thailand, Vietnam and Sri Lanka because the climate is very similar. In that way "ayurvedic" herbs have become part of other traditional medicine forms like the traditional Thai medicine. But the herb will still have similar effects even if used in a slightly different setting because the basic biochemical qualities will stay the same. Based on these thoughts "ayurvedic" herbs, which have been used in clinical studies in countries other than India and in different medical systems have also been included in the review, as long as they have been used in a "ayurvedic" preparation form (as juice, as paste, powdered/in capsules, as decocotion, as infusion, as a jam or as an extract).

Some of the herbs, which already have been used centuries ago and which are also mentioned in the old ayurvedic scriptures are cannabis and opium (Gogte, 2000). These herbs have been used to ease pain and discomfort in severely ill patients (Gogte, 2000). Opium is used as Morphin nowadays and is a restricted drug with high potential of addiction; the same applies to Cannabis (Controlled drugs list UK, 2010). Therefore studies, which investigated Cannabis and Opium to treat adverse effects of cancer treatment haven't been included.

Qualitative studies, in vitro studies and in vivo studies with animals (mice, rodents etc) have also been excluded from the systematic review.

Search strategy:

To get as many articles as possible about the investigated topic, Cochrane database was consulted for guidelines. For my search in the medical databases, I used MeSH (medical substance headings) terms, which I searched in title, abstract and text of the articles with no limitation to just one of the areas. To use the correct MeSH terms I consulted the suggestion of the Cochrane Complementary and Alternative Medicine Field (Manheimer *et al*., 2008), the Cochrane Colorectal Cancer Group (Anderson, 2010) , the Cochrane Gynaecological Cancer Group (Morrisson *et al*., 2011), The Cochrane Breast Cancer Group (Wilcken *et al*.,2009) The Cochrane Prostatic disease and Urologic

Cancer Group (Wilt et al., 2008) and The Cochrane Lung Cancer Group (Tort *et al*., 2010) . Additionally the "search tips" for advanced search from the Cochrane review website were used as well.

Referring to these guidelines I deducted an advanced search strategy specifically for my topic. I searched the databases MEDLINE, PUBMED, AMED and CINAHL, which are the major databases to search for articles in the field of medicine and alternative/complementary medicine, with the following search combinations: (cancer treatment and side effects) AND (herbs or plants, medicinal); (cancer treatment and side effects) AND (herbs or plant remedies); (neoplasm treatment and side effects) AND (herbs or plants, medicinal); (cancer treatment and side effects) AND (plant extracts); Medicine, Ayurvedic; (Quality of life) AND Medicine, Ayurvedic. Ayurvedic Medicine and Chemotherapy side effects. Ayurvedic Medicine and Radiotherapy side effects.

For other simple search terms with no need of a complicated advanced search strategy I used the summon function on the Middlesex University website, which is searching all of the library catalogue and the library resources in one go. Amongst others, the library resources include the databases AMED, CINAHL, Cochrane, MEDLINE and PUBMED. For the search of summon only journal articles were included. And from the beginning those articles which involved advertising, marketing, marketing research, trade, industry, product planning and development, food science and technology, agronomy, horticulture, ethnobotany animal studies (rodents, rats, mice) and in vitro studies were not included in the search.

Summon was searched for the following most commonly used herbs and herb combinations used in ayurvedic medicine :

Aloe vera, Zingiber officinale, Curcuma longa, Allium sativum, Tinospora cordifolia, Emblica officinalis, Asparagus racemosus, Withania somnifera, Terminalia arjuna, Sida cordifolia, Eclipta alba, Bacopa monnieri, Eletaria cardamonum, Ricinus communis, Cinnamomum zeylanicum, Syzygium aromaticum, Coriandrum sativum, Cuminum cyminum, Foeniculum vulgare, Tribulus terrestris, Commiphora mukkul, Ferula asafoetida, Saussurea lappa, Picrorrhiza kurroa, Citrus lemon, Glycyrrhiza glabra, Semecarpus anacardium, Mentha piperita, Brassica nigra, Azadirachta indica, Piper nigrum, Piper longum, Punica granatum, Senna augustifolia, Trigonella fenu graecum, Sesamum indicum, Ocimum sanctum, Triphala and Chyavanaprash.

Additionally summon was searched for the MeSH terms: cancer, tumor, neoplasma, neutropenia, chemotherapy side effects and radiotherapy side effects.

During the search in summon some herbs and herb preparations turned out to be frequently discussed in cancer studies. These herbs where then searched in the Indian Medicine Database in the hope of finding some additional journal articles: Asparagus racemosus, Tinospora cordifolia,

Withannia somnifera, Zingiber officinale, Aloe vera, Punica granatum, Emblica officinalis, Piper longum, Ocimum sanctum Triphala and Chyavanaprash.
Also The Indian Medicine database was searched for the MeSH terms: cancer, tumor, neoplasma, neutropenia, chemotherapy side effects and radiotherapy side effects.
In all the searched databases no limitation was put on the year of publication and the language in which the articles have been published. The reason for that was that I was expecting to find only a limited number of articles due to the comparatively low amount of research done in ayurvedic medicine.

Data Analysis:

The methodological quality of the included trials was assessed by Jadad's scale (Jadad *et al*., 1996; + Appendix 3), which assesses randomisation, double blinding and dropout rate of the trials by ranking them with 1-5 points. The Jadad scale was developed by Dr. Jadad together with his team at Oxford University as a tool to assess the quality of RCTs. It suggests that a low number of points indicate a low quality RCT, whereas a high number of points indicate a high quality trial. The article in which the Jadad scale is described gives no cut off above which a trial can be considered to be a high quality trial. Looking at the guidelines given by the Jadad scale, 1-2 points seem to be like a minimum requirement for a RCT. To get 1-2 points a RCT needs to be described to be randomised and double blinded. To get 2 more points the method of randomisation and double blinding need to be described and need to be appropriate. 1 more point is given if number and reason for drop outs has been stated. If there is no statement about drop outs this item has to be awarded with zero points even if there were no drop outs from the trial.
Refering to the assessment guidelines given by the Jadad's scale I considered trials that scored 1-2 points as low quality and trials that scored 3-5 as high quality trials.
In addition to the Jadad's scale I used the Critical Appraisal sheet for RCT from the Centre of Evidence Based Medicine at Oxford University (Center for Evidence Based Medicine, 2005, www.cebm.net + Appendix 4). This appraisal sheet suggests different points, which mostly can be answered with yes, no or unclear and need to be looked at to make a judgement about the internal validity of a trial: randomisation, similarity of the groups at the start of the trial, equal treatment of the groups, drop outs, double blinding and measurement of the treatment effects. For measurement of the treatment effect, it has to be judged how large the treatment effect is. This should be expressed by way of relative risk, absolute risk reduction, relative risk reduction or number needed to treat. And second a judgement about how precise the treatment effect is should

be made by way of confidence intervals and statistical significance. For getting information about the treatment effects, we have to rely on the statistical analysis of the trial results, which is mostly documented in the results section. Unfortunately in some RCTs there is no standardised statistical analysis and a proper judgement about the treatment effect will not be possible.

Also the external validity of a trial has to be looked at: It has to be decided if the results of the trial are applicable to a specific patient group, if the treatment is feasible in a specific setting and if the potential benefits of treatment outweigh the potential harms of the treatment.

I considered it to be important to use both, the Jadad's scale and the guidelines for the Critical Appraisal for RCT from the Centre of Evidence Based Medicine to assess a clinical trial. The Jadad's scale seems to be more suitable for a fast initial assessment of a trial whereas the RCT appraisal guidelines are more comprehensive and profound. Also, besides giving a structure for assessing a trial they leave room for own thoughts and judgements.

Results:

Excluded and Included Trials:

Totally sixteen RCT, which tested the use of oral ayurvedic preparations in the treatment of chemo- and radiotherapy side effects have been found. Three of these RCT had to be excluded:

One trial investigated "The effect of concord garpe juice on chemotherapy induced nausea and vomiting" (Ingersoll *et al.,* 2010). This trial had to be excluded because concord grapes are a cultivar of grapes and different from the original grapes (vitis vinifera) which are mentioned in the ayurvedic scriptures.

The second trial "Protein and Ginger for the Treatment of Chemotherapy induced Delayed Nausea" (Levine *et al*., 2008), was excluded because ginger was used in combination with proteins and not on its own. The use of proteins as such isn't part of ayurvedic medicine, which was unfamiliar with nowadays biochemical concepts.

The third trial "Effects of Extracts from Indigowood root (Isatis indigotica Fort) on Immune Response in Radiation induced Mucositis" (You *et al*., 2009) was excluded because also Isatis indigotica is not a plant, which is used in ayurvedic medicine.

Of the thirteen RCTs which have been left after exclusion of these three trials, two trials have been published as an abstract only.

Additionally three controlled clinical trials have been found. They couldn't be included in the review because they haven't been randomised and/or double blinded (Misra et al., 1994; Acharya, 1994; Acharya, 2002; + Appendix 2).

Included Randomised Controlled Trials:

In this section I will briefly summarise each of the included trials in narrative form and then assess each trial with the Jadad's scale and the RCT appraisal guidelines from Oxford Center of Evidence Based Medicine.

Joseph et al (1999) report the results of 20 patients, with histologically confirmed neoplasms of various types (lung, breast, uterine, cervix and brain), who were undergoing radiotherapy and chemotherapy. The patients did not have any prior exposure to cancer drugs. All the patients had initially normal total Leucocyte count, absolute Neutrophil count and Platelet count. Creatinine, Urea, Bilirubin, alkaline Phosphatase and Serum GPT were almost within normal range. All the enrolled patients had Karnofsky Functional Scale > 50%. The patients were randomised in two groups using the random number method. One group received Brahma Rasayana (Appendix 5; Sharma et al., 2009, Chikitsasthanam, chapter I, verses 41-61) 50 mg/d po in three split doses after meals for one month during radiotherapy and chemotherapy. The other group only received Radiotherapy and Chemotherapy and no placebo treatment. Depending on the type of cancer, chemotherapy with Cisplatin, Cyclophosphamide, Etoposide, Mitoxantrone and 5- Fluorouracil was given as single agent or combined. RT was given in 30 fractions and did not exceed 6000 cGy. Blood was collected from the patients prior to therapy and after that every third day: total white cell count, differential count, platelet count, alkaline phosphatase, Bilirubin, GPT, Creatinine, Urea, GM-CSF and Lipid Peroxids were analysed.
Patients in the BR group showed higher nadir levels of leucocytes and neutrophils and an accelerated recovery resulting in a rapid rise in the leucocyte and neutrophil count. On day 21 of the treatment, values reached almost normal levels in the BR treated group while they were still much lower in the untreated patients. GM-CSF was progressively increasing in the BR treated group compared to the control group. Serum lipid peroxide was found to be gradually increasing in the control group, whilst BR administration was found to reduce this value significantly in the treatment group.

Jadad's scale (2 points): point 1 for randomisation and point 2 for an adequate method of randomisation. Double blinding hasn't been used which gives 0 points and there isn't a statement about withdrawals (although there aren't any), which also gives 0 points.

RCT appraisal guidelines: the trial was randomised using an adequate method (random number method). The groups were similar at the start of the trial in view of the normal differential blood count and almost normal kidney function and liver function tests. All the patients had no prior exposure to cancer treatment and Karnofsky functional scale >50%. There were some dissimilarities between the groups in view of the types of cancer and the cancer treatment schemes (different chemotherapy and RT combinations used). As the outcome measure was based on blood test for determination of differential blood count, liver and kidney function it is most important that the two groups are comparable at that point initially. This is the case in this trial. Because of that, the dissimilarity of cancer types doesn't seem very significant. But the different treatment schedules, which could have been less or more toxic to the bone marrow and therefore lead to different levels of Neutropenia.
Apart from the intervention and the different treatment schedules the patients have been treated the same. They all had the same number of blood tests.
There haven't been any drop outs from the study. This can be seen in the results tables in the article. No statement about that has been made in the text.
The study hasn't been double blinded. However the RCT appraisal guidelines suggest that if the outcome is objective (in this case blood test) that blinding is less critical.
In this trial it hasn't been calculated how large the treatment effect is and if the results are statistically significant. As the patient number in this trial is quite small, with ten patients per group, it would be necessary to do a more large scale study to make an appropriate judgement about the treatment effect.

All together the trial seems very promising even if no statistical calculations about the treatment effect have been made. Especially the objectivity of the outcome measures (blood test) are a plus point of the study. The results of the study can be applied to cancer patients, who receive a first course of RT and/or Chemotherapy and are still in a relatively good condition. The treatment would be easy feasible in the setting of a cancer clinic provided that an ayurvedic practitioner can supply some good quality Brahma Rasayana. No treatment side effects have been noted in this trial, however a large scale study would be necessary to confirm this.

Pecoraro et al (1998) report the results of 12 patients which were included in randomised, double blind, crossover placebo controlled trial. This trial is assessing the efficacy of ginger as adjunctive therapy for acute chemotherapy induced nausea and vomiting (CINV). Unfortunately this trial is only available in abstract form. Therefore no information about the group of patients, the inclusion criteria and the dose and type of ginger preparation used is available. Also there is no information how the CINV has been assessed, the method of randomisation and about drop outs. A total response has been documented in 34% and 18% in ginger versus placebo treated patients and a partial response in 58% and 83% in ginger versus placebo treated patients. There was a 8% treatment failure in the ginger group and none in control group. No calculations about the statistical significance of the results has been given in the abstract.
It would be very interesting to know which dose and type of ginger preparation has been used and at which points before during or after chemotherapy it has been applied to make a definitive judgement if it might be helpful or not. Also it would be helpful to know, if the chemotherapy given was highly or less emetogenic. With a highly emetogenic chemotherapy probably a higher dose of ginger would be necessary to be helpful. Because this trial is only available in abstract form Jadad's scale and RCT appraisal guidelines are not applicable and I will not try to go through them in the discussion of this abstract.

Vyas et al (2010) present the results of 36 patients, aged 16-70, with carcinoma (different types) stage T1 or T2, which have been submitted for Radio- or Chemotherapy or both. The patients had to suffer from acute short term adverse effects from the treatment to be included into the study. Patients with chronic long term adverse effects and stage T4M2 were excluded from the study. The patients were randomised in two groups using a random sampling method. In the treatment group Rasayana Avaleha (Appendix 5) 30g in the morning along with 10 ml of ghee was given for 75 days along with radiotherapy and chemotherapy. In the control group only radiotherapy and chemotherapy have been given and no placebo. The chemotherapies varied according to the type of cancer and the patient's physical condition. Radiotherapy was given 1.8-2 gray per day, five fractions a week and totally 60-70 gray. From the amounts of radiation given we can deduct that the whole Radiotherapy was going on over 6-7 weeks (42-49 days). Knowing that Rasayana Avaleha was given for a total of 75 days and together with a statement from the discussion section "whenever possible Rasayana Avaleha should be started at least 10 days before commencing the radiotherapy and chemotherapy schedule...." we can assume that Rasayana Avaleha was started 10 days before start of a cycle of chemotherapy and/or Radiotherapy and continued during the whole course of treatment.

In the treatment group 16 out of 23 patients completed the whole course (7 drop outs). In the control group 9 out of 13 patients completed the treatment (4 drop outs). No statement has been made why the patients didn't complete the study.
For assessment of the treatment effects the guidelines for grading adverse effects by the National Cancer Institute Oncology group have been used. Nausea and vomiting, mucositis, fatigue, alopecia, xerostomia, tastlesness and effect of therapy on body weight have been assessed before and after the treatment course. The Rasayana Avaleha group showed an improvement in all the adverse symptoms after 75 days. The improvement was significant in nausea and vomiting, mucositis, and fatigue. The control group showed a not significant decrease of nausea and vomiting, fatigue and alopecia after 75 days and an increase in mucositis, xerostomia and tastlesness. In both groups weight loss was observed. But it was lower in patients treated with Rasayana Avaleha. The overall assessment of the therapeutic effect was the following: in the Rasayana Avaleha group all patients showed a moderate to marked improvement and even complete remission of their symptoms whereas the patients of the control group showed at the most some mild improvement, didn't change or got worse.

Jadad's scale: 3 points (high quality trial): Randomisation has been used and the method was adequate. There was no double blinding. The drop outs were mentioned, however not the reasons for it. As per the guidelines of the Jadad's scale, not mentioning reason for drop outs doesn't need deduction of a point.

RCT appraisal guidelines: adequate randomisation has been used in the trial. The two groups have been similar at the start of the trial in terms of tumor stage but not necessarily similar regarding the tumor type and planned treatment. Most importantly the groups have been similar in terms of acute short term adverse effects, which is the main outcome investigated in the trial. The two groups have been treated equally. Both were assessed with the guidelines from National Cancer Institute at day 0 and after 75 days. The number of patients, which have been lost during the trial has been clearly mentioned. The RCT guidelines suggest that ideally losses to follow up should be less than 20%. In the Rasayana Avaleha group the number of drop outs was nearly 40%, whereas in the control group the drop outs were close to 30%. The drop out rate, especially in the treatment group can't be considered ideal because the number of patients included in the trial is already small anyway and in that case the RCT guidelines suggest that "if few patients have the outcome of interest, then even small losses to follow up can bias the result". For this trial it could mean that we have got a too positive result about the improvement of adverse effects. After all, the treatment with Rasayana

Avaleha couldn't avoid the drop out of nearly 40% of the patients. No statistical power calculation has been made before the start of the trial, and therefore no attempts have been made to add additional patients during the trial to compensate for the drop outs. The trial hasn't been double blinded. No placebo has been given to the control group. As the outcome measure has been subjective (symptom assessment) the lack of placebo treatment might have been of consequence and led to an overestimation of the results in the treatment group.
In this trial no calculations to estimate how large the treatment effect is have been made. But it has been documented that the results are statistically significant.

After discussion of the above points it seems obvious that a more large scale study with more patients is necessary and that the trial should have been double blinded not only randomised to allow a statement if Rasayana Avaleha has a positive effect on adverse cancer treatment effects. Also, it needs to be discussed if Rasayana Avaleha is safe to use together with Radio- and Chemotherapy. No statement about treatment side effects has been made in this trial. We could even assume that the 40% patient drop out in the Rasayana Avaleha group was caused by some herb drug interaction or other adverse effects. But because the reasons for the drop outs haven't been discussed it isn't possible to form an opinion. Otherwise the treatment with Rasayana Avaleha would be easy to use in any cancer clinic as long as the preparation is available.

Saxena et al (2008) present the results of 214 patients with histologically confirmed breast cancer. Patients either had inoperable or locally advanced carcinomas. The patients with inoperable cancer were given 3 cycles of CAF (cyclophosphamide, adriamycin, 5-fluorouracil) as neo-adjuvant chemotherapy followed by surgery provided there was a complete or partial response. After the surgery the remaining 3 cycles of chemotherapy were given. The patients with operable breast cancer (T1,T2-N0 or N1 disease) were generally given CMF (cyclophosphamide, methotrexate, 5-fluorouracil) after mastectomy or wide excision along with full axillary dissection.
The effect of maharishi amrit kalash/MAK-4 and MAK 5 (Appendix 5) on anorexia, vomiting, Karnofsky Performance Status, weight, stomatitis, diarrhoea, leucopenia, alopecia and tumor response was investigated.
A statistical power calculation was done before start of the study: 142 patients needed to be studied (71 in treatment arm and 71 in control arm). The patients were randomised to the two groups using numbered envelopes. The treatment group was given MAK-4 paste 2 TbS BD with 1 glass of milk and MAK-5 2 Tbl BD with water half an hour after MAK-4. This supplementation was given throughout the whole chemotherapy for approximately 18 weeks. The control group did not receive placebos.

Supportive treatment with antibiotics and painkillers has been given to both groups if necessary. Responses to treatment were evaluated by questionnaire and physical examination according to WHO and EORTC response criteria at 21 day intervals. During the course of the trial many patients were dropping out because: they have been lost to follow up, due to progressive disease, which made it necessary to stop the chemotherapy and some patients refused further treatment. Hence more patients were recruited to obtain the necessary statistical power. Totally 102 patients were recruited into the treatment group and 112 patients into the control group. At the end of the trial 85 patients from the treatment group and 96 patients from the control group could be included in the final data analysis: There was no significant difference in baseline parameters in both groups. But throughout the chemotherapy, patients in the treatment group had better appetite and less weight loss compared to the control group. MAK treatment reduced vomiting with statistically significant difference in the 3rd and 4th cycle of chemotherapy and led to a better Karnofsky Performance Status (>80%) in the treated group. No statistically significant difference could be found regarding the extent of stomatitis, diarrhoea, leucopenia, and alopecia. The tumor response (complete-, partial response or disease progression) was similar in treatment and control group.

Jadad's scale 3 points (high quality): randomisation has been used and the method described is adequate. No double blinding has been used. Drop outs and the reasons for drop outs have been well described.

RCT appraisal: the trial has used adequate randomisation. All patients had histologically confirmed breast cancer and the investigated parameters of interest (appetite, vomiting, Karnofsky Performance Scale, diarrhoea, stomatitis, alopecia, white cell count) were comparable at baseline. Except from the investigated treatment all the patients had the same scheme of investigations and supportive treatment. Number and reasons for drops outs have been mentioned. The losses to follow up have been less than 20% in both groups. As per RCT appraisal sheet this means that the results are less likely to be biased. The trial hasn't been double blinded. No placebo medication has been given to the control group. Part of the study outcome has been assessed objectively with EORTC response criteria (tumorregression,- progression) and shouldn't be much affected by the lack of double blinding. A considerable part of the measured outcome however was based on subjective assessment (chemotherapy side effects, assessed with WHO criteria) and could therefore be very well influenced by the lack of double blinding.
It hasn't been calculated how large the treatment effect was but how significant the results are.

Overall the trial is very well planned. A clear plus point is, that a sufficient number of patients have been included in the study (after power calculations have been made), which obviously gives the results more significance. However with the study not being double blinded, the results based on subjective judgement by the patients might be to positive in the treatment group and less positive in the control group because the patients know that they haven't been given an additional treatment, which eventually might be helpful.
Additional treatment with amrit kalash seems easy feasible in a conventional oncology clinic setting. No side effects or herb drug interactions have been mentioned in this trial, which would counteract the beneficial effects of amrit kalash in the treatment of chemotherapy side effects.

Srivastava et al (2000) report the results of 129 breast cancer patients, who were receiving chemotherapy with cyclophosphamide, adriamycin, 5-FU (CAF) or cyclophosphamide, methotrexate, 5-FU (CMF). The patients were randomised to two groups using sealed numbered envelopes. 61 patients were randomised to the treatment group and 68 into the control group. The treatment group received MAK-4 paste, 1 TbS BD with milk and MAK 5 Tbl one BD with water in addition to the chemotherapy.
The control group only received the chemotherapy and no placebo. The abstract doesn't mention the exact duration of the MAK treatment, but as the patient assessment was done over six cycles of chemotherapy we could assume that the treatment was given at least over this period of time. The patients were evaluated for general well being, anorexia, weight loss, leucopenia, stomatitis, vomiting, diarrhoea, haematuria, cardiac toxicity, pulmonary toxicity, Karnofsky score, alopecia, cutaneous allergy, neurotoxicity, fever and constipation. A very detailed scale for assessment of above side effects is documented in the abstract. But there is no mentioning on what guidelines this scale is based on. The results of the study show that MAK helped in maintaining general health, Karnofsky Status, appetite and body weight. There was reduction in other side effects, but they were not statistically significant.

Jadad scale 2 points (low quality): adequate randomisation was used for the trial. The study wasn't double blinded and patient drop outs haven't been discussed.
Because of limited availability of information I will only briefly go through the RCT assessment: The trial went through adequate randomisation. All included patients had confirmed breast cancer and went through defined chemotherapy schemes, which means that there is some similarity of the groups at the start of the trial. But we don't know in which tumor stage and in which basic condition the patients have been included in the trial. It is obvious that this can alter the measured outcome.

Both the treatment groups seem to have been treated equally and have been assessed after each chemotherapy cycle. As I mentioned already, no discussion about drop outs can be found in the abstract. The trial isn't double blinded, which will influence the outcome measure. There are no statistical calculations documented in the abstract.
We can only assume that the authors might have all the missing information available, which hasn't been published in the abstract. Unfortunately this leads to a limited significance of the study but the tendency of the results is certainly interesting and worth following up. The results in this trial are comparable to the results presented in the previous trial from *Saxena et al* (2008).

Amruthesh et al (2010) report the results of 15 patients diagnosed with squamous cell carcinoma of head and neck region. All patients were aged 30-70 and planned for first time Radiotherapy with Co60 given with a minimum dose of 4000 rads. The radiotherapy had to include both the parotid glands in the radiation field. The patients were randomised into two groups with a randomisation schedule provided by the statistician. Eight patients were randomised into the treatment group. They received 20 mg Tinospora cordifolia daily with honey alongside the Radiotherapy. The treatment was given for 8 weeks and started 15 days prior to Radiotherapy. The control group received a placebo (millet flour with sirup) alongside the radiotherapy, which was also started 15 days prior to Radiotherapy. The patients were assessed before and after the Radiotherapy. The tools, used for assessing the effectiveness of Tinospora cordifolia were: The quantity of whole stimulated saliva by making the patient chew on bits of rubber and collecting the saliva into graduated tubes by expectoration over 5 minutes period. And grading of mucositis as per WHO. At the end of the trial the reduction of saliva in the control group was significantly more than the one in the study group with the mean percentage of decrease being 58.6% in the treatment and 82.6% in the control group. The distribution of the mucositis grades showed that the majority of the patients in the treatment group were grade 1 and 2 mucosits (mild forms) whereas all the subjects in the control group had grade 3 mucosits (more severe form). The summary of the results shows that there haven't been any drop outs from this trial, but there isn't a particular statement about that.

Jadad scale 4 points (high quality trial) : an adequate method of randomisation has been used (2 points), the study has been described as double blinded and it was appropriate (2 points). No point can be given for dropouts, although there haven't been any because no statement has been made about it.

RCT appraisal guidelines: adequate randomisation has been used for the trial. The groups have been similar at the beginning: they all had the same type of cancer and were planned for first time Radiotherapy. However we don't know which size and stage the tumors have been in. Because it was the first time to get Radiotherapy for all the included patients we can assume that most of them have been in a reasonably good condition at the start of the trial.
All patients had the same number of assessments at the beginning and end of the trial. Although it hasn't been particularly mentioned there have been no losses to follow up. The trial has been double blinded. The method of blinding was adequate (placebos given to the control group and assessor and patients were unaware of the treatment). Besides being double blinded the measured outcomes were objective: amount of stimulated saliva in ml and mucositis grading mainly based on clinical examination through assessor. Considering the adequate double blinding and the objective assessment of outcome the chance of the results being biased is very small.
It hasn' t been calculated how large the treatment effect was but it calculations showed the results to be significant.

Alltogether the trial of *Amruthesh et al* is of high quality. The most important points for a good quality RCT have been followed and the outcome measures were objective. The small number of patients is the only negative point of the study, although the trial has actually been declared as a pilot study, which explains the small number of included patients. But still, the results of the trial seem overwhelmingly positive and because of that Tinospora cordifolia with honey alongside Radiotherapy would be an amazing addition to use in cancer clinics. Another reason, which would support the use of Tinospora cordifolia alongside Radiotherapy, is, that the risk for herb- drug interactions would practically be inexistent. No side effects have been mentioned in this trial.

Manusirivithaya et al (2004) report the results of 48 gynaecologic cancer patients, who were scheduled for highly emetogenic cisplatin containing chemotherapy at a dose of 75 mg/m² either alone or combined with other chemotherapeutic agents. The patients had to be planned for at least 2 cycles of chemotherapy at the same dose and schedule. They were only included if they didn't have pre-existing nausea or vomiting from any cause or use of antiemetics in the 24 hours before cisplatin treatment. The patients were randomly assigned to two groups by blocks of four. Group A received two capsules with 250 mg of powdered ginger root, 30 minutes before chemotherapy, then one capsule 6 and 12 hours after chemotherapy on day 1. On days 2-5 of the chemotherapy cycle, patients received one capsule with 250 mg powdered ginger root four times a day . Group B received two capsules of placebo 30 min before Chemotherapy, then one capsule of placebo 6 and 12 hours

after chemotherapy on day 1. On day 2-5 of the chemotherapy cycle patients received one capsule of Metoclopramide 10 mg four times per day. Both groups were given 50 mg Metoclopramide intravenously before start of the chemotherapy and then 20 mg Metoclopramide intravenously at 1.5, 3, 4.5, 6, 12, 18, and 24 hours after chemotherapy. Also 20 mg of Dexamethason and 1 mg of oral Lorazepam were administered 30 minutes before and 6 hours after chemotherapy.
For the second cycle of chemotherapy, which was administered 3-4 weeks after the previous cycle the groups were crossed over so that each patient received both regimens.
CINV in the acute phase(first 24hours) was assessed by an investigator in the hospital, whilst in the delayed phase (day 2-5) patients had to record their data in a diary. Nausea and emetic events had to be recorded once a day at bedtime. The intensity of nausea was recorded by means of a 10 cm visual analog scale. Emetic episodes were counted separately from each other by the absence of vomiting or retching for at least five minutes apart. Side effects were assessed by general questioning.
Five patients had to be excluded from the final analysis because they did not receive both antiemetic treatment regimens, leaving 43 patients for the final analysis: In the acute phase nausea and emetic control wasn't significantly different between the two groups. In the delayed phase nausea score and days of nausea haven't been significantly different between the two groups. For the control of emesis both regimens have been equally effective. 1 gram of ginger per day was as effective as 40 mg Metoclopramide per day for control of delayed phase CINV. Patients who received Metoclopramide had an insignificant higher incidence of restlessness compared to those who received ginger. One patient who received Metoclopramide even experienced extrapyramidal symptoms, while no patient in the ginger group experienced these symptoms.

Jadad's scale 5 points (high quality trial): 2 points can be given for adequate randomisation, 2 points for adequate double blinding and 1 point for discussion of number and reasons for drop outs.

RCT appraisal guidelines: adequate randomisation has been used. The two compared groups have been similar at the start of the trial. Most importantly the assessed outcome (nausea and vomiting) hasn't been present in neither of the patients at the start of the trial. Both patient groups received cisplatin containing chemotherapy regimens and the same number of assessments during the trial. The losses to follow up have been minimal, less than 20% of all patients. Also, in both separate groups the losses to follow up have been significantly less than 20%. The trial has been adequately double blinded. The assessed outcome was partly subjective (Intensity of nausea) and partly objective (number of emetic episodes). Because the trial is double blinded, the losses to follow up

are less than 20%, and part of the outcome could be assessed objectively the study results are very unlikely to be biased.
No estimations about how large the treatment effect is have been made, but the results proved to be statistically significant.

All together the trial has been very well made. All the points for a high quality RCT are fulfilled. However also in this trial no power calculation has been made at the start to ensure that a sufficient number of patients can be included. The crossover design of the trial somewhat compensates the lacking power calculation, as the number of the available patients could be nearly doubled this way. The ginger treatment seemed to have been well tolerated by the patients and even if it didn't improve the acute phase vomiting, its effect was comparable with metoclopramide in the delayed phase vomiting. This observation could be helpful for future patients. It could be especially helpful for patients who can't tolerate Metoclopramide.

Zick et al (2009) report the results of 162 patients, aged eighteen and over with various types of histologically confirmed cancers. The patients were on curative or palliative, adjuvant or neoadjuvant chemotherapy depending on the stage of cancer. To be included in the study, the patients must have received at least one previous chemotherapy with the same chemotherapeutic agent and must have experienced CINV as result of that treatment. They had to be scheduled for a single day chemotherapy regimen. Exclusion criteria were multiple day chemotherapy, concurrent radiotherapy, concurrent therapeutic treatments with coumarins, aspirin or heparin, thrombocytopenia, bleeding disorders, allergy to ginger and ginger intake one week before trial. The final sample size was justified in terms of analysis of between treatment differences in delayed nausea.
Eligible patients were randomly assigned to three different groups by computer generated randomisation. One group received placebo capsules for 3 days together with 5-HT 3 Antagonist +/- aprepitant (57 patients), the second group received 1 g encapsulated ginger extract per day over 3 days with 5-HT3 Antagonist +/-aprepitant (53 patients) and the third group received 2 g of encapsulated ginger extract over 3 days with 5-HT3 Antagonist +/- aprepitant (52 patients). The capsules were taken from day 1-3 of a chemotherapy cycle. Additionally the computer generated randomisation process made sure, that participants who received 5-HT3 Antagonists or 5-HT3 Antagonist plus aprepitant were equally distributed between the different groups.
The primary outcome measure of the trial was to compare the effect of low dose (1g) and high dose (2g) ginger root extract versus placebo in reducing the prevalence and severity of delayed CINV.

Delayed CINV was defined as any nausea and vomiting occurring more than 24 hours after chemotherapy. The outcome assessment was done by using a modified patient diary based on MANE (Morrow assessment of Nausea and Emesis): Patients have been asked whether they experienced vomiting during or after chemotherapy treatment, how long in minutes and hours the nausea lasted, how they would describe nausea or vomiting at its worst using a six point Likert scale (very mild to intolerable) and how many hours after the treatment nausea and vomiting was the worst. Additionally patients were questioned verbally about any adverse events or hospitalisations during this 3 day time period. They were also asked if they could identify the treatment, they have been given. Most patients indicated, that they know which treatment they have been given because of the taste of the capsule and because of the way the capsule worked.
Totally there have been 33 drop outs during the trial: 11 drop outs from the placebo group, 10 drop outs from the group on 1g ginger/day and 12 drop outs from the group on 2g ginger/day. All the reasons for drop outs have been stated in the study. Adherence to study medications was moderate to high.
The results showed no significant difference between either of the ginger doses compared to placebo in the prevalence of acute or delayed CINV. Although not significant, participants who received aprepitant and either dose of ginger had more treatment failures compared to those who received aprepitant in addition to placebo, for both, acute and delayed nausea and vomiting. Regarding the severity of delayed CINV ginger extract did not cause any decrease. The 2g dose of ginger extract did even increase the severity of delayed CINV but only when taken together with aprepitant. The severity of acute CINV wasn't affected by ginger extract of either dose.
Ginger appeared to be well tolerated. Despite the lack of statistical significance there were fewer complaints of fatigue in the ginger treatment groups versus placebo and there were borderline significantly fewer laboratory abnormalities in the high dose ginger group.

Jadad's scale 4 points (high quality trial): The trial was randomised and the method used was adequate (2 points). The trial was double blinded, however the method used wasn't completely appropriate as most patients indicated that they could find out which treatment they have been given because of the taste of the capsule (1 point). Number and reasons for drop outs have been mentioned (1 point).

RCT appraisal guidelines: adequate randomisation has been used. The patient groups were similar at the start of the study, the main similarity was the experience of acute and delayed CINV in a previous one day chemotherapy cycle. But the chemotherapy regimens were variable with different

emetogenic potentials. Apart from the intervention the patients were treated the same. All groups had the same kind of outcome assessment and investigations. Losses to follow up were accounted for in the trial. Losses to follow up were slightly more than 20 percent of the total number of patients and also more than 20 percent of the patients in each group. The RCT appraisal guidelines suggest that losses to follow up of more than 20% should be considered as more than just minimal. The high number of drop outs hasn't been compensated by including additional patients into the trial. The trial was double blinded, with two groups of patients receiving ginger in different doses and one control group, which was given placebo. A few patients mentioned that they have been able to guess their treatment because of the taste of the capsules. Because of the lack of optimal double blinding, especially the results based on subjective judgement (Likert scale judging severity of vomiting) might be somewhat in favour of the ginger treatment. The MANE assessment, where presence of vomiting and hours of nausea have been assessed seems more objective, but also these results might have been influenced by knowing which treatment has been taken. No estimations about how large the treatment effect is have been made, but the results proved to be statistically significant.

In summary the trial is of high quality and reaches 4 points on the Jadad's scale. The ginger treatment did not show a significant improvement of acute and delayed CINV. But the ginger was only given day 1-3 of one chemotherapy cycle, which might be not long enough to see an effect. Also the number of patients was relatively low and the dropout rate was high. The chemotherapy regimens were very different. Some of them are less or more likely to produce CINV. An unexpected but interesting finding during the study was, that ginger, when taken together with aprepitant seems to make symptoms worse. A herb drug interaction could be a likely explanation for this finding. Also the not statistically significant finding, that the ginger group was suffering from less fatigue and laboratory abnormalities than the placebo group would be worth further trials

Pillai et al (2011) report the results of 31 patients aged 8 to 21 with bone sarcoma, which participated in 60 cycles of highly emetogenic chemotherapy with cisplatin (40 mg/m²/day) and doxorubicin (25mg/m²/day). Of these 60 cycles in 31 patients, 30 cycles were randomly assigned to the experimental group and 30 cycles to the control group by computer generated randomisation. 8 Patients were enrolled for 1 cycle each, 17 patients for 2 cycles each and 6 patients for 3 cycles each of chemotherapy, which all adds up to a total of 60 chemotherapy cycles. All patients received Ondansetron and Dexamethason intravenously as standard antiemetics for the first three days of the chemotherapy plus tablets of these antiemetics daily in the night during the first three days of

chemotherapy and then three times daily for the next two days after completion of chemotherapy. Patients who have been receiving the antiemetic aprepitant additionally, as well as patients receiving radiotherapy and children and adults with weight ≤ 20 kg or ≥ 60 kg haven't been included in the trial. In the experimental group, patients with body weight 20-40 kg received 2 capsules with 167 mg ginger 1 hour before, 3 hours and 8 hours after chemotherapy (1.2 g ginger/day) from day 1-3 of the chemotherapy (3.6 g totally). Patients with body weight 40-60 kg received 2 capsules with 400 mg ginger 1 hour before, 3 hours and 8 hours after chemotherapy (2.4 g ginger/day) for days 1-3 of chemotherapy (totally 7.2 g ginger). For the control group the scheme was exactly the same, however the capsules were containing starch powder as placebo. All patients had an assessment at baseline, where they were assessed for the presence of nausea and vomiting. From days 1-10 of the chemotherapy cycle, patients and guardians were instructed to complete a diary, which was based on the Edmonton's Symptom Assessment scale (ESAS) and National Cancer Institut (NCI) guidelines. Absence and severity of nausea had to be graded in the ESAS scale. Number of episodes and amount of vomitus had to be graded as per NCI guidelines. Study end points were the incidence and severity of acute and delayed CINV. As the chemotherapy was given over 3 days, acute CINV was defined as nausea and vomiting occurring on days 1-4 of the chemotherapy cycle and delayed CINV as nausea and vomiting occurring more than 24 hours after completion of chemotherapy (days 5-10).
At baseline no patient in both groups had nausea and vomiting. 100 % of the patients in both groups had acute nausea during the chemotherapy. Acute moderate to severe nausea was observed in 28/30 cycles (93.3%) in the control group and 15/27 cycles (55.6%) in the experimental group. There was complete absence of acute vomiting in 1/30 cycles (3.3%) in the control group and in 4/27 cycles (14.81%) in the experimental group. Acute moderate to severe vomiting was significantly more in the control group (23/30 cycles->76.7%) than in the experimental group (9/27 cycles-> 33.33%). In the delayed phase moderate to severe nausea was present in 22/30 cycles (73.3%) in the control group and 7/27 cycles (25.9%) in the experimental group. Moderate to severe vomiting was present in 14/30 cycles (46.7%) of the control group and in 4/27 cycles (14.8%) of the experimental group. All the results appeared to be statistically significant. There were three drop outs from the ginger group, they either couldn't comply with the data collection or with the intervention. No adverse effects caused by ginger, such as rash, bleeding or tachycardia had been observed during the study.

Jadad's scale 5 points (high quality trial): The trial can be given 2 points for adequate randomisation, 2 points for adequate double blinding and 1 point for mentioning numbers and reasons for drop outs.

RCT appraisal guidelines: the trial can be considered as adequately randomised. The groups have been similar at the start of the trial: all the patients had newly diagnosed bone sarcoma and where about to start with a highly emetogenic chemotherapy regimen (cisplatin/doxorubicin). Apart from the intervention the two compared groups were treated the same. They received the same way of assessment and follow ups and same additional treatments. All patients, who entered the trial have been accounted for. Numbers and reasons for drop outs have been stated. The losses to follow up were minimal, less than 20% in the ginger group. There were no losses to follow up in the control group. Because of the minimal losses to follow up and because quite a large number of patients had the outcome of interest (reduction of acute and delayed CINV by ginger) the results are very unlikely to be biased. Adequate double blinding was used in the trial. As the outcome assessment has been based on objective (number and amount of vomits) and subjective assessments (severity of vomiting), the double blinding is particularly important.
No estimations about how large the treatment effect is have been made, but the results proved to be statistically significant.
No power calculation has been made before the trial has been started. The included number of patients is relatively low. By investigating some of the patients over several chemotherapy cycles, the researchers have probably tried to make up for that.

All together the study is well made and the results are encouraging. Generally higher doses of ginger than in the study from *Zick et al*, which did not show much effect of ginger, have been used. The information we can get from this trial about an effective dose of ginger (2.4 g/ day, respectively 1.2g/day for body weight < 40 kg) could be helpful for those doctors, who are considering to prescribe ginger treatment to chemotherapy patients as supportive method alongside the regular antiemetic treatment.

Ryan et al (2011) report the results of a trial, with 744 patients, aged > 18 with various types of cancer . All included patients had experienced nausea in any previous chemotherapy cycle before enrolment and had to be scheduled for at least three additional chemotherapy cycles. Also they had to be planned to receive a 5-HT3 Antagonist plus Dexamethason for all chemotherapy cycles. Exclusion criteria were therapeutic coumarin or heparin treatment, bleeding disorders and platelet count <100'000/µl. Chemotherapy had to be given without concurrent radiation therapy or planned interruption by radiation therapy or surgery. The patients were randomly assigned to four treatment arms by computer generated random number table: placebo (3 placebo capsules twice daily), dried ginger extract 0.5g/day (2 placebo capsules and 1 ginger capsule twice daily), 1.0g/day (1 placebo

and 2 ginger capsules twice daily) and 1.5g/day (3 ginger capsules twice daily. Ginger and placebo capsules were double encapsulated and had a nitrogen cap to mask any difference in smell and colour between ginger and placebo. All the patients took the study medication twice daily for six days, starting 3 days before the chemotherapy (days -3 to -1) and continuing it for the first 3 days of the chemotherapy cycle. Compliance was measured by pill counts at the end of each study. All included patients had to go through a baseline cycle, where they didn't receive any placebo or ginger at all, just the scheduled chemotherapy and antiemetics. The following two chemotherapy cycles were considered as study cycles, where the patients received either placebo or ginger 0.5g, 1.0g or 1.5g daily additionally to their chemotherapy and antiemetics. Of the initially included 744 patients, only 662 patients completed the baseline cycle, 562 (85%) completed study cycle 2 (first cycle of study medication) and 471 (71%) completed study cycle 3 (2^{nd} cycle of study medication). Final data analyses could be conducted on 576 (87%) of the patients, who provided evaluable data from either study cycle 2 or 3. In the placebo arm data of 149/188 patients (79%) could be analysed. In the 0.5 g ginger arm 134/183 patients (73%), in the 1.0 g ginger arm data of 141/187 patients (75%) and in the 1.5 ginger arm data of 152/187 patients (81%). Patients had to document nausea and emesis during day 1-4 of each chemotherapy cycle with a diary developed by Burish and Carey. Patients reported severity of nausea four times a day using a 7 point semantic rating scale. Anti nausea medication use and number of vomiting episodes had to be recorded as well. Additionally a 13 item Symptom inventory was used to assess potential side effects of ginger. Symptom Inventory had to be completed once during baseline cycle and 3 times during study cycles 2 and 3 (before starting study medication on day -4 , before start of chemotherapy on day -1 and after completion of study medication on day 4). Anticipatory nausea was assessed by using the Symptom Inventory completed prior to chemotherapy (day -1) as well as a 11 point scale ranging from 0 to 10. Quality of life was assessed using the 27 item Functional Assessment of Chronic Illness Therapy-General (FACIT-G) at baseline and follow up assessments. The analyses showed, that all doses of ginger significantly reduced acute CIN in both cycles compared to placebo. 0.5 g ginger/day and 1.0 g ginger/day were most effective in reducing acute CIN. Ginger didn't cause much significant reduction in delayed nausea. Also, no significant differences were observed in vomiting and quality of life. Only nine of the reported 24 adverse events during the trial were considered to be related to ginger. The adverse events included grade II heartburn, bruising/flushing and rash and led to withdrawal of the patients from the trial.

Jadad's scale 5 points (high quality): 2 points for adequate method of randomisation, 2 points for adequate double blinding and 1 point for mentioning numbers and reasons for drop outs.

RCT appraisal guidelines: adequate randomisation has been used. The groups were similar at the start of the trial regarding the investigated symptoms. All included patients had experienced CINV in a previous chemotherapy cycle. However the patients were suffering from different types of cancer and were undergoing different types of chemotherapy. Apart from the interventions all the patients were treated the same otherwise. All the patients who entered the trial have been accounted for. Numbers and reasons for drop outs have been stated. Losses to follow up were more than 20% of the total number of patients. When calculated for each treatment arm the losses to follow up were more than 20% in the placebo arm, the 0.5 g daily and 1.0g daily ginger group and less than 20% in the 1.5g daily ginger group. As per RCT appraisal guidelines, losses should be minimal (< 20%), which in this trial is only the case in 1.5g ginger group. No attempts have been made to include further patients into the trial to compensate for the high number of drop outs. However the long duration of the trial over six years (2002-2008) is certainly showing that a lot of effort has been put into the trial. The reason behind the long duration of the trial, is very likely to enable the inclusion of as many patients as possible. Although no statistical power calculation has been presented in the study, the number of included patients seems considerable.
Adequate double blinding has been used in the trial. Because outcome assessment was mainly subjective, the use of adequate double blinding is particularly important.
No estimations about how large the treatment effect is have been made, but the results proved to be statistically significant.

When comparing this trial to previously discussed trials about ginger treatment for CINV, there is the interesting difference that ginger treatment has been started 3 days before the actual chemotherapy. So even with maximum doses of ginger, which have been somewhat lower than in other trials, which used up to 2.4 g daily, a positive effect on acute CIN has been observed. By being able to use ginger in lower dose by starting the treatment earlier, it might be possible to avoid some of the typical side effects caused by ginger (heartburn, rash, hot flashes). This information will be very useful for practitioners, which are prescribing ginger against CINV.

Sontakke et al (2003) discuss the results of 60 patients, aged > 18 with various types of histologically confirmed cancer, receiving cyclophosphamide containing combination chemotherapy. The patients had to have experienced at least 2 episodes of vomiting in a previous chemotherapy cycle to be included in the trial. Exclusion criteria were patients with cancers of GIT, nausea and vomiting due to other reasons than chemotherapy, hypertension, reduced kidney or liver function, concomitant

radiotherapy and additional medication apart from chemotherapeutic drugs. Routine haematological and biochemical assessment was done before each chemotherapy cycle. All patients received cyclophosphamide 500- 1000 mg i.v in combination with other chemotherapy. Interval of two successive chemotherapy cycles was 21 days. The patients were randomly assigned to one of the three following antiemetic regimens: Group 1 received 2 capsules each containing 500 mg ginger powder 20 min prior to chemotherapy and 6 hours after chemotherapy and 20 ml of saline solution intravenously 20 min prior to Chemotherapy. Group 2 received 2 capsules of Lactulose 20 min prior to chemotherapy, 20 mg intravenous Metoclopramide 20 min prior to chemotherapy and 2 capsules Metoclopramide 5 mg 6 hours after chemotherapy. Group 3 was prescribed 2 capsules of lactulose 20 min prior to chemotherapy, Ondansetron 4 mg intravenously 20 min prior to chemotherapy and 2 capsules Ondansetron 2 mg 6 hours post chemotherapy. In these 3 different types of regimens each patient received exactly the same number and amount of injections and capsules, however with different ingredients. The pharmaceutical company, which prepared the trial medication made all the capsules look identical in size, shape, colour and odour. The patients were randomly assigned to receive one of the three antiemetic regimens with their chemotherapy during the first study cycle. They were crossed over to the other antiemetic regimens during the next two successive cycles. So ideally, each patient should have received all the three different antiemetic regimens.
After the chemotherapy patients were transferred to a ward for 24 hours, where time and number of episodes of vomiting have been recorded. Subjective evaluation of severity of nausea was done: none, mild to moderate or severe. Subjective assessment of severity of adverse events was done as well. 50 patients could complete all the three study cycles and antiemetic evaluation. The study showed that complete control of nausea was achieved in 62 % of patients with ginger, 58% with metoclopramide and 86% with ondansetron. Complete control of vomiting was achieved in 68% of patients with ginger, 64% with metoclopramide and 86% with ondansetron. The antiemetic effect of metoclopramide and ginger was not statistically significant, but Ondansetron was better than both. And importantly we can see that the antiemetic effect of ginger in CIN was found to be comparable to that of metoclopramide.

Jadad's scale 5 points (high quality trial) : Adequate randomisation was used (2 points). Even if the used method of randomisation hasn't been mentioned, the method of randomisation can still be considered adequate, because crossover design has been used. By using crossover design each patient had the same chance to get each intervention. Adequate double blinding has been used in this trial (2 points) and number and reasons for drop outs have been stated (1 point).

RCT appraisal guidelines: the trial has been adequatly randomised. The patient groups were comparable at baseline, especially regarding the investigated outcome of interest CINV. All patients had experienced at least two episodes of vomiting in a previous chemotherapy cycle. Apart from the allocated treatment, all groups were treated equally and received the same number of follow ups and tests. All patients were on a cyclophosphamid containing chemotherapy, but additionally chemotherapeutic agents with different emetic potential have been added. All patients who entered the trial have been accounted for: Number and reasons for drop outs have been clearly stated. The losses to follow up were minimal (< 20%). A power calculation, which has been made before the start of the trial, showed that approximately 35 patients should be included to get satisfactory results. By being able to observe 50 patients, the included number of patients was certainly more than sufficient. Adequate double blinding has been used. As the assessed outcome was partly subjective (severity of nausea) and partly objective (number of vomiting episodes) the double blinding was particularly important. No estimations about how large the treatment effect is have been made, but the results proved to be statistically significant.

The trial has been well made and is of high quality. Looking at the end results, the information that ginger is as efficient as metoclopramide in antiemetic control is particularly interesting. Also the trial of *Manusirivithaya et al* which has been discussed earlier came to the same conclusion. For patients, who can't tolerate metoclopramide this information is particularly helpful. But it also has to be said that to control severe CINV Ondansetron is still the most powerful medication. To optimise antiemetic control combination of ondansetron plus metoclopramide or ginger would be most effective. This has been investigated in the trials by *Pillai et al* (2011 and *Ryan et al.* (2011), which have been discussed earlier.

Hien et al (2002) report the results of 72 stage II or III breast cancer patients for whom radiotherapy was indicated following surgery for primary breast cancer. Exclusion criteria were distant metastases, Tbc and hepatitis. All the included patients were scheduled for radiation treatment with Cobalt-60 with a total dose of 5000 rad. The daily dose was 200 rad, given in 5 courses per week. The patients were randomly assigned to two groups (36 patients per group). The treatment group received capsules containing 100 mg active compounds, which have been extracted from Vitexina radiata (green - or mung bean). The patients had to take 4 capsules daily for 6 weeks during the Radiotherapy. The placebo group received 4 identical placebo capsules daily (containing lactose) during the whole course of radiotherapy. Blood samples were taken from patients in Vitexina and placebo group before and after the 6 weeks of radiotherapy. Blood from healthy people was

analysed and used as control. Complete blood counts, liver enzymes (GOT, GPT) and the blast transformation response of lymphocytes were investigated. Blast transformation activity was used to monitor the immune status. Body weight was assessed before and after RT and the patients were evaluated for radiotherapy side effects like headache, restlessness, fatigue, poor sleep and poor appetite. An expert in traditional Vietnamese medicine assessed hot symptoms of the patients by inspection of their tongue.

At the entry in the study characteristics of patients were similar between vitexina and placebo group. Average weight of patients in vitexina group was 46.82 kg and in the placebo group 47.62 kg. In 70 % of the patients in the vitexina group no significant weight loss occurred. There were even patients gaining weight. 73% of the patients in the placebo group lost 1 to 2 kg weight during the 6 weeks of RT. All patients in the vitexina group reported that side effects of the radiation treatment were not noticeable, that they had good appetite and that they slept well. A comparison of the haematological results show and advantage for the vitexina group in erythrocyte, leucocyte and platelet counts as well as haemoglobin after 6 weeks of RT. Erythrocyte and haemoglobin improved in vitexina group and declined in placebo group. Leucocyte and platelet counts declined to approximately 80% of original values in vitexina group and to approximately 60% of original value in placebo group. So the decrease of leucocytes and platelets was considerably more in the placebo group. In the vitexina group 67% of the patients experienced a reduction in platelet count of less than 20%, whereas in the placebo group only 17% of the patients experienced a reduction this low. The lymphocyte blast transformation test showed that in the vitexina groups lymphocytes still responded to blast transformation initiated by PHA (Phytohemagglutinin), whereas this response was almost absent in the placebo group. Hot inspection on the tongue showed that at the start of RT incidence of normal, hot and extreme hot symptoms was similar between vitexina and placebo groups, whereas after RT incidence of hot and extreme hot symptoms was increased in the placebo group.

Jadad's scale 3 points(high quality): The trial has been randomised. Unfortunately the method of randomisation hasn't been documented (1 point). The trial is double blinded, an adequate method with identical placebo capsules has been used (2 points). No statement has been made about numbers and reasons for drop outs (0 points). The only vague statement about drop outs can be found in the methodology section, were two of the exclusion criteria are "patients who did not complete the course of medication or attend the final physical examination have been excluded from the trial".

RCT appraisal guidelines: the trial is randomised, however the method used isn't mentioned. The patient groups were comparable at the start of the trial. All patients were suffering from stage II or III breast cancer and were scheduled for 6 weeks of radiotherapy. The average body weight, full blood count and LFTs were comparable at baseline. Apart from the different interventions (vitexina versus placebo) the two groups were treated the same. Both groups had the same kind of follow ups. In this trial not all patients who entered the trial have been accounted for. No statement has been made about numbers of patients that dropped out of the trial. Because of that no judgement can be made if the losses to follow up were > or < 20% (minimal or high). If the losses to follow up were high, a relatively small number of patients would have been included in the final analyses. This would have made the percentage of patients with the outcome of interest seem much bigger than it actually was. Adequate double blinding method has been used in the trial. As the assessed outcome of interest was mostly objective (blood results, body weight) the results seem to be more credible. But as we have discussed earlier the final analysed number of patients might have been small, so we have to be cautious optimistic about the results. No estimations about how large the treatment effect is have been made, but the results proved to be statistically significant.

Altogether the trial is well set up and highlights the most important radiotherapy side effects and their improvement by supportive treatment with Vitexina radiata from different angles. The side effects like low blood cell count, weight loss and "heat symptoms" are very common and there are not many treatments conventional medicine can offer. By taking Vitexina radiata from start until end of radiotherapy it has been possible to prevent these sometimes very serious side effects. However trials with larger patient numbers are certainly necessary. And as we have seen the trial from *Hien et al* would need some additional technical improvements.

Ishikawa et al (2006) present the results of 50 patients, aged more than twenty with advanced inoperable cancer of liver, pancreas and colon. The patients with pancreatic cancer did not undergo treatment before the study, except for 1 patient who was treated with cisplatin and fluorouracil. All patients with liver cancer were treated with transcatheter arterial embolisation (TAE) and/or percutaneous ethanol injection therapy (PEIT) and 6 of them underwent hepatectomy before start of the study.
During the study 10 patients with liver cancer underwent TAE or PEIT of whom one took fluourouracil. All pancreatic cancer patients were treated with fluorouracil of whom 5 were treated with radiation and 1 took irinotecan along with fluorouracil. The study participants were randomised into two groups by the trial statistician (25 patients in each group). One group received Aged Garlic

Extract (AGE) 2 capsules after breakfast and 2 capsules after dinner (total daily dose of 500 mg AGE). The other group received 2 capsules of placebo (crystalline cellulose) after breakfast and after dinner. The patients took the tablets for 24 weeks. Blood and saliva samples were taken before start of the study, and after 12 weeks. Blood was tested for GOT, GPT, γ-GT, bilirubin, LDH, alkaline Phosphatase, tocopherol, albumin, total cholesterol, triglycerides, Urea, creatinin, sodium, potassium, calcium, chlorine, FBC, NK cell count, NK cell activity, CD4 and CD8 positive cell count and S-Allylcysteine (SAC), which is one of the main organosulfur compounds of garlic. The saliva samples were tested for cortisol. Additionally the patients filled out the quality of life questionnaire (FACT) (28), together with a member of the trial team before the start of the trial, after 3 month and after 6 month. The scores of the individual domains (physical, functional, mental and social) and total score were calculated separately. Of the initially 55 patients who were invited to the trial, 50 consented to participate; 42 patients with liver cancer, 7 patients with pancreatic cancer and 1 patient with colon cancer. During the trial, 8 patients from the AGE group dropped out (3 of those had refused to start with the trial after they have been randomised, 4 died, 1 withdrew because of Angina pectoris) and 6 patients dropped out from the control group (5 patients died and 1 patient withdrew because of diarrhoea). The compliance was relatively good in both groups.

No difference was observed in the QOL between the AGE and control group, not only before but also at 3 and 6 month of the study. The NK cell count and NK cell activity were not different between the AGE and control group before and after 3 month after study treatment began, in fact it showed an insignificant increase in both groups, more significant in the treatment than in the control group. However in 22% of the patients of the control group the NK cell activity decreased rapidly (by 25% or more), whereas none of the patients in the AGE group showed a decrease in NK cell activity. Only 1 of the patients in whom NK cell activity did not decrease died within the following 3 month but 3 (60%) of the 5 patients in whom NK cell activity decreased by 25% or more died within the following 3 month. The SAC concentration in the blood of treatment and control group showed an increase, but less markedly in the control group than in the treatment group. The researchers think that also patients in the control might have taken over the counter garlic preparation, despite they had been instructed not to do so. This could explain that both groups showed some increase of NK cell number and activity. There was no significant change in the CD8+ cells but CD4+ cells significantly increased in the control group. The researchers think that increased inflammation caused by cancer progression might be responsible. No significant difference was observed in the salivary cortisol concentration or the value of blood biochemical parameters between the AGE and the control group either before or after 3 month of administering treatment, but the salivary cortisol increased significantly after 3 month in the control group.

Jadad's scale 5 points (high quality trial): 2 points for adequate randomisation, 2 points for adequate double blinding and 1 point for mentioning number and reasons for drop outs.

RCT assessment: the trial has been adequately randomised. The control and treatment group have been similar at the start of the trial. All patients had advanced inoperable cancer of colon, pancreas or liver and where suitable for palliative treatment options only. The QOL and blood parameters were comparable at the start of the trial. The patients were treated equally apart from the allocated treatment. All the patients who entered the trial were accounted for: numbers and reasons for drop outs were clearly stated. Losses to follow up were > 20% in both groups. The RCT appraisal guidelines state that the losses should be minimal < 20% especially if few patients have the outcome of interest. The study was adequately double blinded, treatment and control group received identical placebo capsules and assessors could not be aware of the patient's treatment. In this trial the double blinding is especially important for the QOL assessment, which is mainly subjective. The blood results, which are objective are less dependent on double blinding.
No estimations about how large the treatment effect is have been made, but the results proved to be statistically significant.
A power calculation has been done at the beginning of the trial, which established that the minimal number of patients which need to be included in the trial is 40. 50 patients have been included in the trial. Totally there were 14 drop outs, which reduce the number of patients with available end results down to 36. Even if the end results showed some statistically significant results (decline of NK cell activity and increase of salivary cortisol in control group) the number of patients still needs to be considered to small to deduct a definitive conclusion from this trial.

All together the trial is very well done. Even if the number of patients hasn't been sufficient to make definitive conclusions, the trial certainly shows a tendency for AGE to have beneficial effects. Considering the possibility that also patients in the control group might have taken additional AGE or garlic after they had been informed about the beneficial effects during the process of informed consent, this actually means that the effects of AGE would be underestimated not overestimated in this trial because of the smaller differences in the end results between the two groups.
Garlic is a spice, which is widely available everywhere and could easily be integrated in patient's diet as supportive measure.

Discussion:

I was able to include thirteen trials in my systematic review. They have been discussed in detail in the previous section. Ten trials have been of high quality. Five of these high quality trials have been of very high quality and reached the maximum of five points on the Jadad's scale. Four of these very high quality trials were investigating ginger for prevention of acute and delayed CINV and one trial was investigating garlic in patients with palliative cancers of liver, colon and pancreas. Two trials reached 4 points on the Jadad's scale. They were investigating Tinospora cordifolia for prevention of mucositis in patients with head and neck cancer receiving Radiotherapy and ginger for CINV. Three trials reached 3 points on Jadad's scale. They were investigating Rasayana Avaleha, Amrit Kalash and Vitexina radiata as supportive treatments against chemotherapy induced side effects. Three trials were of low quality and only reached two points on the Jadad's scale: Brahma Rasayana and Amrit Kalash as supportive treatments against chemotherapy induced side effects and ginger against CINV.

The majority of high quality trials (5/10) investigated ginger treatment in acute and delayed CINV. Besides reaching a high number of points on the Jadad's scale these trials also proved to be well done as per RCT assessment guidelines. Except the trial from *Zick et al*(2009), which did not show any significant influence of ginger on acute or delayed CINV, the other trials showed significant improvement of delayed CINV, which was comparable to the effect of metoclopramide (Manusirivithaya *et al.,* 2004*)*, a comparable effect of ginger and metoclopramide in acute phase vomiting (Sontakke *et al., 2003)*, significant improvement of acute and delayed CINV with high doses of ginger (Pillai *et al*., 2011*)* and significant effect of ginger on acute CIN when starting ginger treatment three days before chemotherapy (Ryan *et al*., 2011*)*. Except the trial from *Ryan et al ,* which included a considerable number of patients, the number of patients included into the trials was relatively low. Some of the trials made up for a low number of patients by using crossover design. But despite some trials have only been able to include a low number of patients there have still been statistically significant results. The trials from *Zick et al, Manusirivithaya et al, Sontakke et al* and *Pillai et al* did all confirm the efficacy of ginger in CINV.

A pharmacologic study, which gives some explanation why ginger could have a positive effect on CINV has recently been published. The study confirmed that some of the biochemical compounds contained in ginger have antagonistic action on 5-HT3 (serotonin) receptors (Abdel- Aziz *et al*., 2005). 5-HT3 receptors play an important role in CINV (Hesketh,2008). Also Ondansetron, a very potent antiemetic frequently used in CINV is antagonising the same receptor (Hesketh, 2008).

The reported number of side effects caused by ginger was relatively low in all trials. *Zick et al* and *Pillai et al* report that ginger has been well tolerated. *Ryan et al* report nine adverse events caused by ginger (heartburn, bruising/flushing and rash). An unexpected finding in the trial from *Zick et al* was the negative interaction between ginger and aprepitant. When combined, symptoms became worse.

Possible reasons for patients not showing to many side effects might be the cautious inclusion and exclusion criteria; Patients on warfarin, aspirin, heparin, patients with liver disorders and patients with clotting disorders have been excluded from the trials. The decisions to use these criteria has most likely been based on knowledge available from studies which show inhibition of platelet aggregation (Nurtjahja *et al*., 2003; Koo *et al,* 2001) by ginger and case reports which show increased anticoagulant effect of warfarin when combined with ginger (Kruth *et al*., 2004; Lesho *et al*., 2004).

Some of the side effects mentioned in the trial of *Ryan et al* might have been avoided if basic principles from ayurvedic medicine would have been followed. These principles are however not based on clinical trials but are documented in ayurvedic medicine books. Amongst others ginger is described to have pungent, heating, dry, light and penetrating qualities (Pole, 2006, Part II, chapter 6). In dried ginger these qualities are even more prominent than in fresh ginger (Pole, 2006). Therefore ginger shouldn't be given to patients who already have symptoms of heat and inflammation in their body like hot flushes, sweating, red irritated skin, loose stools, diarrhoea and heartburn; ginger will very likely make these symptoms worse.

In none of the trials, which I have included in my literature review, emphasis has been put on interactions between ginger and chemotherapeutic agents. As hardly any adverse events provoked by ginger have been mentioned in the trials we can assume that there are no dangerous interactions when combining ginger and chemotherapy. Also whilst doing my extensive database search for the literature review, I didn't come across any studies which described interactions between ginger and chemotherapeutic agents.

Ginger seems efficient and safe to use if the necessary precautions are followed. Some questions about the optimal dose of ginger (0.5-1.0 g/day) and at which point to start ginger treatment (ideally 3 days before chemotherapy) have been answered in the trials.

In addition to the antiemetic effects ginger would have other qualities, from which patients on chemotherapy and radiotherapy could benefit. These qualities haven't necessarily been investigated in clinical trials. Ginger stimulates appetite and the secretion of digestive enzymes, is antispasmodic, toxin digesting and reduces mucous (Pole, 2006). Especially the appetite stimulating quality might be

a lot of help for chemotherapy patients, which tend to suffer from a very low appetite (Griffin *et al*., 1996).

In this next section I will discuss the high quality trial by *Ishikawa et al* (2006). It reaches 5 points on the Jadad's scale and proves to be a good quality trial as per RCT assessment guidelines. Unfortunately the included number of patients is to small and the statistical power of the results insufficient. However the trial was certainly sufficient to show a tendency of garlic to prevent the drop of NK cells in patients on palliative cancer treatments. Further trials with larger numbers of patients should be done to confirm the results. Despite not having sufficient scientific evidence in this actual trial for the efficacy of garlic, another study showed increase of NK cells, NK cell activity and increase in macrophages in mice after they have been given AGE (Kyo *et al*., 2001). These study could support the results found in the trial from *Ishikawa et al* .
The main active components of garlic have been identified (Amagase *et al*., 2001). But I couldn't find any trials which give an explanation why garlic has immunomodulatory effects.
1-3 cloves of garlic daily are recommended to have beneficial effects (Pole, 2006). 1-3 cloves of garlic per day and person, is an amount which can easily be integrated in everyday meals; and because of the recommendation of Pole (2006) we can assume that a regular dietary consumption of garlic wouldn't do much harm. But caution should be used, if consuming AGE in which the active compounds of garlic are more concentrated than in fresh garlic. Garlic constituents can modulate the activity of CYP enzymes in the liver (Foster *et al.,* 2001). Therefore drugs, which are metabolised through these enzymes like warfarin (Evans, 2000) and the HIV medications saquinavir (Piscitelli *et al*., 2002) and ritonavir (Laroche *et al*., 1998) shouldn't be combined with garlic supplements. Patients, who have to take these medications regularly, should be advised not to take AGE on a daily base. But if they want to take some garlic preparations they should prefer a small amount of fresh garlic cloves.

I will discuss the trial of *Amrutesh et al* (2010) now. It reached 4 points on the Jadad's scale and also the RCT assessment proved the trial to be of high quality. The trial showed that patients treated with Tinospora cordifolia and honey during a whole course of radiotherapy developed only mild forms of oral mucositis whereas the patients in the control groups developed more severe forms of mucositis. Also in this trial the included number of patients was to low and follow up trials with larger numbers of patients would be necessary to make a more evidence based statement about the efficiency of Tinospora cordifolia and honey.

Some recently published study could support the findings in the trial of *Amrutesh et al*. Tinospora cordifolia showed radioprotective effects in mice exposed to lethal doses of radiation (Pahadiya and Sharma, 2003). It induced enzymes of antioxidant system and in that way inhibited lipid peroxidation in mice. Lipid peroxidation by free radicals is one of the mechanisms by which radiotherapy produces its severe side effects (Rubin et al., 1995). If Tinospora cordifolia can prevent this from happening and if it exhibits the same mechanism of action in humans, these findings would be an amazing support for patients undergoing radiotherapy.

In addition to Tinospora cordifolia, honey, which had to be taken orally, has been given for the whole duration of radiotherapy. Two studies have been done, which showed the beneficial effects of topical application of honey in prevention of oral mucositis in radiotherapy patients (Motallebnejad *et al*., 2008) and in the management of wounds (Dudhamal *et al*, 2010). The authors of this second study listed some factors which could explain the efficacy of honey: hygroscopic properties, acidic ph, enzymes, minerals and vitamins, which help to repair tissue directly.

It certainly can be said that the trial from *Amruthesh et al* combines two substances which both seem very efficient in radioprotection.

Tinospora cordifolia can be used safely. When given with radiotherapy there is certainly no danger of herb- drug interactions. A study published in 2007 showed that 500 mg Tinospora cordifolia per day taken by healthy volunteers for 21 days did not provoke any adverse advents (Karkal and Bairy, 2007) . Other clinical studies about beneficial effects of Tinospora cordifolia in liver disorders (Keche *et al.,* 2011) and allergic rhinitis (Badar *et al*., 2004) have been published. In none of those studies any severe adverse events have been noted.

I will continue with discussion of the trial from *Hien et al* (2002) now. It reports prevention of radiotherapy side effects low blood count, weight loss and heat symptoms by Vitexina radiata extract, which the patients had to take during their whole radiotherapy treatment. Even if the 3 points on Jadad's scale still qualify the trial to be of high quality the RCT assessment points towards a few structural faults in the set up of the trial and in the reporting of the results. Further trials have to be done to confirm these results.

Vitexina radiata or Phaseolus radiata, which is the green mung bean is frequently used in the far east and asia as part of the daily diet. In the study from *Hien et al* green gram has simply made more potent by producing an extract. For patients receiving radiotherapy, which is likely to produce low appetite (Griffin *et al.,* 1996) and nausea (Partridge *et al*. 2001) the prescription of tablets, which allows to take a small amount of highly concentrated green mung bean, was certainly a safe way to

make sure that each study participant was able to take the necessary amount of medicine. By prescribing tablets it was also easier to double blind the trial.
The fact that Vitexina radiata is used as a food product by large parts of the asian population, should allow us to make the conclusion that Vitexina radiata is quite safe even when consumed regularly.
Charaka Samitha described green mung to be unctuous, heavy, sweet and strength promoting amongst other qualities (Sharma *et al*., 2009; Sutrasthana, chapter XXVII, verses 23-34). A recent study found green mung to have free radical scavenging capacity (Lee *et al*., 2000ab),a mechanism, which potentially protects lipids from oxidative damage. This free radical scavenging capacities could be an explanation why the study from *Hien et al* found Vitexina radiata to have radioprotective effects. As we have seen earlier, free radicals, generated during radiotherapy is one of the main mechanisms for radiotherapy induced tissue damage (Rubin and Farber, 1995).

In the next section I will finally discuss the trial from *Vyas et al* (2010)*, Saxena et al* (2008) and *Joseph et al* (1999). I will discuss the trials together because the investigated preparations have some similarities even if the names are different: Brahma Rasayana, Rasayana Avaleha and Amrit Kalash (Appenidx 5). When looking at the main ingredients of these formulations it immediately strikes that some of the ingredients are also part of the very ancient formulation Cyavanaprash (Sharma *et al*., 2009; Chikitsasthanam, chapter I, verses 62-74 + Appendix 5).
Cyavanaprash is said to increase resistance to infectious disease, build haemoglobin and white blood cells, increase muscle mass and tissues, facilitate recovery from illness and disease, to help clear phlegm from the lung and to be rejuvenating (Pole, 2006, part II, chapter 7).
Brahma Rasayana is mentioned in Charaka samhita and Astanga Hrdayam as a formula, which differs from Cyavanaprash (Sharma et al., 2009; Chikitsasthanam, chapter I, verses 41-61. Murthy, 2008; Uttarasthana, chapter XXXIX, verses, 24-32) On comparison quite a few ingredients of Brahma Rasayana are also contained in Cyavanaprash. The mode of preparation is comparable as well. But additionally, Brahma Rasayana contains herbs which have a positive effect on the central nervous system like Evolvulus alsinoides, Acorus calamus and Centella asiatica (Pole, 2006; Part II, chapter 7; pp 269, 284, 187)
When looking at the ingredients of Amrit Kalash and Rasayana Avaleha, the ingredients and mode of preparation are also very similar to Cyavanaprash. For Amrit Kalash and Rasayana Avaleha no documentation can be found in the ancient scriptures of Caraka Samhita and Sushruta Samhita. But the authors of the trials, in which Amrit Kalash and Rasayana Avaleha have been tested, seem to have deducted their own formulas from of the old original one.

The trial from *Joseph et al* showed that patients on Brahma Rasayana had higher nadirs of white cells and neutrophils, higher GM-CSF levels and lower serum lipid peroxide levels than control patients. The number of included patients however has been very small and no statistical calculations have been done in this trial.

Vyas et al reported that patients on Rasayana Avaleha showed a marked improvement of chemotherapy side effects like nausea, vomiting, mucositis, fatigue and a moderate improvement of xerostomia and tastlesness compared to control group. Also the weight loss was less in the Rasayana Avaleha group. Unfortunately there is an unexplained high dropout rate which makes the included number of patients insufficient.

The trial from *Saxena et al* is of high quality. The trial also proved to be well done as per RCT assessment. A considerable number of patients had been included and the dropout rate was low, which makes the results more significant.

The assessment of the above mentioned three trials shows that the trial from *Saxena et al* is the one most valid to base clinical decisions on and to recommend Amrit Kalash to chemotherapy patients. Chyavanaprash could be given instead of amrit kalash, because of the similarity of the ingredients and because of the easy availability in European countries. But to make this statement based on evidence it would be necessary to prove it in another well structured RCT.

Support for the results of the trial from *Saxena et al* can also be found in other studies, which explain some mechanisms of action of the herbs which are contained in Amrit kalash or Chyavanaprash. One of the most important ingredients is Emblica officinalis. In vitro and animal studies showed cytoprotective, antioxidant and immunomodulatory qualities (Bhattacharya et al., 1999; Kumar et al., 2004).

In another trial it has been demonstrated that pre treatment of rats with Asparagus racemosus, Withania somnifera and Tinospora cordifolia prevented Cyclophosphamide induced neutropenia (Thatte et al., 1987).

A trial with geriatric patients, which have been given a formulation containing Capparis spinosa, Terminalia arjuna, Withania somnifera, Asparagus racemosus, Glycyrrhiza glabra, Centella asiatica and Curcuma longa demonstrated a significant increase in antioxidant status, which was determined by superoxide dismutase, catalase, gluthatione peroxidase, gluthatione reductase, reduced glutathione and malondialdehyde (Banerjee et al., 2011). Except Capparis spinosa and Terminalia arjuna all the ingredients of the above formula are also contained in Amrit Kalash and Chyavanaprash.

Antioxidant activity of Curcuma longa has been proven several trials as well (Motterlini *et al.,* 2000; Selvam *et al*., 1995; Jagetia 2007). And treatment of healthy volunteers with Ocimum sanctum

showed a significant increase in the levels of IFN-γ, IL-4 and percentages of T helper cells and NK cells after four weeks of an extract of Ocimum sanctum (Mondal *et al*. 2011).
It would exceed the limits of this dissertation to discuss all the ingredients of Chyavanaprash and Rasayana Avaleha, Amrit Kalash and Brahma Rasayana respectively, which have been investigated in the trials of *Vyas et al, Joseph et al* and *Saxena et al.*
But I would like to go briefly into the importance of the concept of free radicals and antioxidants, which has been mentioned quite a few times during this discussion as an explanation for the beneficial effects of herbs used in ayurvedic medicine.
Basically, free radicals or reduced oxygen species (transfer of varying numbers of electrons between O2 and H20 molecule) like superoxide (02^-), hydrogen peroxide (H202) and hydroxyl radical (OH^-) can be generated by inflammation, chemical toxicity, like drug therapy and ionizing radiation (Rubin et al, 1995, chapter I; Sies, 1997). Drug therapy and radiation are particularly important causes in this context. There are several mechanisms by which free radicals can damage cell membranes and DNA, which leads to loss of membrane integrity and cell death as a final consequence (Rubin et al., 1995; Machlin and Bendich, 1987; Sies 1997).
Antioxidants can inhibit damage of cell membranes and cell death. Antioxidants can directly scavenge free radicals (Machlin and Bendich, 1987), increase the levels of the antioxidant defence enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) and support antioxidant enzymes in their function (Machlin and Bendich, 1987) .
Important antioxidants contained in plants are Selenium, Mangan, Copper, Zinc, vitamins C, E, carotenoids, flavonoids and polyphenols, which have been detected in a considerable amount of plants, used in ayurvedic medicine (Gupta *et al.,* 2006). Curcuma longa, Emblica officinalis, Foeniculum vulgare, Ocimum sanctum, Withania somnifera, Tinospora cordifolia is just a small selection of antioxidants containing plants; the list would in fact be much longer (Gupta *et al.,* 2006).

Conclusion:

It seems that the plants used in ayurvedic medicine are a treasure chest, which just needs to be opened and explored. There are so many plants out there which only wait to be investigated and tested in clinical trials.
As this dissertation shows, a movement for investigating herbal remedies with modern research methods seems to have started. The amount of clinical trials, concerning my topic, which I could actually include in my systematic review really surprised me. Some of the included trials showed amazing results and proofed the effectiveness of herbal remedies like ginger, and amrit kalash.

Other trials, which were of good quality but unfortunately with a small number of patients, also showed some impressive tendencies about how herbal remedies could support cancer patients during their treatments. Tinospora cordifolia, garlic, Vitexina radiata were some of these plants, which proofed to have positive effects but concerning my particular question would need more investigations with larger trials. As we have seen in the above discussion supportive evidence can come from other clinical trials which investigate these herbs. The questions asked in these trials might be different or the trials might not be with patients but with animals or in vitro studies but the results still might allow us to infer knowledge.

All together the use of herbal remedies as supportive treatments during chemo- and radiotherapy seems to be a promising approach to prevent or improve very distressing symptoms, which can very much deteriorate the quality of life of the affected patients.

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Appendix 1: Included Trials

Study	Study Design	Sample	Inclusion Citeria	Complementary Therapies:	Control Treatment:	Outcome Measures:	Results	Methodology Comments:	Clinical comments:
Joseph et al (India 1999)	RCT, Pilot Study Duration 30 days	20 patients, various cancers Normal FBC and LFTs Control group N=10 (chemo +RT) Treatment group N=10 (chemo+RT +Brahma Rasyana)	no prior exposure to cancer drugs, Karnofsky functional scale >50%	Brahma Rasayana (BR), 50 mg/d po in 3 split doses after meals for one month	RT max 6000cGy in 30 fractions chemos: Cisplatin cyclophos-phamide,Etopo-side, 5-FU, Mitoxantron in various combi-Nations, no placebo	blood test: determination of WC, differen-tial count, Plt count, Bili, Urea, Crea, GPT, Lipid-peroxide, G-CSF, M-CSF	BR accelerated recovery of patients treated with RT and ChT. Rapid rise in Lc and Neutr count Nadir levels of Wc and Lc high in BR administered patients	adaequate randomisation, no double blinding used, no drop outs, small sample size, but is pilot study	appropriate inter-vention, objective outcome measure, Brahma Rasayana from Vaidyarathnam Oushadhasala, India (as per mail enquiry: formula from Murthy, 2008, Uttarasthana, chapter XXXIX, verses 24-32)
Pecoraro et al (USA 1999) Abstract only	RCT, crossover duration 3 month	12 patients, treatment-(ginger) and placebo group with crossover design	none mentioned	ginger: dose and type of preparation not mentioned	placebo	CINV, but nothing precise mentioned	total response in 34% and 18% in ginger versus placebo treated patients; partial response in 58% and 83% ginger versus placebo treated patients 8% treatment failure in ginger group, none in control group	randomisation and double blinding used, no statement about drop outs, small sample size	insufficient information about patients and assessment criteria

Vyas et al (India 2010)	RCT duration 75 days	36 carcinoma patients 23 in treatment group (ChT + RT + Rasayana Avaleha/RA) 7 drop outs 13 in control group (ChT + RT) With 4 drop outs	diagnosed Carcinoma T1 or T2, submitted to RT, ChT or both, age 16-70, with acute short term adverse effects	Rasayana Avaleha 30 g in the morning with 10 ml ghee for 75 days	RT 1.8-2 gray/day 5 fractions/week total 60-70 gray ChT according to cancer type no placebo	grading of adverse effects as per guidelines of National cancer institute: gradding of nausea and vomiting, mucositis, fatigue, xerostomie, alopecia, tastelesness	RA: significant results, on nausea vomiting, mucositis and fatigue. Decrease of xerostomia, alopecia and tastlesness	adaequate randomisation, no double blinding, numbers but not reasons for withdrawals mentioned	subjective assessment, high drop out rate, Rasayana Avaleha formula deducted from Cyavannaprash Avaleha formula and prepared in Jamnagar university hospital pharmacy
Saxena et al (India 2008)	RCT duration 5 years + 9 month	totally 214 breast cancer patients,n= 102 treatment group (adjuvant or neoadjuvant ChT + Amritkalash) 7 drop outs, n=112 Control group (adjuvant or neoadjuvant ChT), 16 drop outs	histologically confirmed breast cancer, no Diabetes	Amrit kalash:, MAK-4 paste 2 TbS BD with 1 glass of milk and MAK-5 2 Tbl BD with water, ½ hour after MAK-4 through whole ChT, approx. 18 weeks	ChT: CMF cyclophosphamide, methotrexate, 5-FU or CAF cyclophosphamide, adriamycin, 5-FU supportive treatments, no placebo	toxicity of ChT assessed according WHO criteria. Tumor regression according EORTC response criteria	Prevention of poor performance status vomiting and anorexia in MAK group. no improvement in stomatitis, leucopenia alopecia and diarrhoea	adaequate randomisation, no double blinding, number and reason for drop outs mentioned	sufficient number of patients included, subjective and objective assessment.Formula for Amrit kalash deducted from ancient ayurvedic formula for Chyavanaprash avaleha.

Srivastava et al (India 2000) Abstract only	RCT duration: over 6 cyles of ChT, Intervals not defined	129 breast cancer patients, n=61 treatment group (ChT amrit kalash. n=68 control group (ChT only)	none mentioned	MAK-4 paste, 1 TbS BD with milk + MAK-5 1 Tbl BD with water, duration not mentionned	ChT: CMF or CAF, no placebo, supportive treatment, duration not mentionned	assessement of adverse treatment effects and Karnofsky performance status	maintenance of performance, appetite and body weight in MAK group, statistically insignificant reduction of diarrhoea, alopecia, stomatits leucopenia	adaequate randomisation, no double blinding, no statement about drop outs	quite a bit of information missing (? duration of treatment, assessment guidelines, how many drop outs, original condition of patients) as abstract only
Amruthesh et al (India 2010)	RCT duration 8 weeks	15 patients with SC Carcinoma of head and neck, age 30-70, study group n= 8 (RT + Tinospora cordifolia), control Group n=7 (RT only)	first time RT with Co 60, 4000 rads and above , parotid and salivary gland have to be in RT field	20 mg Tinospora cordifolia daily with honey for 8 weeks, starting 15 days prior to RT	Placebo (millet flour with sirup) along with RT	measuring stimulated saliva, grading of mucositis as per WHO	significant reduction of mucositis in treatment group, less reduction of saliva in treatment group	adaequate randomisation and double blinding, no statement about drop outs, small sample size	small patient number, objective assessment, no quality criteria for herb of interest, Tinospora cordifolia mentionned

Hien et al (Vietnam 2002)	RCT duration 6 weeks	72 stage II or III breast Ca patients, post surgery for prim Ca breast study group n=36 (RT + Vigna radiata) control group n= 36 (RT only)	Indication for RT post surgery	extract from V. radiata (Cps containing 100 mg extract of V. radiata) 4 Cps daily for 6 weeks during RT	4 placebo Cps daily for 6 weeks during RT	assessement of body weight and RT side effects, not mentioned which criteria used, determination of FBC GOT, GPT,blast transformation	side effects not noticeable in treatment group, no relevant weight loss in treatment group compared to control. Advantage for treatment group in Ec, Lc and Tc counts	randomisation used, but unclear which method. adaequate Double blinding. no statement about drop outs	good number of patients included but unclear if and how many of them dropped out of the trial. adequate intervention, subjective and good objective assessment, standardised preparation of V. radiata cps by pharmaceutical company
Manusirivithaya et al (Thailand 2004)	RCT (crossover design) duration over 2 ChT cycles, 3-4 week intervals	48 gynecologic cancer patients with cisplatin containing chemo study group (chemo+ ginger) control group (chemo + placebo)	cisplatin containing ChT, dose 75 mg per m² alone or combination with other ChT agents, at least 2 cycles of same dose and schedule	2 Cps containing 250 mg powdered ginger root 30 min before ChT, then 1 Cps 6 and 12h after ChT day 1. day 2-5 1 Cps of ginger 250 mg QDS, standard antiemetics day 1	2 Cps placebo 30min before ChT, then 1 Cps 6 and 12 h after ChT. day 2-5:1 placebo Cps QDS. Standard antiemetics day 1	assessement of CINV in first 24 h by hospital investigators. Day 2-5: recording of symptoms in patient diary;intensity of vomiting recorded by VAS, Number of emetic events recorded	no significant difference of CINV in acute and delayed phase between the two groups. Insignificant higher incidence of side effects in metoclopramide group	randomisation not mentioned which method adaequate double blinding number but not reason for drop outs mentioned	adequate number of patients, adequate intervention, no quality control for ginger, but widely available spice, used in everyday diet in asian countries

Zick et al (USA 2009)	RCT duration: 1 Cycle of ChT	162 patients with div. cancers age 18+, on adjuvant, neoadjuvant curative or palliative ChT, study group 1 n=53 (ChT+ 1.0 g ginger) 10 drop outs, study group 2 n=52 ChT+ ginger 2.0g) 12 drop outs control group n=57 (ChT+ placebo) 11 drop outs	histologically confirmed cancer treatment with adjuvant, neo-adjuvant, curative or palliative ChT CINV during at least one previous ChT	1g or 2 g ginger daily for 3 days with 5-HT3 Antagonist and/or aprepitant	placebo for 3 days with 5-HT3 Antagonist and/or aprepitant	patient diary based on MANE (Morrow Assessment of nausea and emesis)day 1-3 of ChT. Likert 6 point scale for grading most severe nausea event documentation how long in min nausea lasted verbal queries about adverse events	no significant difference between either dose of ginger and placebo in acute and delayed phase of vomiting, no significant increase of treatment failures in patients who received aprepitant together with ginger compared to those who got aprepitant with placebo	adaequate randomisation and double blinding, numbers and reason for drop outs mentioned	sufficient number of patients, well standardised preparation of ginger cps by pharmaceutical company, unexpected interaction ginger and aprepitant
Pillai et al (India 2011)	RCT , duration : over 2 cycles of ChT	31 patients with bone sarcoma, age 8-21, 60 ChT cycles in 31 patients used for randomisation n=30 control cycles; ChT +placebo) n=27 study Cycles (ChT+ginger) totally 3 drop outs	newly diagnosed bone sarcoma, age 8-21, ChT with cisplatin 40 mg/m²/day + doxorubicin 25mg/m²/day for 3 days	BW 20-40kg: 2 cps with ginger 167 mg 1 h before, 3 h and 8h after start of ChT. BW 40-60 kg 2 cps with 400 mg ginger 1h before, 3 h and 8 h after start of ChT. Stan-antiemetics in both groups	BW 20-40 kg: 2 cps placebo (167 mg starch powder 1h before, 3h and 8 h after start of ChT BW 40-60 kg: 2 cps with 400 mg starch powder 1 h before, 3h and 8h after start of ChT. standard antiemetics in both groups	patient diary: grading of nausea and vomiting with ESAS (Edmonton symptom assessment scale) and NCI (National Cancer Institute) guidelines. Number and amount of vomitus per day graded as per NCI guidelines	moderate to severe vomiting was signifyscantly more in control group as compared to study group in the acute as well as the delayed phase of CINV	adaequate randomisation and double blinding. statement about number and reason for drop outs	average patient number, mainly subjective assessment, well standarddised ginger cps, prepared by pharmaceutical company, adequate intervention

Ryan et al (USA 2011)	RCT, duration: over 3 cycles of ChT	744 patients with div. cancers, age > 18, Control group n=188 (ChT +placebo), Study groups n=183 (ChT+0.5g ginger), n=187 (ChT+ 1.0g ginger) n=187 (ChT+ 1.5g ginger) final Data available for 576 patients	confirmed cancer scheduled for >3 ChT cycles, ChT without RT or Interferon at the same time, patient must have experienced nausea in previous cycle	Cps with ginger extract 250 mg: 0.5 ginger/d. (2 placebo +1 ginger cps BD 1g ginger/d: (1 placbo+2 ginger cps BD) 1.5 g ginger/d: (3 ginger cps BD) standard antie-Metics. Start of Study medication 3 days before ChT For totally 6 days	250 mg Placebo cps 3 Cps BD Standard Antie-metics. start of placebo 3 days before ChT for totally 6 days	4 day patient diary recording developed by Burish and Carey: Rating of CINV with 7 point semantic rating scale 4x per day on day 1-4 of each ChT cycle. 13 item symptom Inventory to assess adverse effects of ginger and anticipatory nausea	all doses of ginger significantly reduced acute CIN compared to placebo. 0.5+ 1.0g ginger were most effective. no significant reduction in delayed nausea in all the ginger groups compared to placebo	randomisation, unclear which method used, adaequate double blinding, statement about number and reason for drop outs	very high number of patients included, mainly subjective assessment, well standardised ginger extract from pharmaceutical company, adequate intervention
Sontakke et al (India 2003)	RCT, crossover design,duration 3 ChT cycles	60 patients with various cancers and cyclophosphamide containing ChT age > 18. Study group (ginger+ChT) Control group 1 (lactulose, metoclopramide + ChT) control group 2 (ondansetron +ChT), Totally 10 drop outs	histologically confirmed malignancy, Cyclophosphamide containing ChT. At least 2 episode of vomiting in previous ChT cycle	Cps with 500 mg ginger powder, 2 Cps 20 min prior to ChT and 6 h after ChT, 2ml NaCl iv 20 min prior to ChT	Control 1: 2 Cps of Lactulose po 20 min prior to ChT. 20 mg i.v Metoclopramide 20 min prior ChT + 2x 5 mg cps metoclopramide 6h post ChT.Control 2: 2 cps Lactulose po 20 min prior ChT, Ondansetron 4 mg i.v. 20 min prior ChT. 2x 2mg cps ondansetron 6 h post ChT	routine haematolgic, biochemical assessement before each ChT. time and number of episodes of vomiting was recorded 24h post ChT whilst patient was on ward. Subj. Assessment of Severity of adverse events	antiemetic effect comparable to metoclopramide. Ondansetron was found to be better than both. Ginger most effective in CINV induced by cyclophosphamide in combination with mildly emetogenic cytotoxics	randomisation, method not mentioned, adaequate double blinding, number and reason for drop outs mentioned	good patient number, optimised by cross-over design subjective and objective assessment, ginger from local market, identified from university botany department and prepared by local pharmaceutical company, adequate intervention

Ishikawa et al (Japan 2006)	RCT, duration 24 weeks	50 patients, aged 20 or more with advanced Inoperable liver, Pancreas or colon ca Study group n= 25: AGE (8 drop outs) Control group n=25 Crystalline cellulose (6 drop outs)	see sample section	2 cps of AGE after breakfast and after dinner, Totally 4 cps daily Containing 500 mg Of AGE each	2 cps of placebo after breakfast and after dinner, totally 4 cps daily	blood and saliva samples before and 3month after start of study treatment. FACT 28 questionnaire Before, after 3 And 6 month Of treatment	no difference in QOL between the groups at 3 and 6 month. No difference in NK cell count and activity. Rapid decrease of NK cells in control group, but not AGE group	adequate randomisation, and double blinding, numbers and reasons for outs mentionned	small patient number, high drop out rate, mainly objective assessment, adequate intervention, well standardised preparation of AGE cps by pharmaceutical company

Appendix 2 : Excluded Trials

Excluded Trials	Study type	Reason for exclusion
Gail et al (USA 2010)	RCT	concord grapes are grape cultivar, different from original grapes (vitis vinifera), which are mentioned in ayurvedic scriptures
Levine et al (USA 2008)	RCT	use of proteins together with ginger isn't part of ayurvedic medicine.
You et al (Taiwan 2009)	RCT	indigowood root (Isatis indigotica) isn't a plant which has been mentioned in ayurvedic sriptures
Misra et al (India and USA 1994)	CCT	
Acharya (India 1994)	CCT	
Acharya (India 2002)	CCT	

Appendix 3: Jadad's scale (Jadad et al., 1996)

Read article and try to answer following questions:

1. Was the study described as randomised (this includes the use of words such as randomly, random and randomisation)

2. Was the study described as double blind?

3. Was there a description of withdrawals and drop outs?

Scoring:
Either give a score of 1 point for each "yes" or 0 points for each "no". There are no in between marks.

Give 1 additional point if:	For question 1, the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer generated etc)
and/or:	If for question 2, the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy etc)
Deduct 1 point if:	For question 1, the method to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number etc)
and/or:	For question 2, the study was described as double blinded but the method of blinding was inappropriate (e.g. comparison of tablet vs. Injection with no double dummy)

Guidelines for assessment:

1. Randomisation

A method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

2. Double blinding

A study must be regarded as double blind if the word “double blind” is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

3. Withdrawals and dropouts

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, the item must be given no points.

Appendix 4

Critical Appraisal for Therapy Articles

THERAPY STUDY: Are the results of the trial valid? (Internal Validity)

What question did the study ask?

Patients -

Intervention -

Comparison -

Outcome(s) -

1a. R- Was the assignment of patients to treatments randomised?	
What is best?	Where do I find the information?
Centralised computer randomisation is ideal and often used in multi-centred trials. Smaller trials may use an *independent* person (e.g, the hospital pharmacy) to "police" the randomization.	The ***Methods*** should tell you how patients were allocated to groups and whether or not randomisation was concealed.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
1b. R- Were the groups similar at the start of the trial?	
What is best?	Where do I find the information?
If the randomisation process worked (that is, achieved comparable groups) the groups should be similar. The more similar the groups the better it is. There should be some indication of whether differences between groups are statistically significant (ie. p values).	The ***Results*** should have a table of "Baseline Characteristics" comparing the randomized groups on a number of variables that could affect the outcome (ie. age, risk factors etc). If not, there may be a description of group similarity in the first paragraphs of the ***Results*** section.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
2a. A - Aside from the allocated treatment, were groups treated equally?	
What is best?	Where do I find the information?
Apart from the intervention the patients in the different groups should be treated the same, eg., additional treatments or tests.	Look in the ***Methods*** section for the follow-up schedule, and permitted additional treatments, etc and in ***Results*** for actual use.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
2b. A - Were all patients who entered the trial accounted for? - and were they analysed in the groups to which they were randomised?	
What is best?	Where do I find the information?
Losses to follow-up should be minimal – preferably less than 20%. However, if few patients have the outcome of interest, then even small losses to follow-up can bias the results. Patients should also be analysed in the groups to which they were randomised – '*intention-to-treat analysis*'.	The ***Results*** section should say how many patients were andomised (eg., Baseline Characteristics table) and how many patients were actually included in the analysis. You will need to read the results section to clarify the number and reason for losses to follow-up.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
3. M - Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	
What is best?	Where do I find the information?
It is ideal if the study is 'double-blinded' – that is, both patients and investigators are unaware of treatment allocation. If the outcome is *objective* (eg., death) then blinding is less critical. If the outcome is *subjective* (eg., symptoms or function) then blinding of the outcome assessor is critical.	First, look in the ***Methods*** section to see if there is some mention of masking of treatments, eg., placebos with the same appearance or sham therapy. Second, the ***Methods*** section should describe how the outcome was assessed and whether the assessor/s were aware of the patients' treatment.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	

What were the results?

1. How large was the treatment effect?

Most often results are presented as dichotomous outcomes (yes or not outcomes that happen or don't happen) and can include such outcomes as cancer recurrence, myocardial infarction and death. Consider a study in which 15% (0.15) of the control group died and 10% (0.10) of the treatment group died after 2 years of treatment. The results can be expressed in many ways as shown below.

What is the measure?	What does it mean?
Relative Risk (RR) = risk of the outcome in the treatment group / risk of the outcome in the control group. In our example, the RR = 0.10/0.15 = 0.67	The relative risk tells us **how many times more likely** it is that an event will occur in the treatment group relative to the control group. An **RR** of **1** means that there is no difference between the two groups thus, the treatment had **no effect**. An RR < 1 means that the treatment decreases the risk of the outcome. An RR > 1 means that the treatment increased the risk of the outcome. Since the RR < 1, the treatment decreases the risk of death.
Absolute Risk Reduction (ARR) = risk of the outcome in the control group - risk of the outcome in the treatment group. This is also known as the **absolute risk difference.** In our example, the ARR = 0.15 - 0.10 = 0.05 or 5%	The absolute risk reduction tells us the absolute difference in the rates of events between the two groups and gives an indication of the baseline risk and treatment effect. An **ARR** of **0** means that there is no difference between the two groups thus, the treatment had **no effect**. The absolute benefit of treatment is a 5% reduction in the death rate.
Relative Risk Reduction (RRR) = absolute risk reduction / risk of the outcome in the control group. An alternative way to calculate the RRR is to subtract the RR from 1 (eg. RRR = 1 - RR) In our example, the RRR = 0.05/0.15 = 0.33 or 33% Or RRR = 1 - 0.67 = 0.33 or 33%	The relative risk reduction is the complement of the RR and is probably the most commonly reported measure of treatment effects. It tells us the reduction in the rate of the outcome in the treatment group relative to that in the control group. The treatment reduced the risk of death by 33% relative to that occurring in the control group.
Number Needed to Treat (NNT) = inverse of the ARR and is calculated as 1 / ARR. In our example, the NNT = 1/ 0.05 = 20	The number needed to treat represents the number of patients we need to treat with the experimental therapy in order to prevent 1 bad outcome and incorporates the duration of treatment. Clinical significance can be determined to some extent by looking at the NNTs, but also by weighing the NNTs against any harms or adverse effects (NNHs) of therapy. We would need to treat 20 people for 2 years in order to prevent 1 death.

2. How precise was the estimate of the treatment effect?

The true risk of the outcome in the population is not known and the best we can do is estimate the true risk based on the sample of patients in the trial. This estimate is called the **point estimate**. We can gauge how close this estimate is to the true value by looking at the confidence intervals (CI) for each estimate. If the confidence interval is fairly narrow then we can be confident that our point estimate is a precise reflection of the population value. The confidence interval also provides us with information about the statistical significance of the result. If the value corresponding to **no effect** falls outside the 95% confidence interval then the result is statistically significant at the 0.05 level. If the confidence interval includes the value corresponding to **no effect** then the results are not statistically significant.

Will the results help me in caring for my patient? (ExternalValidity/Applicability)

The questions that you should ask before you decide to apply the results of the study to your patient are:

- Is my patient so different to those in the study that the results cannot apply?
- Is the treatment feasible in my setting?
- Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?

Appendix 5:

Ingredients of Chyavanaprash (Pole, 2006, part 2, chapter 7; Sharma et al. 2009, Chikitsasthanam, chapter I, verses 62-74):

29 mg each of the following:
Tinospora cordifolia (guduchi), Phyllanthus niruri (bhumiamalaki), Pueraria tuberosa (vidari), Curcuma zeodaria (karchur), Elettaria cardamomum (ela), Cyperus rotundus (musta), Boerhaavia diffusa (punarnava), Bambusa arundinaceae (vamsa lochana), Tribulus terrestris (gokshura), Solanum xanthocarpum (kantakari), Adhatoda vasica (vasa), Aegle marmelos (bilva), Vitis vinifera (draksa), Santalum album (chedana), Inula racemosa (pushkaramoola), Sida cordifolia (bala), Asparagus racemosus (shatavari), Crocus sativus (kesar), Cinnamomum zeylanicum (cinnamon), Cinnamomum tamala (tamalapatra), Foeniculum vulgare (satapuspa).
90 mg each of the following: Trikatu (three spices: Piper nigrum, Piper longum, ZIngiber officinale), Triphala (three fruits: Emblica officinalis, Terminalia chebula, Terminalia belerica)
125 mg each of the following
Sesamum indicum (taila), Honey, clarified butter (ghee)
2778 mg of:
Sacharum officinalis (jaggery)
1000 mg of:
Emblica officinalis (amalaki)

Other herbs are also mentioned but for reasons of sustainability and manufacturer choice are not always included (Pole, 2006; part 2, chapter 7):

Aquilaria agallocha (agaru), Gmelina arborea (gambhari), Martynia diandra (kakanasa), Pistacia interrima (karkatshringi), Saussurea lappa (kustha), Solanum xanthocarpum(kantakari), Teramnus labialis (mashaparni), Phaseolus trilobus (mudgaparni), Mesua ferrea (naga keshara), Nymphoea stellata (nilotpala), Stereospermum suaveolens (patala), Uraria picta (prishniparni), Desmodium gangeticum (shalparni), Oroxylum indicum (shyonaka), Dioscorea bulbifera (varahikand), Glycyrrhiza glabra (yasthimadhu)

Ingredients of Brahma Rasayana (Sharma et al., 2009, Chikitsasthanam, chapter I, verses 41-61):

Typ 1:
480 gramms of each following group:
Vidarigandhadya group:
Roots of Pueraria tuberose (vidarigandha), brhati (Solanum indicum), Uraria picta (prusniparni), Solanum xanthocarpum (kantakari), Tribulus terrestris (svadamstra)
Brhat panchmoola group:
Roots of Aegle marmelos (bilva), Premna integrifolia (agnimantha), Oroxylum indicum (syonaka), Gmelina arborea (kasmarya),Trichosanthes dioica (patola)
Punarnavadi panchamoola group:
Boerhavia diffusa (punarnava), both types of Teramnus labialis (surpaparni),Sida cordifolia (bala), Ricinus communis (eranda)
Jivaniya panchamoola group:
Roots of Microstylus wallachii (jivaka), Litsea chinensis (meda), Luffa echinata (jivanti), Asparagus racemosus (satavari)
Trna panchamoola group:
Roots of Sacharum munja (sara)Sacharum officinarum (iksu),Eragrotis cynasuroides (darbha), Sacharum spontaneum (kasha), Oryza sativa (Sali)
1000 fresh fruits of haritaki, 3000 fresh fruits of amalaki
192 gramms of each of the following:
Centella asicatica (mandukaparni),Piper longum (pippali),Convolvulus pluricaulis (shankapuspi), Cyperus scariosus (plava),Cyperus rotundus (musta),Embelia ribes (vidanga),Santalum album (candana),Aquillaria agallocha (aguru),Madhuka indica (madhuka), Curcuma longa (haridra),Acorus calamus (vaca),Mesua ferrea (kanaka), Elettaria cardamonum (suksmaila),Cinamomum zeylanicum (tvak)
52.8 gramm of sugar, 6.144 l til (sesamum indicum) oil, 9.216 l of clarified butter (ghee)

Typ 2:

1000 fruits of Emblica officinalis (amalaki)
1/8 of the amount of Emblica officinalis of:
Desmodium gangeticum (sthira), Boerhavia diffusa (punarnava), Luffa echinata (jivanti), variety of Sida cordifolia (nagabala), brahma suvarcala (not correctly identified), Centella asiatica (mandukaparni),Asparagus racemosus (satavari), Convolvulus pluricaulis (sankhapuspi), Piper longum (pippali), Acorus calamus (vaca), Embelia ribes (vidanga), Mucuna pruriens (svayamgupta),Tinospora cordifolia (amrta),Santalum album (candana), Aquillaria agallocha (aguru), Madhuka indica (madhuka),Nymphaea stellata (utpala),Nelumbium speciosum (padma),Jasminum grandiflorum (malati), yuvati (not correctly identified), Jasminum auriculatum (yuthika)
Clarified butter(ghee) and honey in double quantity

Ingredients of Brahma Rasayana (Murthy, 2008; Uttarasthana, chapter XXXIX, verses, 24-32)

Decoction of 1000 fruits of Terminalia chebula (haritaki), 3000 fruits of Emblica officinalis (amalaki) + drugs of the five pancamoola (not mentioned which of the 5 groups of panchamoola should be used)
Paste of Terminalia chebula (haritaki),Emblica officinalis(amalaki)
192 gramms of powder of Cinnamomum zeylanicum (tvak),Elettaria cardamomum (ela),Cyperus rotundus (musta), Curcuma longa (haridra), Piper longum (pippali), Aquillaria agalocha (aguru),Santalum album (candana),Centella asiatica (mandukaparni),Mesua ferrea (kanaka),Convolvulus pluricaulis (sankhapuspi),Acorus calamus (vaca), Cyperus scariosus (plava),Glycerhiza glabra (yastyahva),Embelia ribes (vidanga),
sugracandy, clarified butter (ghee), oil of taila (sesame), honey

Ingredients of Rasayana Avaleha (Vyas *et al*., 2010):

Emblica officinalis (Amalaki) 1 part, Withannia somnifera (ashwaganda) ¼ part, Tinospora cordifolia (guduchi) ¼ part, Glicyrrhiza glabra (yasthimadhu) ¼ part, Piper longum (pippali) 1/10 part, Ocimum sanctum (tulasi) 1/10 part, one part of sugar, sufficient quantity of ghee

Ingredients of Maharishi Amrit Kalash (MAK) (Saxena *et al.*, 2008)
MAK 4 and MAK 5 are taken in combination

MAK 4 paste:
Terminalia chebula, Phyllanthus emblica, Elettaria cardamomum, Cyperus rotundus, Curcuma longa, Piper longum, Santalum album, Cyperus scariosus, Mesua ferrua, Convolvulus pluricaulis, Glycyrrhiza glabra, Embelia ribes, Centella asiatica,ghee, honey and sugar

MAK 5 tablets:
Withania somnifera, Glycyrrhizza glabra, Ipomoea digitata, Asparagus adescendens, Emblica officinalis, Tinospora cordifolia, Asparagus racemosus, Convolvulus pluricaulis, Vitex trifolia, Argyreia speciosa, Curculigo orchioides, Capparis aphylla, Acacia arabica

Appenidx 6: Abreviations:

AGE	Aged Garlic Extract
BR	Brahma Rasayana
BW	Body Weight
CCT	Clincal Controlled Trial
ChT	Chemotherapy
CIN	Chemotherapy induced Vomiting
CINV	Chemotherapy Induced Nausea and Vomiting
γ - GT	Gamma Glutamat Transpeptidase
FBC	Full Blood Count
G-CSF	Granulocyte Colony Stimulating Factor
GIT	Gastrointestinal Tract
GM-CSF	Granulocyte Monocyte Colony Stimulating Factors
GOT	Glutamat Oxalat Transaminase
GPT	Glutamat-Pyruvat-Transaminase
LDH	Lactat dehydrogenase
LFT	Liver Fuction Test
NK	Natural Killer Cell
RA	Rasayana Avaleha
RCT	Randomised Controlled Trial
RT	Radiotherapy
Tbc	Tuberculosis
Tbl	Tablett
TbS	Tablespoon