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# Adverse events associated with complementary and alternative medicine use in ovarian cancer patients

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## Abstract

Many women with ovarian cancer are choosing to include complementary and alternative medicine (CAM) substances in conjunction with their conventional treatment for ovarian cancer. A 2004 study by Navo et al., found between 44% and 53% of women with ovarian cancer use some form of CAM. Many oncologists express concern about the concomitant use of CAM during conventional treatment, particularly during chemotherapy. Specifically, some providers theorize that the adjunct use of CAM substances may be detrimental to the achievement of therapeutic levels of chemotherapy by inhibiting or inducing cytochrome P450 enzyme activity leading to increases in drug toxicity, under-treatment of disease or other adverse events. Chemotherapeutic agents have complex pharmacological profiles and narrow therapeutic windows and many factors can affect the pharmacodynamics of these drugs. In an effort to ascertain the extent of the potential problem with simultaneous use of CAM with conventional treatment we undertook comprehensive systematic review of published case reports describing CAM-related adverse events among ovarian cancer patients.

**Study design—**This article describes a systematic literature review.

**Methods—**The Natural Medicines Comprehensive Database (NMCD). PubMed, EMBASE® and the Cochrane Central Register of Controlled Trials (CCTR) were systematically reviewed for research articles pertaining to known CYP mediated CAM-drug interactions; case reports describing adverse events in patients, and clinical trials which examined the effects of herbs and supplements used during cancer treatment.

**Results—**Only one case report and one clinical trial were identified which met our inclusion criteria and were relevant to the current investigation.

**Conclusion—**Although there are concerns about the potential for adverse events related to concurrent use of CAM substances during conventional treatment we found few case reports and clinical trials in the literature which support this. However, CAM substances have the potential to affect the action of pharmacological agents through the modulation of elements of the P450 enzyme system. Therefore, it is prudent to assume that herbs and drugs using the same isoforms in

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the CYP450 pathway may be contraindicated for simultaneous use. However, there are few human studies evaluating herb-CYP interactions and additional research is needed as these precautions may not be necessary.

### Keywords

ovarian cancer; oncology; complementary and alternative medicine; integrative oncology; herbs; supplements; chemotherapy; CAM-drug interactions

## INTRODUCTION

Many women with ovarian cancer use complementary and alternative medicine (CAM) treatments during and after their conventional treatment for their cancer[1]. Concurrent use of CAM and chemotherapy is controversial. Many CAM activities are presumed safe regardless of their efficacy however, there exists a potential for risk for interactions that may reduce the effectiveness of ovarian cancer chemotherapy or put women at increased risk for toxicities or other adverse effects. The pharmacodynamics and pharmacokinetics of these agents are complex and an increasing number of interactions between CAM and prescribed medications are being identified. Of particular concern is that the adjunct use of CAM substances may be detrimental to the achievement of therapeutic levels of chemotherapy by inhibiting or inducing cytochrome P450 (CYP) enzyme activity leading to increases in drug toxicity, under-treatment of disease or other adverse events.

Although there are limits to the extent to which data currently available allow for the evaluation of what is or is not a safe combination of CAM and conventional medicine, this paper reviews available case reports and clinical trials describing CAM-related adverse events among ovarian cancer patients.

## BACKGROUND

While breast cancer patients appear to be the group of cancer patients most likely to use CAM[2–9] rates of use reported among ovarian cancer patients are almost as high[10–15]. One study found between 44% and 53% of women with ovarian cancer use some form of CAM[16]. Use of herbal preparations varies but often exceeds 25% and approaches 50% of patients in populations studied[17]. Herbal therapies and other plant extracts may be used by 23% of ovarian cancer CAM users and high-dose vitamins or minerals by 14% of ovarian cancer CAM users, accounting for approximately 12% and 7% of all patients, respectively[13]. A recent survey of 192 ovarian cancer patients from Canada and the United Kingdom shows that 44% of women surveyed were identified as CAM users, the majority (61%) using multiple CAM therapies. The frequency of CAM use was the same in primary compared with recurrent disease. Eighty-nine percent of CAM users considered it important for their oncologist to be aware of CAM use. Motivations for CAM use included assist healing (60%), boost the immune system (57%), improve quality of life (48%), and relieve symptoms (45%). Thirteen percent thought CAM could cure cancer, whereas 17% thought it would prevent recurrence[18].

Oncologists seeking to inform themselves about the use of adjunctive CAM face a considerable challenge[19–22]. Conventional chemotherapeutic agents have narrow therapeutic windows and CAM use cannot be assumed to be safe without individual evaluation[23, 24]. Chemotherapeutic agents have complex pharmacological profiles and many factors can affect the pharmacodynamics of these drugs. In vitro studies show that it is possible for many forms of dietary and herbal supplements to impair or enhance drug metabolism through modification of the action of CYP450 isoforms. The CYP cytochrome P450 3A4 isoform (CYP3A4) is responsible for metabolizing greater than 50% of the drugs which pass through the liver and therefore the largest number of potential drug-herb interactions are those metabolized using this pathway[25, 26]. Concurrent use of these therapies may be detrimental to the achievement of doses of chemotherapy within a defined therapeutic window leading to under treatment of disease or to increased drug toxicity. In most cases, although there is *in-vitro* and perhaps *in-vivo* evidence that herbs have the potential to influence CYP450 isoforms, there are rarely data on specific doses associated with these effects and many potentially problematic combinations may have no identifiable influence on patient outcomes. Although there are hundreds of CAM substances which may influence the pharmacodynamics of conventional treatment, it is reassuring to realize that only a small subset of CAM substances are commonly used as adjunctive cancer treatments and most gynecologic oncologists use a relatively small number of chemotherapies.

## METHODS

For this review, we utilized two complementary approaches to understanding the potential for adverse interactions of CAM substances of biological activity and conventional chemotherapy for ovarian cancer. Firstly, we reviewed the theoretical concerns that have been raised in prior reviews and concerns based on known biological activities of herbs commonly used by naturopathic oncologists to describe the potential extent of the problem. Secondly, the Natural Medicines Comprehensive Database (NMCD) was queried for CAM substances of interest and evaluated for relevance to the main topics of this review. NMCD citations were then entered into the PubMed database in order to capture a more extensive review of the literature. PubMed, EMBASE® and the Cochrane Central Register of Controlled Trials (CCTR) were then systematically reviewed for research articles pertaining case reports describing adverse events in patients, and clinical trials which examined the effects of herbs and supplements used during cancer treatment. National Library of Medicine Medical Subject Headings (MeSH) and key word search terms were used in order to identify all references relevant to CAM-related drug herb interaction case reports and clinical trials. PubMed and EMBASE query results were further filtered by the subject ‘cancer’ in order to limit the search results to the most relevant articles (see TABLE 1 for a complete description).

In an effort to minimize bias, inclusion and exclusion criteria were established *a priori*. All case reports and clinical trials of human participants from all available records in each database were included. Database searches were conducted through August 2011. Search terms eliciting greater than 150 hits were considered too broad to be useful and thus were not utilized for the purposes of this review. Reports in the literature discussing adverse events associated with CAM substances in the non-Western tradition are not well described

in the English language literature. Additionally, the biological mechanisms of action associated with these substances are often described in a culture-specific context which is not amenable to Western translation. We therefore limited this review to English-only articles regarding CAM substances with a tradition of use in Western Naturopathic medicine. Additional exclusion criteria included non-ingestible CAM substances, morbidities other than cancer and trials which showed potential benefit from CAM use. The body of research on natural products is limited. In order to ensure the most current information was included in this review, every effort was made to limit the documents retrieved to articles published in the last ten years. Finally, qualitative research and other reviews of the literature were excluded.

## RESULTS

In total, one case report and one clinical trial were identified which met the inclusion criteria and were relevant to the current investigation.

### Case Reports

Only one case report discussed the concurrent use of supplements during ovarian cancer treatment. Mukai et al. describe three cases of severe hepatic damage in three patients who were taking Agaricus blazei, a medicinal mushroom. The first was a 66 year-old woman with stage IIIc ovarian cancer on combination chemotherapy with cisplatin and cyclophosphamide. Following her first cycle of chemotherapy she developed fever and elevated liver enzymes, which eventually normalized. She was diagnosed with chemotherapy-induced hepatitis after the second cycle of chemotherapy and all further treatment was suspended. She developed recurrent disease within 8 months but persistent elevation of liver enzymes levels prevented the use of additional chemotherapy. The patient eventually disclosed that she had been using an Agaricus blazei extract throughout chemotherapy. She was advised to discontinue her use of the supplement and her liver enzymes returned to normal. The second patient was a 58 year-old woman with a history stage IIIA breast cancer who had completed 6 cycles of cyclophosphamide, doxorubicin and 5-FU. She was admitted to the hospital 3 months after completing treatment for fatigue. Here liver enzymes were elevated at admission without evidence of associated risk factors including drug or alcohol use or hepatitis infection. She had begun taking Agaricus blazei several days prior to admission. Her condition rapidly deteriorated and she died of fulminant hepatitis 7 days after admission.. The final case was a 48 year-old woman with breast cancer with metastasis to the bone who was also a chronic carrier of hepatitis B with normal liver enzymes. She was being treated with combination doxorubicin and cyclophosphamide. After 3 cycles of chemotherapy she was admitted to the hospital with severe hepatic dysfunction. She disclosed she had been using Agaricus blazei and no other drugs for several days before admission. She was diagnosed with acute hepatitis which rapidly became fulminant and she died 6 days later. Dose, form of supplement used and duration of use were not discussed by the authors. Although several other factors cannot be completely ruled out as the causes of liver damage, a strong causal relationship between the Agaricus blazei extract and liver damage was suggested and, at least, taking the Agaricus blazei extract made the clinical decision-making process much more complicated[27]. The possible mechanisms by which

Agaricus blazei asserts its effects are poorly understood. Preliminary research in animal models has shown hepatoprotective effects against chemical-induced injury and normalization of liver function in patients with hepatitis[28, 29].

Five other case reports are also reported here. Although they did not involve ovarian cancer patients specifically, they represent the only other adverse event reports found during the review process. These reports do describe adverse events associated with CAM supplements (CAM supplements alone or drug-CAM interactions) in other cancer patients. Norred et al. describe a breast cancer patient who experienced extensive postoperative bleeding which required emergency surgical re-exploration and hematoma evacuation. Preoperatively the patient had a history of long-term use (6 weeks to 10 years) of several CAM substances including vitamin E, gingko (Gingko biloba), ginseng (genus species not specified) and huang qi (Astragalus membranicus) ingestion and an approximately 4 month duration of use of the drugs quinine sulfate and sertraline hydrochloride. Postoperative recovery from the second surgery was reportedly unremarkable[30]. Gingko is known to inhibit platelet-activating factor (PAF) and cases of spontaneous and postoperative bleeding have been attributed to its use[31]. Ginsenosides, a constituent of ginseng, are known to inhibit platelet aggregation in vitro and in laboratory rats, prolong both coagulation time of thrombin and activated partial thromboplastin. One study suggests that the antiplatelet activity of ginseng may be irreversible in humans.[31] Cheng et al. report on an elderly Korean male with prostate cancer who presented with hypokalemic paralysis, symptoms of which included marked limb paralysis, myalgias, and mild hypertension. He had consumed eight packs (100 ml/pack) of a Korean herbal tonic daily to treat his prostate cancer for the past 2 months in which a significant amount of glycyrrhizic acid (0.23 mg/ml), an active ingredient of licorice, was detected[32]. These signs and symptoms are consistent with other case reports going back to 1975 of psuedoaldosteronism induced by consumption of large doses of glycyrrhizic acid[33, 34]. Bromley et al. discuss a 68-year-old woman with uroepithelial cancer of the bladder who ingested her first dose of (3 g) of amygdalin and also ingested a daily dose of 4800mg vitamin C. The patient presented to the ER with cyanide toxicity requiring intubation and ventilation. The authors postulate that vitamin C is known to increase the in vitro conversion of amygdalin to cyanide and reduce body stores of cysteine, which is used to detoxify cyanide. An interaction with vitamin C is a plausible explanation for this life-threatening response. Severe reactions had previously not been reported with this dose[35]. Hwang et al. report on a 36-year-old female with adenocarcinoma of the lung who ingested multiple complementary herbal medicines including ginseng and selenium along with gefitinib. She experienced continued disease progression with concurrent CAM use and upon cessation of CAM therapies, a partial sustained response using gefitinib alone was achieved within 4 weeks[36]. Finally, Altan et al. discuss a 43-year-old female with metastatic synovial carcinoma of the knee undergoing Ifosfamide and etoposide treatment with concurrent daily injections of Nerium oleander (Anvirzel™, Phoenix Biotech, Mississauga, Ontario) at 1.2mL/$m^2$/day for 2 months. The patient developed hepatotoxicity, worsening ascites and disseminated intravascular coagulation with death due to cardiopulmonary arrest[37]. However, Block et al. dispute these conclusions citing a lack of published evidence and posit the hepatotoxicity was a direct result of chemotherapy[38] and not a result of Nerium oleander injections.

### Clinical Trials

One clinical trial was identified using the above described search criteria which included ovarian cancer patients[39]. Piao et al. describe a randomized, open, prospective clinical trial consisting of a total of 233 patients suffering from breast (n=68), ovarian (n=71) and non-small cell lung cancer (NSCLC; n=94) conducted in three oncological centers on the efficacy safety and side-effects of the standardized mistletoe extract, Helixor®. They report seven non-serious adverse events, including harmless local inflammatory reactions at the injection site and four cases of fever, which were self-limiting and did not demand therapeutic intervention. Only one serious adverse event (angioedema) was reported[39]. The cancer type is not specified in the authors' reporting of adverse events. These side effects are characteristic of Helixor use and are discussed in the Helixor Summary of Product Characteristics. It states that, "A slight increase of body temperature and local inflammatory reactions (redness, swelling, subcutaneous infiltration) limited to the subcutaneous injection site are commonly reported side effects harmless and signs of the patient's response to the applied dosage." Although uncommon, serious allergic reactions to mistletoe therapy have previously been reported, including angioedema and anaphylaxis[40, 41].

The results of a second clinical trial are also presented here. Again, although the trial was not specific to ovarian cancer it was the only other clinical trial reporting adverse events related to CAM use that was identified as a result of this review. Mathijssen et al. found that in a small group of cancer patients (2 colorectal, 2 lung, 1 sarcoma), plasma levels of the active metabolite of irinotecan, SN-38, decreased by 42% (95% confidence interval [CI] = 14% to 70%) following co-administration of St. John's Wort. The authors conclude this suggests that irinotecan metabolism and toxicity are altered by SJW which may have a deleterious impact on treatment outcome[42]. The case reports and clinical trial results discussed here are summarized in TABLE 2.

## DISCUSSION

It should be noted that clinical recommendations regarding drug-CAM interactions are most frequently based on evidence from *in vitro* studies. For many CAM therapies, the results of *in vitro* studies regarding the potential for interactions with CYP isoforms are conflicting with other *in vitro* studies of the same interactions. Human studies evaluating herb-CYP interactions are limited but may mitigate concerns regarding the potential for these interactions as the results of some *in vitro* studies suggest For example, Gurley et al. evaluated CYP2D6-mediated herb-drug interactions in humans by summarizing the results of 3 separate studies each incorporating 2 botanical extract preparations. Three groups of 16 healthy adults were assessed for CYP2D6 activity after the oral administration of varying dose and duration of milk thistle (Silybum marinarum), black cohosh (Cimicifuga racemosa), goldenseal (Hydrastis canadensis), kava (Kava kava), St. John's wort (Hypericum perforatum), and purple coneflower (Echinacea purpura). The study found that five of the botanicals evaluated exerted no significant effects on CYP2D6 activity with goldenseal as the only herb which demonstrated significant inhibitory effects on human CYP2D6 in vivo[43]. The clinical relevance and usefulness of this information is unknown although the authors suggest that simultaneous of these specific botanicals with drugs

metabolized by CYP2D6 is unlikely to result in clinically relevant herb-drug interactions. This type of data should be regarded as information about the potential for interaction between CAM and conventional therapies. Many CAM therapies commonly used by ovarian cancer patients have multiple physiologic effects and examination of the literature for other pharmacologic actions is warranted. Many possess potent anti-tumor constituents and have palliative effects which may prove to be more beneficial to the patient than the potential risks associated with the concomitant use of these therapies during conventional treatment.

Cautious interpretation of both *in vitro and in vivo* results in conjunction with an informed evaluation of each patient's CAM use is warranted in order to minimize the possibility of interference with conventional treatment and to identify potential CAM-related adverse events. Discussions between physicians and patients about CAM use also serves to improve patients overall perceptions about their cancer experience. A study of ovarian cancer patients and involvement in decision making by Andersen, et al. showed that greater involvement in decision-making about use of CAM changes was associated with greater emotional health related quality of life[44]. When patients are interested in using CAM substances during active treatment, consultation with, or referral to a board-certified naturopathic oncologist (N.D., FABNO) in states where Naturopathy is licensed may be indicated or desired by either the oncologist or the patient. An appropriately trained specialist N.D. may be able to provide the best evidence-based information to patients regarding appropriate CAM use and protect patients from potential toxicity which may result from the concomitant use of chemotherapy and CAM and ensure that the efficacy of conventional chemotherapy is not compromised. Excellent referral resources include The American Association of Naturopathic Physicians (www.naturopathic.org) and the Oncology Association of Naturopathic Physicians (www.oncanp.org), which are professional organizations for board-certified naturopathic physicians and offer nationwide referral services. Communication between patients and medical oncologists about CAM use is essential to ensure both the safety and efficacy of conventional treatment. There are a growing number of resources available which support conventional oncologists in initiating these conversations. Schofield et al. conducted a systematic review of regarding effective communication of CAM use in an oncology setting literature from 1997 to 2007. The findings from 78 original papers were qualitatively synthesized into structured the first comprehensive evidence based guidelines for discussing CAM[45]. Utilizing tools which improve the ability of physicians and patients to discuss CAM use can improve the quality of the therapeutic relationship between doctor and patient and support a patient-centered model of integrative cancer care.

There are limitations which hinder a thorough understanding of the inherent risks of CAM use and the risks of co-use of ingestible CAM substances in addition to conventional chemotherapy in ovarian cancer patients. CAM is widely used throughout the world and not limited to English-speaking countries practicing medicine in the Western tradition. Non-Western medical systems such as Traditional Chinese Medicine and Ayurveda utilize culturally–specific descriptive terms for disease processes and the biologic mechanisms of CAM which are not readily understood in the context of Western medicine. Therefore, our decision to include English-only articles regarding CAM substances with a tradition of use in Western Naturopathic medicine limits our ability to more fully describe CAM-related

adverse events and the potential for drug-CAM interactions. In addition to a lack of randomized controlled trials (RCTs) in humans, adequate reporting of safety in publications of randomized controlled trials is a pre-requisite for accurate and comprehensive profile evaluation of conventional as well as complementary and alternative medicine (CAM) treatments. An evaluation of safety reporting in the reports of CAM RCTs across 15 different CAM interventions demonstrated that the reporting of harms was largely inadequate[46]. The reasons for inadequate reporting are currently unclear. Ascertainment of this type of information is limited by barriers to communication regarding CAM use between patients in physicians. Adverse events related to CAM use may not be recognized as such if CAM use is routinely underreported. The mechanisms of action of CAM substances are also often poorly understood. CAM modalities and prescribing methods are highly diversified and tremendous variation exists in the standardization of herbal products and other dietary supplements. In particular the lack of product standardization creates difficulty in ascribing causation of any adverse event to these substances. Additionally, high-quality research of CAM modalities may not be found on routine literature searches secondary to publication bias. Raschetti et al. conducted a systematic literature search of MEDLINE in order to identify all articles dealing with CAM, in the human setting. They found that during the period 1997–2002, a total of 20,209 articles about CAM were published, representing the 0.7% of the total number of MEDLINE-listed articles. Approximately 50% of CAM articles published in 1996–2002 appeared on journals with no impact factor. The proportion of randomized clinical trials was only 7.6% of total CAM articles[47]. These findings underscore the need for rigorous CAM research in order to support evidence-based approaches to these therapies and to elucidate harmful side effects and contraindications for use.

Additionally, there are limitations of our study methodology. Our search only included chemotherapeutic agents commonly used in the treatment of ovarian cancer and was not exhaustive. We also did not include other agents which may be used in cancer treatment including monoclonal antibodies and other molecular target drugs. Furthermore, search terms eliciting greater than 150 hits were excluded as were review articles, which may have led to incomplete ascertainment of case reports and clinical trials which reported adverse events.

## CONCLUSION

The growing concern about the potential for adverse events related to concurrent use of CAM substances during conventional treatment may be tempered by this review. We found few case reports and clinical trials in the literature describing adverse events associated with polypharmacy including both CAM therapies and chemotherapeutic treatments for ovarian cancer. Considering the frequency of CAM use by ovarian cancer patients, caution regarding CAM use is warranted as there exists the theoretical potential for adverse events or reactions with chemotherapy. *In vitro* data show that CAM substances have the potential to affect the action of pharmacological agents through the modulation of elements of the P450 enzyme system. Therefore, it is prudent to assume that herbs and drugs using the same isoforms in the CYP450 pathway may be contraindicated for simultaneous use. Taking into consideration the few case reports and clinical trials in the literature describing adverse

events associated with CAM-drug interactions, and the lack of human data to support CAM-CYP interactions, precautions regarding simultaneous use may be premature.

Increased levels of research interest in these issues should increase in vivo research that will improve the ability of physicians to guide patients' use of CAM therapies during active treatment. Until those data are available, ensuring patients get competent advice regarding the use of CAM during active chemotherapy can help both complementary and conventional oncologists and their patients work more effectively together minimize the potential for harm.

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## TABLE 1

Search Terms and Results

| MeSH and Key Word Search Terms | Case Reports* | | Clinical Trials* | |
|---|---|---|---|---|
| **GENERAL** | **Total Hits** | **Excluded** | **Total Hits** | **Excluded** |
| Phytotherapy and adverse events | 2 | 2 | 67 | 66 |
| **SURGERY** | | | | |
| Complementary medicine and surgery | 404 | 404 | 536 | 536 |
| Complementary medicine and postoperative bleeding | 6 | 6 | 34 | 34 |
| Complementary medicine and narcotic analgesics | 42 | 42 | 86 | 86 |
| Complementary medicine and anesthesia | 88 | 87 | 419 | 419 |
| Complementary medicine and adverse surgical outcomes | 4 | 4 | 54 | 54 |
| Herbal medicines and perioperative care | 0 | 0 | 9 | 9 |
| Herbal medicines and bleeding | 0 | 0 | 42 | 42 |
| Herbal medicines and surgery | 9 | 8 | 173 | 173 |
| **CYPs** | | | | |
| Complementary medicine and cytochrome P450 | 5 | 5 | 20 | 19 |
| Complementary medicine and liver enzymes | 26 | 24 | 42 | 42 |
| Herbal extracts and cytochrome P450 | 1 | 1 | 25 | 18 |
| Complementary medicine and cytochrome P450 interactions | 4 | 4 | 12 | 11 |
| Herbal medicines and drug metabolism | 4 | 4 | 22 | 19 |
| Complementary medicine and drug metabolism | 185 | 184 | 986 | 985 |
| Complementary medicine and drug metabolism interactions | 7 | 7 | 65 | 61 |
| **CAM, CYPs AND CHEMOTHERAPY** | | | | |
| Complementary medicine and paclitaxel | 13 | 13 | 69 | 69 |
| Complementary medicine and Docetaxel | 1 | 1 | 41 | 41 |
| Complementary medicine and cyclophosphamide | 37 | 37 | 121 | 121 |
| Complementary medicine and Ifosfamide | 7 | 7 | 18 | 18 |
| Complementary medicine and carboplatin | 10 | 10 | 41 | 41 |
| Complementary medicine and cisplatin | 17 | 17 | 130 | 130 |
| Complementary medicine and Gemcitabine | 9 | 9 | 57 | 55 |
| Complementary medicine and Etoposide | 11 | 11 | 48 | 47 |
| Complementary medicine and Vinorelbine | 2 | 2 | 22 | 22 |
| Complementary medicine and Doxorubicin | 26 | 26 | 116 | 116 |

*Search terms providing greater than 150 results were considered too broad to be useful and were thus not utilized for the purposes of this review

## TABLE 2

Summary of Relevant Case Reports and Clinical Trials

| AGENT | CANCER TYPE | STUDY TYPE | AUTHOR (YEAR) | OBSERVATIONS |
|---|---|---|---|---|
| Vitamin E Gingko Ginseng Huang qi | Breast | Case Report | Norred et al. (2000)[30] | Patient had extensive postoperative bleeding requiring surgical re-exploration following vitamin E, gingko, ginseng and huang qi ingestion when combined with the drugs quinine sulfate and sertraline hydrochloride |
| Licorice | Prostate | Case Report | Cheng et al. (2004)[32] | An elderly Korean male presented with hypokalemic paralysis. He consumed eight packs (100 ml/pack) of a Korean herbal tonic daily to treat his prostate cancer for the previous 2 months. A significant amount of glycyrrhizic acid (0.23 mg/ml), an active ingredient of licorice, was detected in the tonic |
| Amygdalin Vitamin C | Uroepithelial carcinoma of the bladder | Case Report | Bromley et al. (2005)[35] | A 68-year-old patient ingested (3 g) of amygdalin and used 4800mg vitamin C presented to the ER with cyanide toxicity requiring intubation and ventilation |
| Agarics blazei | Ovarian | Case Report | Mukai et al. (2006)[48] | A 66-year-old female with stage IIIC ovarian cancer<br>A 58-year-old female with stage IIIA breast cancer<br>A 48-year-old female with metastatic breast cancer in the bone who was also a chronic hepatitis B carrier with normal liver transaminase values prior to chemotherapy<br>All showed severe hepatic damage and two died of fulminant hepatitis |
| Ginseng Selenium | Lung | Case Report | Hwang et al. (2008)[49] | A 36-year-old female with adenocarcinoma of the lung ingested multiple complementary herbal medicines, including ginseng and selenium along with gefitinib, experienced continued disease progression with concurrent CAM use. A partial treatment response was obtained upon cessation of CAM use |
| Nerium oleander | Metastatic synovial carcinoma | Case Report | Altan et al. (2009)[37] | A 43-year-old female undergoing Ifosfamide and etoposide treatment with concurrent daily injections of Nerium oleander (Anvirzel™, Phoenix Biotech, Mississauga, Ontario) at 1.2mL/$m^2$/day for 2 months developed hepatotoxicity, worsening ascites and disseminated intravascular coagulation with death due to cardiopulmonary arrest |
| St. John's Wort | Colorectal, Lung, Sarcoma | Clinical Trial (N=6) | Arnold et al. (2002)[42] | Systemic exposure to SN-38, an active metabolite of irinotecan, decreased by about 42% when St. John's wort was taken in conjunction with irinotecan. |
| Mistletoe | Breast, Ovarian, Non-small cell lung | Clinical Trial (N=233) | Piao et al. (2004)[39] | Seven non-serious adverse events which did not require therapeutic intervention and one serious adverse event (angioedema) were reported. |