

Review Article

Conventional Chemotherapy: Problems and Scope for Combined Therapies with Certain Herbal Products and Dietary Supplements

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Abstract

Cancer, the dreadful disease, is one of the burning issues that need collective efforts to successfully combat and cure. Chemotherapy is one among many options like surgery, radiation therapy, targeted molecular therapy etc., which is widely used to successfully treat certain types of cancer, but its use is restricted for the adverse side-effects of most of the chemotherapeutic drugs. A comprehensive search by utilizing data from the Pubmed, Cochrane Library, Embase and ISI Web of Knowledge and some related books was made to gain insight into the modern trend of research to combat the obstacles that come in the way of waging a successful war against cancer. The toxic by-products of some chemotherapeutic drugs are deposited mainly in liver producing hepatotoxicity, leading to many side-effects like loss of appetite, nausea, vomiting, diarrhea, abdominal cramps and constipation, anemia, fatigue, hyperthermia, loss of hair etc. In this review, the benefits and problems of chemotherapy have been highlighted and the scope and obstacles of combined therapy with some biologically based complementary and alternative medicines (CAM) derived from certain herbal products and dietary supplements, plant extracts and their active components, and some of their nano-encapsulated forms have been discussed.

Keywords: Chemotherapy; Complementary and alternative medicines; Cancer hepato and cyto-toxicities; Plant extracts; Plant products; Combined therapies

Abbreviations

CAM: Complementary and Alternative Medicines; FDA: Food And Drug Administration; NCCAM: National Center for Complementary and Alternative Medicine; WHO: World health organization

Introduction

Cancer has been earmarked as one of the major global public health concerns [1]. Its frequency of occurrence and the rate at which it causes fatality continue to be a serious health problem. A survey in 2008 by the World Health Organization (WHO) [2] estimated about 12.7 million people to be affected with cancer and among them, some 7.6 million people died from cancer worldwide. Further, if we go by the prediction of WHO, then the scenario would be really grave by 2030 when an estimated 21.4 million new cases of cancer will occur, resulting in death of some 13.2 million cancer patients annually around the world. Surgery, chemotherapy and radiotherapy, the present day weapons would hardly be sufficient to tackle a problem of such a magnitude, and newer avenues must be explored utilizing knowledge emerging in medical regimens such as complementary and alternative medicines (CAMs), at least for use as supportive medicines for alleviating toxicity produced by conventional therapy, apart from the more conventional orthodox medicines for providing a better way of life and longevity to the cancer patients.

Conventional chemotherapy means the treatment of disease

specially cancer by the use of chemical substances and regimens that have been in use for the past fifty years or so. Conventional chemotherapy is given with one drug at a time or few drugs at one time or combined with other cancer treatments, like radiation therapy, surgery followed by several cycles of chemotherapy. In general, chemotherapeutic drugs effectively damage the fast proliferating cells and prevent mitosis by hampering DNA synthesis and inhibition of the cellular machinery involved in cell cycle process, which in turn induce apoptosis, a programmed cell death [3]. Alkalyting agents are the oldest chemotherapeutic agents that have been used since the late 1940s after it became known that the use of mustard gas in the World War I caused leucopenia [4,5]. It is proved that different drugs can destroy tumor cells by triggering common apoptotic pathways but mode of molecular events required for activation of apoptosis process is different [6].

Although chemotherapy is the key way to control cancer but due to a difficulty in dosage selection, lack of specificity which produces Cytotoxicity to normal cells as well, rapid drug metabolism, both intrinsic and acquired drug resistances varying in patient status and mainly harmful side effects, success of chemotherapy has been limited so far. On the other hand, certain complementary and alternative medicines (CAM) have occasionally been claimed [7-9] to have anticancer potentials and have no or negligible side-effects, which prompted us to examine if they could be used with potential benefits to the patients, at least by lessening/ameliorating their sufferings and

pains that arise due to the disease as well as the side-effects of the chemotherapeutic drugs.

Data Source and Methods

A comprehensive search was made by utilizing data from the Pubmed, Cochrane Library, Embase and ISI Web of Knowledge, WHO and NCCAM reports and some related books to gain insight into the modern trend of research to combat the obstacles that come in the way of waging a successful war against cancer. Our focus was mainly on delineating the major problems encountered in chemotherapy and possible conjoint use of some herbal products and dietary supplements that could be beneficial to the abatement of sufferings and pains of the patients undergoing simultaneous orthodox treatment.

Problems of chemotherapy: Side-effects

Chemotherapeutic drugs are designed on the basis of their killing ability of cells that grow faster, the main characteristic feature of cancer cells. However, chemotherapeutic drugs also kill normal cells that divide; e.g. bone marrow cells, gut cells, etc. For this reason, the range and effectiveness of chemotherapy becomes restricted.

The growing capability of cancer cells to resist the chemotherapeutic drug is one of the main drawbacks of conventional chemotherapy. In drug-resistant cancer cells, expression of surface small pump like p-glycoprotein and intercellular antioxidant efflux prevent the chemotherapeutic agents from entering into the cells [10]. Many critical molecular types of machinery are involved in chemotherapeutic drugs and tumor cell interactions. Genotoxic drugs used in chemotherapy may induce alteration of gene expressions causing aggravation of DNA damage, resulting in cell death. But sometimes, structural changes in protein induced by genetic mutation prevent binding of drug with target protein, which in turn can resist the chemotherapeutic effect [11]. Acquired capabilities of cancer cells to produce gene amplification and alteration of gene expressions by mutation on coding genes for apoptosis-inducing proteins play an important role in generating resistance against chemotherapeutic drugs [4]. Defect in apoptotic pathway by genetic alteration of normal cells that involve in tumor genesis can also resist the chemotherapeutic drugs which kill the cancer cells by apoptosis. Thus, mutation in genes involving development of cancer cell can prevent apoptosis and also play important role in drug resistance.

Over-dosage in chemotherapy can produce much harmful effects in the patients. Therefore, much care has to be taken to determine the effective dosage. Several factors like body surface area (BSA) formula, mathematical calculation on the basis of the patients' weight and height had been approved in early 1950s for calculating individual chemotherapeutic dosage. The effectiveness of chemotherapeutic drug varies with concentration of the drug in the patient's bloodstream which is subjected by multiple factors, including metabolism, cancer state, drug-target interactions, and patients' physiological and genetically state [12]. Now-a-days researchers are trying to establish a formula by which individual patient can achieve optimal systemic drug exposure which can maximize the drug efficacy and minimize cytotoxic effects.

Determination of cancer type and cancer stage is a very important phenomenon for success of chemotherapy. In certain cancer type

where drug delivers through circulatory system, chemotherapy fails because of improper blood vessel in tumor cells [13]. Patients with late stage cancer may not fully cure and face greater risk of early death because they may not tolerate chemotherapeutic side-effects. Thus, side-effects are one of the major and leading problems of chemotherapy and often limit its use [14].

Side-effects occur mostly when the chemotherapy damages the healthy cells that maintain the body's function and appearance. Different side-effects arise depending on the nature of the drug. As for example, the Alkalyting agents and anti metabolites directly damage DNA to prevent the cancer cells from reproducing; thus they can cause long-term damage to the bone marrow, which can eventually lead to acute leukemia. Similarly, Anthracyclines are anti-tumor antibiotics that interfere with enzymes involved in DNA replication. These drugs work in all phases of the cell cycle. A major consideration when giving these drugs is that they can permanently damage the heart if given in high doses for a long time. For this reason, lifetime dose limits are often put on place on these drugs. In the same way, some plant alkaloids and other compounds derived from natural products are often known to be mitotic inhibitors. They can stop mitosis or inhibit enzymes from making proteins needed for normal cell reproduction. These drugs are known for their potential to cause peripheral nerve damage, which can be a dose-limiting side effect. Likewise, topoisomerase inhibitors that cause DNA damage to cancer cells produce harmful side effects like symptoms of allergic reaction including fast heartbeat, itching or hives, swelling in the face or hands, swelling or tingling in the mouth or throat, chest tightness, and wheezing. Cytotoxic medicines are generally very powerful but often cause many unwanted side-effects. Since cytotoxic medicines mainly work by killing cells in their divisional stages, irrespective of whether they are normal or cancer cells, protection to normal cells is of prime importance while a patient is undergoing cancer therapy.

Immune-suppression during chemotherapy causes various side-effects also. Bone marrow suppression decreases the production of blood cells leading to anemia and thrombocytopenia. Another serious problem of immune compromised patients, caecitis-infection of the gut- includes diarrhea, nausea, vomiting, fever and distended abdomen etc [15]. Prolonged autoinfection manifests as systemic disease conditions like sepsis [16].

In early stage of chemotherapy mucositis, a painful inflammation and ulceration of mouth begins by damaging of normal cells lining the mouth [17]. Chemotherapeutic drugs target rapidly dividing cells like gastrointestinal cells resulting in nausea, vomiting, anorexia, diarrhea, abdominal cramps, and constipation etc. Gastrointestinal damage causes gastro paresis, decreased gut motility or delayed emptying of the stomach and small intestines leading to malnutrition and dehydration [18]. Fatigue, one of the most frequent and long lasting side-effects of chemotherapy, is a very problematic issue and it imposes limitations on normal daily activities of about 70% patients [19,20]. Every chemotherapeutic agent targets and damages fast dividing hair follicles resulting in vigorous hair loss leading to certain type of alopecia like alopecia totalis, telogen effluvium, or less often alopecia areate [21]. Some Alkalyting chemotherapeutic agent constructs secondary neoplasia like acute myeloid leukemia which increases in frequency [22]. It has been observed that many chemotherapeutic patients lack their interest in sex [23]. Infertility arises in both female

and male patients by some gonad toxic chemotherapeutic agents [24]. During pregnancy chemotherapy makes congenital abnormalities including growth retardation, delayed mental development or other congenital disorders [25]. Patients may suffer from peripheral neuropathy, a damage or disease affecting nerves which produces symptoms like numbness, abnormalities in brain and spinal cord, tremor, and gait abnormality [26]. Many chemotherapeutic agents cause non-specific neuro-cognitive problems in which patients suffer from inability to concentrate. Some chemotherapeutic drugs rapidly break down and cancer cells in turn release chemicals from inside the cells producing high levels of uric acid, potassium, phosphate and calcium in the blood. One of the decisive problems during chemotherapy is damages inflicted on normal organs. Organ-specific toxicities arise by specific chemotherapeutic agents. Most chemotherapeutic drugs generate many free radicals producing Cytotoxicity, which in turn causes DNA damage in the cells leading finally to apoptosis. Cardio toxicity, hepatotoxicity, nephrotoxicity and ototoxicity, are some of the leading problems generating from the non-specific cytotoxic nature of these chemotherapeutic drugs [27-30]. Chemotherapeutic drugs may also produce many other side-effects like dry skin and mouth, water retention, dental problem, digestive problem, emotional difficulties etc.

Supportive approaches with conventional chemotherapy

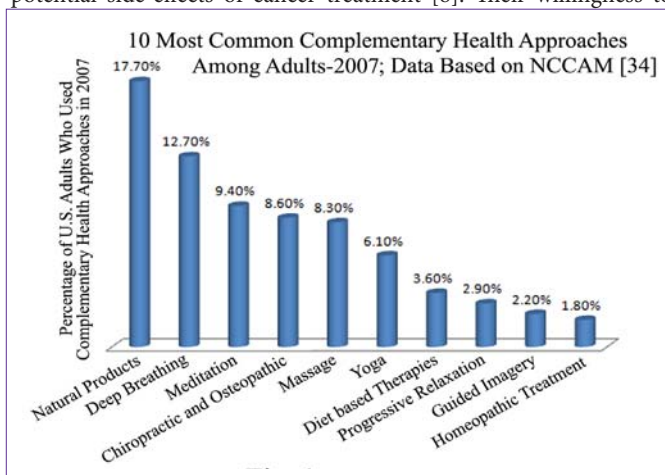
In recent years, in the Western countries where the occurrence of various types of cancer is very high (about 80%) in the US cancer population [9,31], use of complementary and alternative medicines (CAM) is gaining popularity among cancer patients, particularly for alleviating Cytotoxicity and side-effects of orthodox therapy. More and more patients now solicit CAM treatment combined with conventional Western medicine (chemotherapy and/or radiotherapy), as this approach has been found to yield a better effect in providing supportive care for cancer patients. Further, CAM has been found to render great advantages in terms of increasing the sensitivity of chemo- and radio-therapeutics, along with reduction of side-effects and complications associated with these otherwise effective therapies, and thereby improving quality of life and survival time [32] of the patients.

Complementary and Alternative Medicine treatments (CAM)

Complementary and alternative medicines, as defined by NCCAM are a group of various nonstandard, unproven, and irregular medicines and health care systems, practices, and products that generally fall outside of mainstream or conventional medicines. However, the application of these nonstandard approaches is now widespread in cancer therapy [33-36]. According to WHO, “complementary” means to use “a non-mainstream approach” together with conventional medicine and “alternative” means to use “a non-mainstream approach in place of conventional medicine”. Alternative medicine is any practice that is put forward as having the healing effects of medicine, but is not always based on evidence gathered using the scientific method. Examples include new and traditional medicine practices such as homeopathy, naturopathy, chiropractic, and energy medicine, various forms of acupuncture, Traditional Chinese medicine, Ayurvedic medicine, and Christian faith healing. The US National Center for Complementary and Alternative Medicine (NCCAM) put CAM into the following

categories: (i) alternative medical systems defined by complete systems of theory and practice like homeopathy and naturopathy, (ii) mind-body medicine defined by variety of techniques designed to enhance the mind’s capacity to affect bodily function and symptoms like meditation and prayer, (iii) biologically based therapies defined by using substances found in nature like dietary supplements, herbal products, etc., (iv) manipulative and body-based methods defined by manipulation and/or movement of one or more parts of the body like chiropractic, massage and energy therapies, (v) bio electromagnetic-based therapies defined by involvement of the unconventional use of electromagnetic fields like pulsed fields and magnetic fields (Figure 1) [37].

CAM emerges as an international phenomenon of usage of some non-western medicines. The estimated data of early 2000 surveys indicated that 80% of cancer patients used one form of alternative or complementary therapy [9, 38]. The cumulative result of 26 surveys across 13 countries (mostly in US and European countries) estimated that the popularity of CAM increased overall by 31.4% (range, 7% to 64%) [39], in cancer patients. The use of CAM as a supporting care is more popular among adult cancer patients but recent surveys on children with cancer have revealed that 31–84% of children also opt for CAM therapies in the North Western US, South Australia and the United States [40-42]. Many research articles, approximately 1500 on CAM are published annually in the literature covered by MEDLINE [43]. The popularity of the use of CAM is likely to vary according to factors that are not fully understood. There are many different reasons for the growing interest in use of CAM, one of them being patient’s discontent with standard orthodox medicine [44], particularly after not getting the desired effect through conventional therapy [45] or due to patient’s individuality factors [46,47]. However, a recent study [9] on patients of Anderson Cancer Centre, USA showed that they were more prone to using CAM because majority of them (73%) felt this will make them feel hopeful; they also felt inclined to use CAM because they believed these approaches were relatively nontoxic (48.9%) and asserted that they should have the right of more control in the decision making about their medical care (43.8%). One aspect which is important is that most cancer patients, particularly children, prefer the use of complementary therapies along with mainstream cancer treatment and primarily as supportive therapies to alleviate pain and symptoms of cancer, and especially to reduce actual or potential side-effects of cancer treatment [8]. Their willingness to



adopt concurrent CAM therapy rests mostly on adjunctive approaches that tend to control symptoms and enhance quality.

Although oncologists know that patients may like to use CAM along with the orthodox treatment, yet few oncologists in the US discuss these therapies with them [48,49]. One of the reasons may be because many surveys carried out in USA indicate that there are various savior risks involved in using CAM [50]. First, one possibility that discourages an oncologist from giving patients an option of treatment with CAM is that a patient may like to stop or forego effective orthodox treatment and opt for a relatively ineffectual alternative approach once their apparent sufferings and pain are temporarily reduced. If treatment is for a minor illness this may be relatively harmless but if the cancer type is life-threatening, but it is a curable form of cancer, it may really cause a great harm. Even delay in consulting a doctor practicing orthodox medicine and starting effective treatment late may reduce the chance of a cure. Secondly, if a patient aspires to receive both conventional and CAM therapies together, sometimes some undesirable, even dangerous interactions, between the two forms of treatment, may actually aggravate the situation to a more complicated end. Therefore, patients should inform their specialist doctor of any additional form of treatment they may be using simultaneously. Thirdly, some CAM practitioners sometimes exploit desperate patients and families by promising them good and fast results and charging them excessive fees.

However, research on CAM is still in a nebular state and many researchers are yet not convinced as to how safe are the CAM treatments or how well CAM can really work. Therefore, studies are now focused more on the determination of safety and usefulness of many CAM practices. Further, to minimize the health risks of CAM treatment, there should be an open and free discussion between the patients and doctors, because only a doctor knows if such concurrent treatment may have an adverse reaction to generate unwanted side effects. Experienced and qualified CAM practitioners should be selected after going through their credentials and reputation in the field carefully. Extensive research is necessary to establish CAM therapies more convincingly and scientific evidences have started to appear in favor of some CAM therapies along with the standard ones. Some key questions regarding benefits of some CAM therapies, particularly in regard to their safety and work potential, are still daunting in the minds of people believing in rationale use of proper medicines that will only give them additional benefits but no cause for concern in improper state of medical conditions.

However, despite some reservations in use, some CAM therapies have been reported to be very helpful against side-effects of chemotherapy. Mind-body intervention is one type of approach made to overcome patients from stress and symptoms associated with cancer chemotherapy. Positive effects on overcoming chemotherapy related pain, anxiety, depression and chemotherapy-induced nausea have now been documented [51]. Music therapy is recommended in the palliative care setting, with randomized trials indicating benefit for reducing anxiety [52], depression [53] and pain [54]. Even gentle massage was found to be superior when compared to the controls in reducing anxiety, nausea, and fatigue and improving general well-being [55].

In this regard, another approach through acupuncture, a

popular method of CAM, is being increasingly harnessed in many countries both in the South Eastern and Western countries. The use of acupuncture for emesis [56,57] and pain [58] has been claimed to bring about substantial relief. Acupuncture has been approved by NIH for adult postoperative and chemotherapy-associated nausea and vomiting, and for postoperative dental pain [59,60].

Many surveys conducted in the US [9,45] have been conducted to ascertain how knowledgeable the cancer patients are about CAM. In fact, overwhelming majority of patients (99.3%) participating in the survey had heard of CAM, and 83.3% had used at least one CAM therapy during the course of their treatment. Among them, spiritual practices were found to be quite high (35.5%) among cancer patients, apart from the other popular practices like consuming vitamins and herbs (41.9%), and following specific movements and physical exercises suitable for the patient. The most popular therapies among those who responded were vitamins and herbs (41.9%), spiritual practices (35.5%) coupled with mind/body approaches (10.1%) [45]. Preliminary data from the Women's Health Eating and Living study conducted in Cancer Center, University of California, USA showed that up to 80% of non-stage IV breast cancer patients took dietary supplements such as vitamins, anti-oxidants and herbs [61]. However, in recent years, an increased use of herbal products instead of other supplements is gaining momentum in an advanced country like the US [62].

One interesting aspect that needs a mention is that general public tends not to be aware that herbs are dilute natural drugs that contain scores of different chemicals, the function and dose of most of which have not been documented [63]. Therefore, their effects are not always predictable [64]. Patients undergoing active treatment should be told to stop concurrent herbal medication, if there is a deteriorating condition due to problematic interactions with chemotherapeutic agents, sensitization of the skin to radiotherapy, dangerous blood pressure swings, and other unwanted interactions with anesthetics during surgery [65].

Although most participants (about 96%) in some surveys revealed that they did not really experience any obvious ill-effects with CAM, still the potential for harmful drug-herb-supplements interactions do exist [66,67]; therefore there is a need for greater physician/patient communication and more reliable information from patients. It is possible that some herbs or vitamins can mask or distort the effects of conventional treatment; however, results indicate that concurrent use of antioxidants may either enhance standard chemotherapy or reduce side-effects, depending on the agent and antioxidant combination [50,68,69]. In the absence of conclusive evidence, the issue remains unresolved. Thus more focused research initiatives to determine the safety and efficacy of the drug vis-a-vis herb-drug interactions are warranted to get the best results of combined therapies.

Another important aspect is the integration of some CAM agents into the mainstream treatment arena. It happens sometimes that what starts as a CAM medicine, after a thorough research that proves its worth as an effective and safe therapy is transformed into a practically patented orthodox medicine. With such prospect in mind, it also becomes necessary for understanding the efficacy of a CAM in combinatorial treatment, so that it can be adopted as a strategic addition to conventional health care system. Therefore, a free flow

of information between the cancer patients and the oncologist can be mutually beneficial as indications for the need or for that matter any specific contra-indication can be brought to light for a better treatment strategy.

Combined use of chemotherapy with herbal products and dietary supplements

Biologically based therapy uses substances occurring in nature like herbal products and dietary supplements. Herbal supplements can be defined as products made from plants for use in the treatment and management of certain diseases and medical conditions. Many natural/purified plant products and their derivatives [70-72] are already available across the counter as medications declared safe for use by the FDA. Such plant supplements may contain entire plants or plant parts. Further, these may be available in all forms: dried, chopped, powdered, capsule, or liquid; these can be used in various ways; as for example, they can be swallowed as pills, brewed as tea, applied to the skin as gels, or even added to bath water. Although the use of herbs and herbal dietary components dates back to thousands of years, after a lean phase, this appears to be again coming back with a bang as many recent studies on many plant extracts and their active ingredients suggest convincingly that these have potential anti-cancer effects [73-90]; people of Asian countries as well as in some advanced western countries are now more inclined to take recourse to herbal products for lesser diseases. However, proper caution should be taken while these products are to be used in serious cancer patients because some herbal products can cause problems for persons undergoing cancer therapies, such as chemotherapy or radiation therapy. Thus, the use of plant products and their derivatives is under careful scrutiny of the FDA or other governing agencies. For this reason, self-medication of these products is not advisable or wise although many of them can be obtained from medicine shops as over-the-counter medications.

Some interesting recent studies in animal models as well as on cancer cells *in vitro* also demonstrated enhanced anti-cancer potentials of some nano-encapsulated plant extracts and their ingredients [91-97], opening up a new avenue of research to assess the possibility of their use in cancer patients.

Recent research indicates that herbs in combinations with anticancer drugs can re-sensitize the chemo-resistance developed from repeated use of the anticancer drug(s) [98]. Thus, in cancer chemotherapy, the use of herb-drug combination to enhance therapeutic effect may yield the desirable result, often showing reduction/amelioration of the toxic side-effects of chemotherapy [99]. However, more works would be necessary to establish univocally that this may help all cancer patients and the dose has to be carefully selected, for a more confident and deliberate human use.

Some popular herbs and dietary supplements in use and some associated concerns

Ginseng is a widely used drug popular in many countries including China, Japan, Germany, France, Austria, and the United Kingdom. In both Asian countries and Western Europe, this drug is commonly used as an adjuvant for cancer therapy [100,101]. In the US also it is used mostly as a dietary or herbal supplement although its use has not yet been approved as a drug by the Food and Drug Administration [102]. Nevertheless, the benefit of ginseng

consumption in cancer patients is well documented, because its use improves clinical outcomes, enhances quality of life, and helps in enhancing the effects of chemotherapeutic agents. Elaborate reviews are available on ginseng-drug interaction [103-105] but none of these studies highlighted it as an anticancer drug combination for improvement of chemotherapy. In fact, ginseng possibly acts as a tonic to benefit cancer patients, especially in Asia. But several *in vitro*, *in vivo*, and human studies mention ginseng as a potential supportive drug in chemotherapy, because of its low toxicity and many desirable properties such as anti-angiogenesis, anti-proliferation, anti-inflammation, anti-oxidation, apoptosis, and immune modulation effects [105].

Although ginseng had considerable promise as a supportive medicine, some other plant extracts tested did not yield suitable result against cancer. As for example, aqueous fermented mistletoe extracts used in clinical concentration did not apparently have any cytostatic and cytotoxic activity against cancer cells [106]. On the other hand, research on Isadora herb extract showed indication that it could be used concomitantly with conventional oncological drugs without producing any hazard by herb drug interactions [107]. Similarly, a well-designed double-blind, placebo-controlled trial of 70 participants undergoing cancer chemotherapy with the drug 5-FU evaluated the potential benefits of the supplement glutamine for reducing chemotherapy-induced diarrhea [108]. The use of glutamine at a dose of 18 g daily reduced intestinal damage and ameliorated symptoms of diarrhea. The supplement active hexose correlated compound (AHCC) [109] and colostrums [110] also have been reported to have positive action in reducing chemotherapy-induced gastrointestinal side effects. However, the use of creatine as supplement helped to maintain muscle mass in people undergoing chemotherapy for colon cancer [111]. The supplement N-acetylcysteine has shown promise for reducing various side effects of the drug ifosfamide [112-115].

The spice ginger has been shown to reduce nausea caused by the chemotherapy drug 8-MOP [116]. However, ginger was not found effective for nausea in people using the drug cisplatin [117] or in case of chemotherapy-induced nausea and vomiting [118].

Various antioxidants have shown ability to prevent various side-effects of the drug doxorubicin including protection to heart damage. Similarly the herb milk thistle can protect against kidney damage caused by the drug cisplatin [119]. Further, acetyl-L-carnitine, glutamine, and vitamin E supplementation might each reduce peripheral neuropathy symptoms in patients (painful damage to nerves outside the spinal column) receiving cisplatin or Paclitaxel [120]. In some cases, sea buckthorn berry has been reported to reduce side effects of chemotherapy, but more studies are needed to confirm this claim. A review that included results of some 33 studies mainly conducted in the US and other western countries supports the view that antioxidants in general (with the exception of vitamin A) may reduce the toxic effects of chemotherapy [121]. However, it is not clear which antioxidants give the best result. One study suggests that the herb guarana may help to improve fatigue in breast cancer patients undergoing chemotherapy [122]. A list of some useful herbs has been summarized in Table 1 [123-135].

In this context, one factor that seems to be important is the need for standardization of the potency and concentration of the

Table 1: Some valuable herbal agents for chemo preventive and adjunctive therapy.

Common name or family	Scientific name	Proposed therapeutic action	References
Turmeric	<i>Curcuma longa</i>	Anti-inflammatory, antioxidant, anticancer; inhibits carcinogenesis and modulates chemo-resistance and radio-resistance	[123,124]
Radix astragali	<i>Astragalus membranaceus</i>	Immunomodulatory, anticancer, antiviral; Potentiates the activity of chemotherapeutic agents, prolongs survival, reduces the adverse toxicity of chemo- or radio-therapy	[125-127]
Garlic	<i>Allium sativum</i>	Anti-bacterial, anti-hypertensive, anti-thrombotic, anticancer, immuno-stimulant, hyperglycemic; garlic reduces the incidence of stomach, esophageal, and colorectal cancer	[128,129]
Sea buckthorn	<i>Hippophae rhamnoides</i> L.	Preventive and curative effects; reduces the adverse toxicity of chemo- or radio-therapy	[130]
Menisoermaceae	<i>Tinospora bakis</i> L.	Hepatoprotective	[130]
Verbanaceae	<i>Premna tomentosa</i>	Hepatoprotective	[130]
Amla	<i>Emblica officinalis</i>	antioxidant, immunomodulatory, antipyretic, analgesic, cytoprotective, antitussive and gastroprotective	[131]
Decalepis	<i>Decalepis hamiltonii</i>	antimutagenic, anti-inflammatory, anticlastogenic and anticarcinogenic activities	[132]
Mushroom	<i>Agaricus bisporus</i>		[133]
Dill	<i>Anethum graveolens</i> L.	antimicrobial, antihyperlipidaemic and antihypercholesterolaemic activities.	[134]
Alfiler	<i>Bidens pilosa</i> L..	Gastric antisecretory and antiulcer activities; reduces the adverse toxicity of chemo- or radio-therapy	[135]

herbal preparation. This is particularly true for some homeopathic preparations where the dilution and succession method plays a great role [136,137]. Further, the amount of the active ingredient may be altered by the conditions of diluting/processing methods. The problem gets further complicated by the fact that the presence of large numbers of untested or unidentified compounds makes the actual determination of the concentration of the biologically active ingredient difficult. Many herbal preparations, especially those unlicensed and imported under uncontrolled conditions, have been identified with potentially dangerous components, some of them being naturally occurring and some may even be part of the additional chemical used during processing. Therefore, patients who opt to use herbal preparations alongside conventional drugs should think of the risk of serious side-effects. Further, unless specifically tested on this line, some herbal compounds may be found to either increase the activity of given drugs while others may block the action of anti-cancer drugs. One confusion can simply arise out of mistaken use of the plant known by its common name, because the actual species having medicinal property may be a different one which goes by the same common name. There has been report of many cases of misidentification of plants leading to toxic plants being used instead of the non-toxic plant actually meant to be used. Thus authentic plant identification is an absolute necessity before taking it's an herbal remedy.

There are also many possible side-effects from intake of certain types of diet and dietary components which are sometimes reported to cause symptoms such as weakness, diarrhea, or kidney problems. The manufacturers of such diet should invariably put up cautionary note or label on such products. Because improper use of even nourishing components used at a wrong time may prove to be dangerous and even life-threatening. Therefore, any change in diet or

dietary supplements should be under advice of a qualified physician only having knowledge of the constitution of the patient and his disease history, particularly in case of dreadful disease like cancer.

Conclusion

An appraisal of the available literature would undoubtedly lead one to conclude that conventional chemotherapy is the ultimate therapy against cancer. This therapy is more successful for some types of cancer like testicular cancer and certain leukemia; however, its success rate is very low for many cancers like breast cancer, colon cancer, and lung cancer. The main drawback of conventional chemotherapy is Cytotoxicity to the normal cells which in turn produce many adverse side-effects. CAM has been used in a vast spectrum of health care system from historical periods. Historically, the idea behind combination chemotherapy was that by using agents with distinct targets, one could overcome the problem of resistance and harmful side- effects. This is simply due to the probability that individual cells will have, by chance, developed mutations that affect independent mechanisms of drug action.

Many cancer patients in recent years are opting for use of complementary and alternative therapies [138], at least as a supportive one. These patients should first discuss with his oncologist the pros and cons of such an option. Oncologists on their part should be knowledgeable about the CAM options to give an authentic advice, or provide them latest information bits by directing them to the reliable sources of information to satisfy themselves. For the interest of readers, a few helpful web sites are mentioned [139-141].

Because cancer has so long denied mostly all advanced medical approaches after the disease progresses beyond a certain level, and because orthodox chemotherapy approach is bestowed with serious

side-effects, many patients as well as oncologists are now open to using various form of CAM practices simultaneously with the orthodox treatment, primarily with a view to giving the patient a better way of life and to reduce the pain of the disease as well as the treatment. But the choice should be weighed in terms of the disease condition and the anticipated well being of the patient. Therefore, patients should be advised to adopt the right kind of CAM that may help them achieve the goal, but at the same time advise them to avoid all questionable alternative therapies that are not evidence-based. There should be much caution in trying any unproven alternatives just for the sake of experiment or based on unconvincing research promoted by some vested interests. Health-care providers should be convinced before approving the use of any CAM because there is sufficient risk involved in using non-conventional therapies that may aggravate the situation instead of actually helping recovery. However, non-harmful complementary therapies that have proven ability to play a supportive role should not be discouraged just on the basis of its CAM status [142]. Further, CAM provides great hope of immense benefit in children and other sensitive patients who cannot normally tolerate some essential orthodox medicines and are allergic to some indispensable medicines; however, CAM therapies may have a protective role in some cases where they may be used as a supportive medicine to alleviate the toxicity of the orthodox drugs, particularly in normal cells.

On the other hand, complementary therapies that specifically are designed to help manage pain, nausea, fatigue, anxiety, and other symptoms should be integrated into the patient's overall care. Various forms of CAM like Ayurvedic, unani, homeopathy, yoga, acupuncture etc and some non-pharmacological therapies, such as mind-body medicine, bio field therapies, and manipulative and body-based methods may be suitably integrated depending on the condition of the patient and the disease state. In general complementary therapies improve patients' qualities of life, patient satisfaction, and the physician-patient relationship. Combination of CAM with chemotherapeutic agent may reduce harmful toxicity and can increase effectiveness of chemotherapy which may lead to a new age of cancer chemotherapy. Therefore, more rigorous research is warranted to achieve the best results in multi-therapy cancer management.

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