Integrating Dietary Supplements Into Cancer Care

Moshe Frenkel, Donald I. Abrams, Elena J. Ladas, Gary Deng, Mary Hardy, Jillian L. Capodice, Mary F. Winegardner, J. K. Gubili, K. Simon Yeung, Heidi Kussmann and Keith I. Block

Integr Cancer Ther 2013 12: 369 originally published online 25 February 2013
DOI: 10.1177/1534735412473642

Integrative Cancer Therapies
12(5) 369–384

DOI: 10.1177/1534735412473642
ict.sagepub.com

Integrating Dietary Supplements Into Cancer Care

Moshe Frenkel, MD[1,2,*], Donald I. Abrams, MD[3], Elena J. Ladas, MS, RD[4], Gary Deng, MD[5], Mary Hardy, MD[6], Jillian L. Capodice, LAC, MS[7], Mary F. Winegardner, PA-C, MPAS[8], J. K. Gubili, MS[5], K. Simon Yeung, PharmD, MBA, LAc[5], Heidi Kussmann, ND, FABNO[9], and Keith I. Block, MD[10]

Abstract

Many studies confirm that a majority of patients undergoing cancer therapy use self-selected forms of complementary therapies, mainly dietary supplements. Unfortunately, patients often do not report their use of supplements to their providers. The failure of physicians to communicate effectively with patients on this use may result in a loss of trust within the therapeutic relationship and in the selection by patients of harmful, useless, or ineffective and costly nonconventional therapies when effective integrative interventions may exist. Poor communication may also lead to diminishment of patient autonomy and self-efficacy and thereby interfere with the healing response. To be open to the patient's perspective, and sensitive to his or her need for autonomy and empowerment, physicians may need a shift in their own perspectives. Perhaps the optimal approach is to discuss both the facts and the uncertainty with the patient, in order to reach a mutually informed decision. Today's informed patients truly value physicians who appreciate them as equal participants in making their own health care choices. To reach a mutually informed decision about the use of these supplements, the Clinical Practice Committee of The Society of Integrative Oncology undertook the challenge of providing basic information to physicians who wish to discuss these issues with their patients. A list of leading supplements that have the best suggestions of benefit was constructed by leading researchers and clinicians who have experience in using these supplements. This list includes curcumin, glutamine, vitamin D, Maitake mushrooms, fish oil, green tea, milk thistle, Astragalus, melatonin, and probiotics. The list includes basic information on each supplement, such as evidence on effectiveness and clinical trials, adverse effects, and interactions with medications. The information was constructed to provide an up-to-date base of knowledge, so that physicians and other health care providers would be aware of the supplements and be able to discuss realistic expectations and potential benefits and risks.

Keywords

dietary supplements, nutritional supplements, cancer care, complementary medicine, integrative medicine, herbal medicine, vitamins

Introduction

Dietary supplements (DS) are one of the most easy to access complementary and integrative therapies. Use of DS is increasingly common among the US adult population. More than 40% used supplements in the 1988 to 1994 period, and more than one half of the population used them in 2003 to 2006.[1] In 2010, it was estimated that the sale of all US herbal DS exceeded $5.2 billion.[2]

Many studies confirm that the majority of patients undergoing cancer therapy also use self-selected forms of complementary therapies, including DS.[3-5] Compared with healthy populations, cancer patients appear to be more frequent users of DS.[5,6] Previous reports estimate that these products are used by 20% to 55% of cancer patients.[7-11] In more recent reports of women with breast cancer undergoing treatment

[1]University of Texas, Houston, TX, USA
[2]Oncology Institute, Meir Medical Center, Kfar Saba, Israel
[3]San Francisco General Hospital, San Francisco, CA, USA
[4]Columbia University, New York, NY, USA
[5]Memorial Sloan-Kettering Cancer Center, New York, NY, USA
[6]Simms/Mann UCLA Center for Integrative Oncology, Los Angeles, CA, USA
[7]Columbia University Medical Center, New York, NY, USA
[8]Integrative Medicine Consultants, Clear Lake, IA, USA
[9]Cancer Treatment Centers of America, Tulsa, OK, USA
[10]Block Center for Integrative Cancer Treatment, Skokie, IL, USA

*This is a project of the Clinical Practice Committee of The Society of Integrative Oncology.

Corresponding Author:
Moshe Frenkel, Integrative Oncology Consultants, Hashoftim 1B, Zichron Yaacov 30900, Israel.
Email: frenkelm@netvision.net.il

and up to 9 years postdiagnosis, DS use ranged from 67% to 87%.[5,12] Patients may take DS to reduce side effects and organ toxicity, to protect and stimulate immunity, or to prevent further cancers or recurrences. Patients often do not report their use of supplements to their provider.[13,14] As a result, there is a gap in communication between the providers and their patients.

This gap in communication may result from (*a*) patients' perception that their physicians are indifferent or negative toward complementary therapies or (*b*) physicians' emphasis on scientific studies and evidence-based medicine, rather than patient preferences, in the selection of such therapies.[14,15]

The failure of physicians to communicate effectively with patients on complementary and integrative medicine topics may result in a loss of trust within the therapeutic relationship, and in the selection by patients of harmful, useless, or ineffective and costly nonconventional therapies when effective integrative interventions may exist. Poor communication may also lead to diminishment of patient autonomy and self-efficacy and thereby interfere with the healing response.[14-17] Although scientific and evidence-based thinking is fundamental to contemporary medical practice, failure to recognize that patients often do not reason in this way interferes with the physician's ability to address the unspoken needs of the patient with cancer. Psychological, social, and spiritual dimensions of care may be ignored if the physician cannot adapt to the individual needs of the patient or provides care without sensitivity. Particularly when physicians are faced with a question regarding an unfamiliar complementary therapy, they may feel "de-skilled" by being forced outside their zone of comfort and competence. This discomfort can lead to defensiveness and a breakdown in communication with the patient. In contrast, the physician who is receptive to patient inquiries and aware of subtle, nonverbal messages can create an environment of safety in which a patient feels and is protected and can openly discuss potential integrative medicine choices.[16-18]

The physician faces multiple questions and challenges in approaching a patient with cancer who is using DS; the most important issues should be safety and efficacy.[14,19] Often, no adequate studies of a particular supplement have been published. If no safety issues are documented, and there are clinical clues that suggest possible effectiveness, should we discourage the patient from using those supplements despite the limited evidence? Even though we try to base our work on reliable scientific evidence, one cannot overlook the patient perspective in this equation. Patients frequently see natural product consumption as an avenue that they can use to empower themselves, attempt to take control of their health, and increase their quality of life.[17,18,20] Many believe that the physician has limited knowledge on supplements or has no interest in discussing the topic; as a result, most patients do not consult with their physician prior to their decision to use these supplements.[9,21]

However, some patients expect their physician to study the appropriate use of the supplements that are specific to their situation, so they can obtain educated advice and cooperation in decision making.[20] If their physician is not a responsive and reliable source of information, patients obtain and collect information on supplements from a variety of sources, such as advice from friends and relatives, nonprofessional literature, popular magazines, journals, daily newspapers, the Internet, advertisements, and other information provided at the health food store. At times this information is not accurate and occasionally it may even be dangerous.[22]

To be open to the patient's perspective, and sensitive to his or her need for autonomy and empowerment, physicians may need a shift in their own perspectives. Today's informed patients truly value physicians who appreciate them as empowered participants in making their own health care choices. The physician or other health care provider is an informed intermediary, an expert guide, a consultant. Ultimately, the patient must be encouraged and supported to make his or her own choices, informed by the best knowledge of the doctor. Perhaps the optimal approach is to discuss both the facts and the uncertainty with the patient, in order to reach a mutually informed decision.[23]

In 2009, The Society of Integrative Oncology (SIO) came up with a set of guidelines for integrating complementary medicine into cancer care.[24] One of the recommendations related to the use of nutritional supplements:

> *For cancer patients who wish to use nutritional supplements, including botanicals for purported antitumor effects, it is recommended that they consult a trained professional. During the consultation, the professional should provide support, discuss realistic expectations, and explore potential benefits and risks. It is recommended that use of those agents occur only in the context of clinical trials, recognized nutritional guidelines, clinical evaluation of the risk/benefit ratio based on available evidence, and close monitoring of adverse effects.*

To reach a mutually informed decision about the use of these supplements, the Clinical Practice Committee of the SIO took the challenge of providing basic information to physicians who wish to discuss these issues with their patients. Members of that committee, clinicians, and researchers got together to address this need. The clinicians are all members of the SIO, and have extensive experience in integrating supplements to patients affected by cancer and actually provide consultations to patients about this use.

The process of selecting the leading 10 supplements involved the following steps:

1. Each clinician in this project was requested to construct a list of supplements that they tend to use frequently in their practice
2. An initial list of close to 25 supplements was constructed. This list included supplements that have suggestions of some possible benefit and likely to carry minimal risk in cancer care.
3. From that long list, the group agreed on the 10 leading supplements that have the best suggestions of benefit.
4. Each participant selected 1 to 2 supplements that they have interest and experience in their use and wrote a manuscript related to the selected supplement in a uniformed and agreed format. The agreed format was constructed to provide a base of knowledge, so physicians and other health care providers would be able to discuss realistic expectations and potential benefits and risks with patients and families that seek that kind of information.
5. The revised document was circulated among participants for revisions and comments.

In the following pages, we provide the final document that resulted from this process as mutually agreed among the participants about these 10 leading DS.

Curcumin

Background

Curcumin (diferuloylmethane) is the major component of the Indian spice turmeric (*Curcuma longa*). It is found in just about every dish in India and is used as a coloring and flavoring additive in many foods. It has attracted interest because of its anti-inflammatory and chemopreventive activities. Epidemiological evidence indicates that the incidence of certain cancers is less in people who consume curcumin than in those who do not. Basic science research and observational and clinical studies demonstrated that curcumin has some activity against cancer, as well as other inflammatory conditions.[25,26]

Mechanism of Action in Cancer

Curcumin has been shown to prevent a large number of cancers in animal studies. Laboratory data indicate that curcumin can inhibit tumor initiation, promotion, invasion, angiogenesis, and metastasis.[27-31]

Curcumin has been shown to interfere with multiple cell signaling pathways, including cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and downregulation of antiapoptotic gene products), proliferation (HER-2, EGFR, and AP-1), survival (PI3K/AKT pathway), invasion (MMP-9 and adhesion molecules), angiogenesis (VEGF), metastasis (CXCR-4), and inflammation (NF-κB, TNF-α, interleukin [IL]-6, IL-1, COX-2, and 5-LOX).[32]

Curcumin also acts as a chemosensitizer and radiosensitizer for tumors in some cases. Curcumin has also been shown to protect normal organs such as liver, kidney, oral mucosa, and heart from chemotherapy- and radiotherapy-induced toxicity.[33]

The activity of curcumin reported against leukemia and lymphoma, gastrointestinal cancers, familial polyposis, pancreatic cancer, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, and sarcoma reflects its ability to affect multiple targets.[32-36]

Safety and Side Effects

Curcumin has been used for centuries as a spice and food additive with minimal adverse effects, and the FDA is considering it as a GRAS (Generally Recognized as Safe) supplement.[37]

Curcumin may cause an upset stomach, especially in high doses or if given over a long period of time.[38]

Patients with gallbladder problems should be cautioned about the use of curcumin due to the fact that curcumin is capable of contracting the gall bladder and might exacerbate gall bladder disease.[39]

Historically, curcumin has been considered safe when used as a spice in foods during pregnancy and breastfeeding. However, curcumin has been found to cause uterine stimulation and to stimulate menstrual flow, and caution is therefore warranted during pregnancy. Animal studies have not found curcumin taken by mouth to cause abnormal fetal development.[40]

Dosage

There is no clear recommendation for curcumin dosage. In clinical trials, dosage has reached 12 g with no major side effects, but it seems from recent clinical trials that to obtain a clinical effect 500 to 3000 mg is sufficient. Taking the epidemiological data from India, the use of the spice is averaging around 5 g (equals to 150-250 mg of curcumin).

Curcumin has poor bioavailability due to its rapid metabolism in the liver and intestinal wall. To increase the availability, some suggest combining the use with piperine, which improves this bioavailability considerably.[41] Consuming curcumin with meals increases its absorption, especially with fatty foods such as olive oil, avocado, fish oil, milk, seeds, and so on.

Interactions

Based on laboratory and animal studies, curcumin may inhibit platelets in the blood and increase the risk of bleed-

ing caused by other drugs, such as aspirin, anticoagulants, antiplatelet drugs, and nonsteroidal anti-inflammatory drugs.[42] The same caution should be applied to combining curcumin with herbs such as *Ginkgo biloba*, garlic, saw palmetto.

Caution should be used if curcumin is combined with cyclophosphamide and camptothecin due to possible interaction and reduction of apoptosis.[43]

Glutamine

Background

Glutamine is an essential amino acid that has biologic functions including gastrointestinal (GI) cell growth and regeneration. Glutamine is a precursor for glutathione and regulates intracellular redox reactions. It is essential during metabolic stress and injury and metabolized via splanchnic tissue, lymphocytes, kidney, and the liver to glutamate and ammonia.[44]

Mechanism of Action in Cancer Care and Clinical Trials

Glutamine may be useful in the oncologic setting as it has been shown to reduce cytokine production and improve the GI tract mucosal barrier. In various cancer patients undergoing chemotherapy and radiation, when glutamine was added to their treatment, there was decreased rates and severity of mucositis, neuropathy, and intestinal toxicity.[44,45] Additional benefit was observed in decreased use of pain medication in patients suffering from stomatitis, with improved nutrition, as a result of this intervention.[46,47]

Glutamine may be promising for the treatment of chemotherapy-induced peripheral neuropathy possibly via upregulation of nerve growth factor. A recent study of glutamine (10 g PO TID) in breast cancer patients receiving dose dense taxane-based chemotherapy demonstrated reduced frequency of moderate to severe numbness in the glutamine versus nonglutamine group (P = .016) and a trend toward reduced moderate to severe paresthesias.[48]

Another study tested 30 g oral supplementation of glutamine in colon cancer patients receiving oxaliplatin-based chemotherapy and found a lower percentage of chemotherapy-induced peripheral neuropathy in the glutamine group after 4 cycles of treatment versus the control (no supplementation), respectively (P = .05).[49]

Safety and Side Effects

There is need for caution in patients with hepatic and renal impairment. Frequency of adverse reactions has not been defined but side effects, which are rare, include edema, headache, fever, pain, rash, abdominal pain, flatulence, nausea, vomiting, arthralgia, flu-like syndrome, and vomiting.

Dosage

It is commonly used in the powder form to produce oral solution, the dosage in that form is 10 g TID (range = 5-30 g/d). The supplement can be given orally, with enteral formula, or via feeding tube. It also may be given with meals or snacks.

Interactions

Glutamine might decrease the effectiveness of lactulose. The aforementioned trials have not noted that glutamine decreases the effectiveness of chemotherapeutic agents; however, research is inconclusive. Glutamine may interact with antiseizure medications.

Vitamin D

Background

Vitamin D is a vitamin with hormone-like action that controls calcium, phosphorus, and bone metabolism. It is the only vitamin that the body can manufacture from sunlight. An increasing proportion of the world's population is becoming deficient in vitamin D because of indoor living, clothing customs, heliophobia, and sunscreen use.[50] The first suggestion that vitamin D was related to cancer risk came from an observation that colon cancer mortality rates were lower in the southwestern United States compared with the northeast.[51,52] Subsequent studies have supported the finding that lower serum 25-hydroxyvitamin D levels are associated with increased risks of breast and prostate as well as colorectal and possibly other cancers, although the data are considered inconclusive.[53-55] An increasing body of evidence suggests that lower serum levels are also related with poorer prognoses in patients diagnosed with various malignancies.[52]

Mechanism of Action in Cancer Care and Clinical Trials

The mechanistic explanation for the protection of vitamin D and its metabolites against cancer is unclear at present but an area of tremendous ongoing research. The 25-hydroxyvitamin D metabolite, 1, 25-dihydroxyvitamin D, is the biologically active moiety that works through the vitamin D receptor to regulate gene transcription.[51,56,57] Administration of vitamin D analogues produce antiproliferative effects, can activate apoptotic pathways, and inhibit angiogenesis. Additional benefits of vitamin D may be by way of enhancing of the anticancer effects of cytotoxic agents. Other chemoprotective mechanisms by which vitamin D may work include enhancing DNA repair, antioxidant protection, and immunomodulation. One randomized

trial of calcium and vitamin D conducted in Nebraska demonstrated that supplementation reduces all-cancer risk in postmenopausal women.[58] A meta-analysis that included 2 additional randomized studies suggested that high dose (1000 IU/d) vitamin D supplementation can not only reduce the risk of total cancer but also found that higher 25-hydroxyvitamin D concentrations might be associated with increased risk of cancer.[59]

Safety and Side Effects

Vitamin D supplementation is generally safe with few side effects, most commonly gastrointestinal. In one large study of vitamin D and calcium supplementation, an increased risk of renal and urinary stones was noted.[59] Excess vitamin D supplementation can lead to hypercalcemia.[50]

Dosage

Measurement of serum 25-hydroxyvitamin D level should guide dosing.[60] The Institute of Medicine guideline that a level greater than 20 ng/mL is adequate for maintaining bone health may not be appropriate in the care of patients with malignant diagnoses although conclusive evidence of the optimal 25-hydroxyvitamin D level in these patients is lacking.[61] A safe recommendation would be to achieve a 25-hydroxyvitamin D level in the 40 to 80 ng/mL range. Although some food products (eggs, fortified dairy, mushrooms, and fish) may provide small amounts of vitamin D_2 (ergocalciferol), ultraviolet light from the sun is the best source of vitamin D_3 (cholecalciferol), but its production is impaired with age, obesity, and pigmentation. Hence, oral supplementation is advised. Vitamin D is a fat-soluble vitamin, so a liquid or gel-bead preparation will lead to maximal absorption. In severe deficiency, each 1000 IU dose increment should increase 25-hydroxyvitamin D levels by 10 ng/mL, decreasing as optimal levels are achieved.[62]

Interactions

There are no reported interactions between vitamin D supplements and individual antineoplastic agents.[63] Vitamin D is metabolized by the cytochrome P450 hepatic enzyme system so theoretical interactions are possible. Concurrent use with bisphosphonates may have added benefit in increasing bone density. Through its immunomodulatory effects, vitamin D could theoretically interfere with immunosuppressants.

Maitake Mushrooms

Background

Medicinal mushrooms have a long history of use, especially in Asia where hot water fractions (decoctions and essences) are used for treating a number of conditions.[64-66] Most *Basidiomycetes* mushrooms contain biologically active polysaccharides in their fruit bodies, culture mycelia, or culture broth. Mushroom polysaccharides exert their antitumor action by activation of the host immune response. The mushroom β-glucans, resembling bacterial cell walls, complex with complement on macrophages and activate an immune response leading to release of various cytokines that are active in tumor inhibition.[67,68] An intact T-cell immune system is essential for the antitumor activity of medicinal mushrooms. *Grifola frondosa* (Maitake) is an edible soft-fleshed polypore extensively used in traditional Asian medicine for numerous health-promoting purposes. The Maitake D-fraction, a bioactive extract, is a protein-bound polysaccharide (proteoglucan) that has been most widely studied as an adjunct to conventional radiation and chemotherapy.[66,69,70] Whether the "pharmaceuticalization" of single bioactive substances is preferable to the potential synergistic interaction of the many constituents of the whole mushroom or crude extracts has not been established.[65] Interest in the West in the investigation of medicinal mushrooms as potential anticancer agents was piqued by epidemiological studies from Japan and Brazil suggesting that long-term exposure to local medicinal mushroom species was associated with lower cancer mortality rates.[64,65]

Mechanism of Action in Cancer Care and Clinical Trials

The presumed mechanism of action of the Maitake mushroom has been assumed to be that of a biologic response modifier, providing T-cell dependent immune enhancement and activation that enhanced antitumor effect. A carefully conducted phase I/II study investigating immune outcomes detected both immune stimulation and inhibition in a battery of tests.[66] When Maitake D-fraction was given to patients receiving chemotherapy for a number of different cancers, response rates reportedly increased from 12% to 28%.[67] Various chemotherapy side effects were also said to be ameliorated in patients receiving Maitake D-fraction. In the absence of toxicities, it is felt to be a useful adjuvant to chemotherapy. There are also reports of synergy when used with vitamin C as suggested by in vitro and animal model studies.[66] A recent study suggests a direct antitumor effect of Maitake D-fraction with induction of apoptosis observed in breast cancer cell lines.[70]

Safety and Side Effects

The Maitake mushroom is edible and generally regarded as safe. There are no reported side effects of the mushroom extracts or the Maitake D-fraction.[66,71] As Maitake may lower blood sugar, it should be used with caution in patients with diabetes on hypoglycemic agents with careful monitoring of glucose levels while a stable dose is being estab-

lished. Because of immune modulating effects, both stimulation and suppression, some integrative oncologists are reluctant to recommend medicinal mushrooms to patients with lymphoproliferative disorders until further studies have been conducted.

Dosage

A safe and effective dose has not been established.[66,70] The manufacturer's recommended dose should be followed. Although the Maitake D-fraction has been most widely studied, numerous unfractionated whole mushroom preparations are also available.

Interactions

No known interactions are reported. Caution is advised with concurrent diabetes therapies as Maitake may have a hypoglycemic effect. As an adaptogen, Maitake may act as an immune stimulator and/or an immune suppressant, so care should be used in patients on immunomodulatory therapies. Maitake may increase the effect of antineoplastic therapies as an adaptogen, immunostimulant, or by inducing tumor cell apoptosis.

Fish Oil

Background

Fish oil supplements contain oils from cod, krill, menhaden, salmon, sardines, and other species that are high in long-chain polyunsaturated fatty acids. The omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, are most abundant. Fish oils are given in capsules, as part of oral nutritional supplements, or in parenteral or enteral forms.

Mechanism of Action and Clinical Trials

Epidemiological studies do not show that fish intake reduces cancer risk; several factors may mask this effect including cooking methods and dietary omega-6 fatty acids.[72] A randomized trial observed reduction of rectal polyps in familial adenomatous polyposis by fish oil.[73] Fish oil may affect cancer cachexia by inhibiting proinflammatory cytokines that contribute to the acute phase protein response and consequent muscle degradation.[74] Multiple studies of fish oil have shown mixed results in maintaining weight and lean body mass in advanced cancer patients.[75] Recent studies in patients with earlier stage cancers, especially those receiving chemotherapy or chemoradiation, have shown beneficial effects on body weight and quality of life.[76,77] Fish oil also reduces inflammation through changes in membrane fluidity, cell signaling, and production of anti-inflammatory eicosanoids and resolvins.[78] These effects may retard cancer progression. Two studies in prostate cancer paired fish oil with low-fat diets. The interventions reduced prostate-specific antigen levels, delayed need for conventional treatment in a watchful waiting population, and reduced Ki-67 proliferation index.[79,80] A third study found no difference on rates of postsurgical biochemical failure in Japanese prostate cancer patients.[81] Fish oil may increase apoptosis and decrease resistance by suppressing NF-κB.[82] Higher rates of response and clinical benefit with a tendency toward longer survival were observed in lung cancer patients supplemented with fish oil during chemotherapy, with no increase in dose-limiting toxicities.[83] Fish oil improved neutrophil number and function during chemotherapy, and reduced weight loss.[84]

Finally, fish oil is used as perioperative immunonutrition—enteral supplements containing fish oil with arginine and other nutrients have been found to reduce hospital stays and postoperative complications.[85,86]

Dosage Safety and Side Effects

Dosing in clinical studies is 2 to 3 g per day. Bloating, loose stools, fishy aftertaste, and eructations are the most commonly observed toxicities at these levels; enteric coating of capsules reduces them. High vitamin A levels and environmental contaminants are concerns that are typically addressed in processing; fish oil is also easily oxidized and is often formulated with antioxidants. Fish oil may increase bleeding time, although observational studies of patients using fish oil before surgery do not observe clinical concerns.[87,88]

Interactions

Anticoagulant/antiplatelet drugs. Caution and monitoring should be exercised while supplementing patients on anticoagulant/antiplatelet drugs with vitamin A, especially at doses higher than 3 g per day.

Chemotherapy-induced thrombocytopenia. Because of the risk of increased bleeding tendency, some clinicians suggest holding fish oil administration during chemotherapy for patients with platelet levels below 50,000.

Antihypertensive drugs. Clinicians need to be aware that fish oil has hypotensive effects and may accentuate the effect of antihypertensive medications.

Green Tea (*Camellia sinensis*)

Background

Green tea consists of unfermented *Camellia sinensis* tea leaves with a high polyphenol content, 40% of which is epigallocatechin gallate (EGCG).

Mechanism of Action and Clinical Trials

Green tea has multiple mechanisms of action including pro-apoptotic effects, inhibition of NF-κB and other signaling molecules,[89] antimetastatic,[90] and prooxidative and antioxidative effects. In lab studies, it enhances activity of some chemotherapy agents.[91]

Clinical trials in prostate cancer suggest that green tea may be more effective in early than later-stage conditions[92,93]; short-term administration before prostatectomy suggests favorable chemopreventive effects.[94,95] Premalignant oral lesions are suppressed by green tea supplements.[96] Positive effects were shown for a topical preparation in human papilloma virus–infected cervical lesions. Breast cancer patients drinking green tea had improved high-density lipoprotein cholesterol and nonsignificant improvements in insulin resistance and weight.[97] Asymptomatic early stage patients with chronic lymphocytic leukemia received high-dose Polyphenon E in a phase I trial; improvements in absolute lymphocyte count and adenopathy as well as one partial remission were observed.[98]

Safety and Side Effects

For preparations that contain caffeine, caffeine-related side effects are observed, including increased gastric acidity, effects on blood glucose, and elevated catecholamine levels. For caffeinated and decaffeinated green tea and supplements, several incidents of liver toxicity have been observed, although prevention of liver disease has been observed in epidemiological studies.[99] Clinical studies have reported grade 1 transaminitis[98]; low-grade gastrointestinal toxicity has also been reported. A canine study suggested that taking green tea supplements on an empty stomach increased toxicity, although bioavailability was also enhanced.[99] Liver enzymes should be monitored in patients taking high-dose green tea supplements.

Interactions

Anticoagulants. Theoretical concerns and a case report suggest that large quantities (about 1 gallon/day) of green tea may antagonize warfarin, perhaps due to vitamin K content.[100] Green tea also has antiplatelet activity.

Bortezomib. In vitro and in vivo testing suggest that EGCG could inhibit activity of bortezomib in multiple myeloma (for which bortezomib is approved).[101] However, in vivo testing found this effect only at unrealistically high concentrations in an experimental prostate cancer model.[102] Still with that concern in mind, some clinicians suggest to consider caution about the combined use of green tea and bortezomib.

Cytochrome P450 isoform 3A4 (CYP450 3A4).High dose of green tea may inhibit CYP450 3A4, and one case of clinically significant interaction with tacrolimus has been reported. Based on human trials, beverage use and low-dose supplements (<800 mg/d) are found unlikely to affect this enzyme.[103]

Hepatotoxic drugs. Liver enzymes must be monitored more closely due to potential hepatotoxicity.[99]

P-glycoprotein. EGCG inhibits P-glycoprotein and may cause interaction with irinotecan or verapamil; it prolongs the half-life of irinotecan, potentially enhancing both activity and adverse potential.[104,105]

Sunitinib. A case and laboratory study suggests a possible interaction between green tea and sunitinib.[106]

Tamoxifen. Green tea may increase tamoxifen bioavailability.[107]

UGT (uridine 5′ diphospho-glucuronosyltranferase) substrates. Green tea may increase side effects of drugs metabolized by this enzyme due to increased exposure.[99]

Milk Thistle

Background

Milk thistle, *Silybum marianum*, is a plant whose fruit and seeds have been used for more than 2,000 years as a treatment for liver and biliary disorders as well as for protection from hepatotoxins. The most active compounds found in extracts of milk thistle are flavonoids and flavonolignans, which may be found in the dried milk thistle seeds. Silymarin, a complex of flavonolignans and one flavonoid, constitutes 65% to 80% of milk thistle extracts.[108]

Mechanism of Action in Cancer

Clinical trials of silymarin have been conducted primarily in patients with either hepatitis or cirrhosis.[109] Silymarin is the only known drug effective in protection from *Amanita phalloides* toxin, which targets the liver.[110,111]

Three case reports,[112-114] 3 pharmacokinetic studies,[115-117] and 2 double-blind randomized trials[118,119] have been conducted with varying degrees of scientific rigor. In the only report describing the use of silymarin (450 mg/d) for the treatment of hepatocellular carcinoma, the authors reported spontaneous regression of the tumor in the absence of initiation of anticancer therapy.[112] In a double-blind, placebo-controlled randomized trial, 50 children who were undergoing treatment for acute lymphoblastic leukemia and who had chemotherapy-related hepatotoxicity were given silymarin (80-360 mg/d) for a 30-day period.[118] The treatment group had a significantly lower aspartate aminotransferase and a trend toward a significantly lower alanine aminotransferase. Vidlar et al[119] explored the effect of milk thistle (570 mg) in combination with selenium on quality of life, lipid profile, oxidative stress, and testosterone levels. Thirty-seven men who underwent radical prostatectomy were randomized to milk thistle and selenium or placebo for

a 6-month period. The authors reported significant improvements in quality of life and lipid panel (total cholesterol and low-density lipoproteins); however, no effect was observed on measures of oxidative stress or testosterone levels. No adverse events were reported.

Safety and Side Effects

Milk thistle may be safely administered with drugs that are substrates for CYP450 3A4 and UDP glucuronosyltransferases isoform 1A1 (UGT1A1).[117] However, the safety of this combination may be dose dependent. A phase I study found that doses of ≤13 g are likely safe but higher doses may inhibit UGT1A1.[115] Hoh et al[116] explored the role of silibinin in 24 patients with colorectal carcinoma who were administered a daily dose of 360, 720, or 1440 mg of silibinin for 7 days before surgery. No adverse events were associated with silibinin at any of the dose levels.

Dosage

There is no clear recommendation for milk thistle dosage. An average of 200 to 400 mg per day in divided doses has been used in most of the studies investigating silymarin for hepatic disorders and antilipidemic effects. Teas made from the crushed seed are used for mild gastrointestinal upset; however, because of its lipophilic properties only a small percentage of silymarin is found in aqueous solution. Daily doses ranging from 2 to 13 g are safe.[115]

Interactions

Two studies have evaluated the combination of milk thistle with irinotecan. Irinotecan is a substrate for many enzymes that are involved in the metabolism of many classes of chemotherapy agents. van Erp et al investigated the interaction between milk thistle (200 mg, 3 times per day) and irinotecan in 6 patients undergoing treatment for cancer.[117] No adverse events or altered pharmacokinetics were found.

Astragalus membranaceus

Background

The root of *Astragalus membranaceus* (aka *Radix astragali*, milk vetch, or *huang qi* in Chinese) is commonly used in traditional Chinese medicine herbal formulations. It is thought to have tonifying properties that "strengthen Qi (energy)". It is used as a supportive agent during cancer treatment, and data from clinical studies suggest that it may be beneficial when used in conjunction with chemotherapy.[120]

Major constituents of astragalus include triterpenoid saponins (cycloastragenol, astragaloside I to VIII, and cyclocanthoside), cycloartane triterpene, polysaccharides, isoflavonoids, and amino acids.[121] Astragalus demonstrated immunomodulatory properties in laboratory studies, which may be responsible for its in vivo effects.

Mechanism of Action

The polysaccharides in astragalus were found to potentiate the immune-mediated antitumor activity of IL-2 in vitro,[122] improve lymphocyte responses in both healthy subjects and cancer patients, enhance natural killer (NK) cell activity in healthy subjects, potentiate activity of monocytes,[123] and increase phagocytosis perhaps by regulating tumor necrosis factor (TNF) production.[124] The saponins potentiate NK cell activity and restore steroid-inhibited NK cell activity in vitro. They also increase phagocytosis and demonstrate hepatoprotective effects on chemical-induced liver injury in vitro[125] and in vivo.[126]

Astragalus has been reported to have direct anticancer effects: Astragalus extracts inhibit tumor growth,[124] delay chemical-induced hepatocarcinogenesis in rats,[126] have antiangiogenic property,[127] and may also enhance the effects of platinum-based chemotherapy.[120]

Clinical Trials

There have been many studies of astragalus related to cancer treatment. Astragalus tends to be well tolerated, and preclinical studies support the immunomodulatory activities of astragalus extracts. Quite a few randomized controlled trials have also been conducted to compare the combination of astragalus with chemotherapy versus chemotherapy alone. Beneficial effects were observed. However, current evidence is not conclusive because of the low quality of the studies. The majority of the clinical trials were conducted in China using multiherb formulas that contain astragalus as the major component.

A meta-analysis of 45 randomized controlled trials suggests benefits of astragalus-based treatments for hepatocellular cancers, but the quality of the original reports was poor.[128]

Another meta-analysis was conducted in the setting of platinum-based chemotherapy for advanced non-small-cell lung cancer. Thirty-four randomized studies involving 2815 patients were analyzed. Results suggest that when used in conjunction with platinum-based chemotherapy, astragalus-based medicine improved survival, tumor response, performance status, and reduced chemotherapeutic toxicity when compared with chemotherapy alone. However, the quality of the original trials is not high, and the results are, therefore, not conclusive.[120]

In a Cochrane systematic review, 4 clinical trials were included to assess the effectiveness of astragalus on the quality of life, side effects of chemotherapy, and on adverse effects in colorectal cancer patients. A reduction in nausea and vomiting along with a decrease in the rate of leucopenia and an increase in T-lymphocytes were observed in the astragalus group compared with those treated with chemotherapy alone in the 3 studies, or with other Chinese herbal formulas in the fourth study. A major limitation of this review is that it includes only 4 studies and that the studies are of poor quality.[129]

Safety and Side Effects

Astragalus is well tolerated. Adverse effects have not been reported.

Dosage

Astragalus is frequently used as a component of a multiherb formulation. The amount of raw herb required to make the formulation varies between 10 and 90 g. It is unclear what the optimal dose is when only the astragalus extract or when a major constituent is used.

Interactions

Because of its immunomodulatory effects, astragalus may antagonize the effects of immunosuppressants such as tacrolimus and cyclosporine. It was reported to reduce immunosuppression following cyclophosphamide treatment and potentiate tumoricidal activity of aldesleukin (IL-2).[123,130,131] Astragalus should not be used in patients who are on immunosuppressants.

Melatonin

Background

Melatonin is the hormone secreted from the pineal gland following synthesis from tryptophan. Interest in melatonin for cancer therapy followed single institution reports of improved survival. Subsequent randomized trials and meta-analyses suggest a role for melatonin in the management of oncologic disease, although much of the data comes from basic science research.[132,133]

Melatonin secretion correlates with circadian rhythms and sleep patterns and shows decline with age. Melatonin regulates a number of physiological functions, including growth hormone production, stimulation of apoptosis, upregulation of antioxidant enzymes, suppression of tumor and endothelial growth factors, and downregulation of pro-oxidative enzymes.[132-134]

Melatonin activity at physiologic levels suppresses tumor cell proliferation and at higher levels is cytotoxic. Supplemental melatonin is effective in improving sleep for individuals with delayed sleep phase. Of epidemiologic interest is the relationship between nocturnal light exposure (third-shift workers) and reported increased incidence of breast cancer and colon cancer. Shift work is now recognized as a probable carcinogen by the International Agency on Research on Cancer.[135-138]

Mechanism of Action

Melatonin levels are low during the day and rise in the early evening in response to dimming light and darkness, thereby cueing the mind and body to rest and hence the concerns about activities, which interrupt sleep cycling and sleep–darkness correlation. Melatonin has been postulated to play a key role in increased breast cancer among those with nocturnal light exposure.

Multiple mechanisms have been postulated and identified to explain these observations. Several of the previously mentioned physiologic functions regulated by melatonin are tumor suppressive. Other mechanisms under study, which affect breast tumor growth and are modulated by melatonin, include interference of estrogen synthesis by melatonin and action on estrogen receptors as a selective estrogen enzyme modifier.[139-141]

Safety and Side Effects

Two recent meta-analyses have indicated improved survival at 1 year among cancer patients using melatonin as adjuvant. Wang et al[142] pooled data from 8 randomized controlled trials comparing melatonin (20 mg) concurrently administered with chemotherapy and/or radiotherapy to conventional therapy alone. Complete and partial remission rates were 32.6% (melatonin arm) versus 16.5% (conventional therapy arm; $P < .00001$) with a 1-year survival rate of 52.2% (melatonin) versus 28.4% (control; $P < .001$). The melatonin group reported less thrombocytopenia, neurotoxicity, and fatigue. Seely et al[143] reviewed 21 clinical trials of solid tumors comparing conventional treatment with and without adjuvant melatonin. The meta-analysis reported pooled relative risk of 1-year mortality at 0.63 (95% confidence interval = 0.53-0.74; $P < .001$). The data suggest that melatonin can be used safely with benefit and without adverse impact on conventional therapy outcomes.[142,143]

Dosage

Common sleep supplement dosages range from 0.5 to 3 mg daily with dosages of up to 20 mg daily used in solid tumor

adjuvant therapy. The melatonin dosage referenced in previous studies was 20 mg.

Interactions

Cautions in the use of melatonin include the possibility of CYP1A2 and CYP2C9 metabolized drug interactions. Melatonin may theoretically affect glucose tolerance and anticoagulant pharmacology. Many substances and medications endogenously suppress melatonin production including caffeine, alcohol, nonsteroidal anti-inflammatory drugs, beta-blockers, benzodiazepines, diuretics, and calcium channel blockers. Luvox has been shown to significantly increase bioavailability of exogenous melatonin when taken concurrently.[144-147]

Probiotics

Background

Probiotics are live microorganisms that, when administered in adequate amounts, are intended to have a health benefit on the host. These microorganisms exist in the body and have immune modulating properties. They affect gut mucosal maintenance, dietary nutrient absorption, and defense against exogenous bacterial pathogens. There is some evidence that the use of probiotics may be of benefit in the prevention and treatment of antibiotic associated diarrhea, infectious diarrhea, irritable bowel syndrome, *Helicobacter pylori, Clostridium difficile*, and others.[148-170]

Use in Cancer Care and Clinical Trials

The main use of probiotics in cancer care is in the treatment of intestinal toxicity during both chemotherapy and radiation.[162-169] Colorectal cancer patients receiving one of two 5-flurouracil chemotherapy regimens were randomized to receive either *Lactobacillus rhamnosus* GG or guar gum. Subjects receiving the probiotic had fewer episodes of high-grade diarrhea and less abdominal discomfort. They also needed less hospital care and had fewer reductions in chemotherapy dose related to bowel toxicity. There was no toxicity associated with the Lactobacillus therapy.[162] Similar findings were found in 206 subjects receiving abdominal and pelvic radiation combined with probiotics.[163] A larger cohort of subjects (n = 490) who underwent adjuvant postoperative radiation therapy after surgery for sigmoid, rectal, or cervical cancer were assigned to either the high-potency probiotic preparation or placebo.[165] Treated subjects showed a lower incidence of radiation-induced diarrhea (32% vs 52%; $P < .001$), less severe high-grade diarrhea (1% vs 33%; $P < .001$), and less bowel movements (15 vs 5; $P < .05$). Again, the therapy was well tolerated. In another study, patients with locally advanced cervical cancer receiving radiation therapy combined with live *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* reduced the incidence of radiation-induced diarrhea and the need for antidiarrheal medication. Of the 63 patients enrolled, grade 2 to 3 diarrhea was observed in 45% of the placebo group (n = 31) and 9% of the study drug group (n = 32; $P = .002$). Antidiarrheal medication use was significantly reduced in the treatment group ($P = .03$). The patients in the study drug group had a significantly improved stool consistency ($P < .001$).[166]

Safety and Side Effects

There are no known safety issues with most probiotic bacteria at appropriate doses in healthy people, but some people occasionally notice a temporary increase in digestive gas. Some raise theoretical concerns about the possibility of sepsis from probiotic use in patients with grade 2 or higher neutropenia. But in a study with a group of 11 patients undergoing chemotherapy and taking probiotics, tolerance of the probiotic was excellent, even though some of the patients developed grade 3/4 neutropenia secondary to the chemotherapy.[170]

On the other hand, a report from Spain about 3 cases of fungemia with *Saccharomyces cerevisiae* revealed that the only identified risk factor for that infection was treatment with a probiotic containing *Saccharomyces boulardii*, probiotics that are commonly used in Europe for the treatment and prevention of *Clostridium difficile*–associated diarrhea. The authors concluded that probiotics should be carefully used, particularly in immunosuppressed or critically ill patients.[171]

Patients should be aware that any lactose fermenting probiotics (eg, Lactobacilli and Bifidobacterium) can potentially contain residual milk proteins and be allergenic.

Dosage

The types and number of organisms taken as probiotics depend on their intended use. In the case of chemotherapy-induced diarrhea, a dose of 10 to 20 billion cells of *Lactobacillus GG* (*Culturelle*) daily has shown to be effective.[162]

Interactions

At the time of writing this article, there are no known clear interactions with conventional cancer treatments and probiotic species. There is a theoretical concern that probiotic efficacy might be reduced when taken at the same time as antibiotics. So it is suggested by some practitioners that

patients take probiotics at least 2 hours after antibiotics to maintain efficacy of both. Others express caution about taking iron supplementation simultaneously with probiotics as iron may hinder probiotic growth.[172]

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Gahche J, Bailey R, Burt V., et al. *Dietary Supplement Use Among US Adults has Increased Since NHANES III (1988-1994)* (NCHS Data Brief, No. 61). Hyattsville, MD: National Center for Health Statistics; 2011.
2. Blumenthal M. Herb sales continue growth: up 3.3% in 2010. *HerbalGram*. 2011;90:64-67.
3. Richardson M, Sanders T, Palmer J, et al. Complementary alternative medicine use in a comprehensive cancer center and the implications for oncology. *J Clin Oncol*. 2000;18:2505-2514.
4. Sparber A, Bauer L, Curt G, Greisinger A, Singletary SE. Use of complementary medicine by adult patients participating in cancer clinical trials. *Oncol Nurs Forum*. 2000;17:623-630.
5. Velicer CM, Ulrich CM. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. *J Clin Oncol*. 2008;26:665-673.
6. Giovannucci E, Chan AT. Role of vitamin and mineral supplementation and aspirin use in cancer survivors. *J Clin Oncol*. 2010;28:4081-4085.
7. Sandler S, Halabi S, Kaplan E, Baron JA, Paskett E, Petrelli NJ. Use of vitamins, minerals, and nutritional supplements by participants in a chemoprevention trial. *Cancer*. 2001;91:1040-1045.
8. Newman V, Rock C, Faerber S, Flatt SW, Wright FA, Pierce JP. Dietary supplement use by women at risk for breast cancer recurrence. The womens healthy eating and living study group. *J Am Diet Assoc*. 1998;98:285-292.
9. Von Gruenigen V, White L, Kirven M, Showalter AL, Hopkins MP, Jenison EL. A comparison of complementary and alternative medicine use by gynecology and gynecologic oncology patients. *Int J Gynecol Cancer*. 2001;11:205-209.
10. Boon H, Stewart M, Kennard M, et al. Use of complementary/alternative medicine by breast cancer survivors in Ontario: prevalence and perceptions. *J Clin Oncol*. 2000;18:2515-2521.
11. Paltiel O, Avitzour T, Cherny N, et al. Determinants of the use of complementary therapies by patients with cancer. *J Clin Oncol*. 2001;19:2439-2444.
12. Kwan ML, Weltzien E, Kushi LH, Castillo A, Slattery ML, Caan BJ. Dietary patterns and breast cancer recurrence and survival among women with early-stage breast cancer. *J Clin Oncol*. 2009;27:919-926.
13. Eisenberg D, Davis R, Ettner S, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA*. 1998;280:1569-1575.
14. Frenkel M, BenArye E, Baldwin CD, Sierpina V. Approach to communicating with patients about the use of nutritional supplements in cancer care. *South Med J*. 2005;98:289-294.
15. Tasakli K, Maskarinec G, Shumay D, et al. Communication between physicians and cancer patients about complementary and alternative medicine: exploring patients' perspectives. *Psychooncology*. 2002;11:212-220.
16. Frenkel M. Clinical consultation, a personal perspective: components of a successful integrative medicine clinical consultation. *J Soc Integr Oncol*. 2008;6:129-133.
17. Frenkel M, Ben Arye E, Cohen L. Communication in cancer care: Discussing complementary and alternative medicine. *Integr Cancer Ther*. 2010;9:177-185.
18. Frenkel M, Cohen L, Peterson N, Swint K, Palmer L, Bruera E. Integrative medicine consultation service in a comprehensive cancer center: findings and outcomes. *Integr Cancer Ther*. 2010;9:276-283.
19. Weiger W, Smith M, Boon H. Advising patients who seek complementary and alternative medical therapies for cancer. *Ann Intern Med*. 2002;137:889-903.
20. Eliason B, Huebner J, Marchand L. What physicians can learn from consumers of dietary supplements. *J Fam Pract*. 1999;48:459-463.
21. Eliason B, Myzkowski J, Marbella A, Rasmann DN. Use of dietary supplements by patients in a family practice clinic. *J Am Board Fam Pract*. 1996;9:249-253.
22. Gotay C, Dumitriu D. Health food store recommendations for breast cancer patients. *Arch Fam Med*. 2000;9:692-698.
23. Ben-Arye E, Frenkel M, Margalit R. Approaching complementary and alternative medicine use in patients with cancer: questions and challenges. *J Ambul Care Manage*. 2004;27:53-62.
24. Deng GE, Frenkel M, Cohen L, et al. Evidence-based clinical practice guidelines for integrative oncology: complementary therapies and botanicals. *J Soc Integr Oncol*. 2009;7:85-120.
25. Thamlikitkul V, Bunyapraphatsara N, Dechatiwongse T. Randomized double blind study of *Curcuma domestica Val*. for dyspepsia. *J Med Assoc Thai*. 1989;72:613-620.
26. Hanai H, Iida T, Takeuchi K, Watanabe F. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol*. 2006;4:1502-1506.
27. Kaur C, Kapoor HC. Anti-oxidant activity and total phenolic content of some Asian vegetables. *Int J Food Sci Technol*. 2002;37:153-161.

28. Gupta SC, Kim JH, Kannappan R, Reuter S, Dougherty PM, Aggarwal BB. Role of nuclear factor-{kappa}B-mediated inflammatory pathways in cancer-related symptoms and their regulation by nutritional agents. *Exp Biol Med (Maywood)*. 2011;236:658-671.
29. Karin M, Greten FR. NF-kappaB: linking inflammation and immunity to cancer development and progression. *Nat Rev Immunol*. 2005;5:749-759.
30. Shishodia S, Chaturvedi MM, Aggarwal BB. Role of curcumin in cancer therapy. *Curr Probl Cancer*. 2007;31: 243-305.
31. Kunnumakkara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett*. 2008;269:199-225.
32. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Lett*. 2008;267:133-164.
33. Goel A, Aggarwal BB. Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs. *Nutr Cancer*. 2010;62:919-930.
34. Cruz-Correa M, Shoskes DA, Sanchez P, et al. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. *Clin Gastroenterol Hepatol*. 2006;4:1035-1038.
35. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res*. 2008;14:4491-4499.
36. Vadhan Raj S, Weber D, Giralt S, et al. Curcumin downregulates NF-KB and related genes in patients with multiple myeloma: results of a phase1/2 study [abstract]. Paper presented at: 49th American Society of Hematology Meeting; December 8-11, 2007; Atlanta, GA.
37. US Food and Drug Administration. Center for Food Safety and Applied Nutrition, Office of Premarket Approval. EAFUS: A food additive database. http://www.usc.es/caa/EdulcWeb/EAFUS.pdf. Accessed December 27, 2012.
38. Sharma RA, McLelland HR, Hill KA, et al. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clin Cancer Res*. 2001;7:1894-1900.
39. Rasyid A, Rahman AR, Jaalam K, Lelo A. Effect of different curcumin dosages on human gall bladder. *Asia Pac J Clin Nutr*. 2002;11:314-318.
40. McGuffin M, Hobbs C, Upton R, Goldberg A, eds *American Herbal Products Association's Botanical Safety Handbook*. Boca Raton, FL: CRC Press; 1997.
41. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med*. 1998;64:353-356.
42. Shah BH, Nawaz Z, Pertani SA. Inhibitory effect of curcumin, a food spice from turmeric, on platelet-activating factor- and arachidonic acid-mediated platelet aggregation through inhibition of thromboxane formation and Ca2+ signaling. *Biochem Pharmacol*. 1999;58:1167-1172.
43. Somasundaram S, Edmund NA, Moore DT, Small GW, Shi YY, Orlowski RZ. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. *Cancer Res*. 2002;62:3868-3875.
44. Access Medicine. Glutamine. www.accessmedicine.com. Accessed April 7, 2012.
45. Hardy ML. Dietary supplement use in cancer care: help or harm. *Hematol Oncol Clin North Am*. 2008;22:581-617.
46. Anderson PM, Schroeder G, Skubitz KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. *Cancer*. 1998;83:1433-1439.
47. Skubitz KM, Anderson PM. Oral glutamine to prevent chemotherapy induced stomatitis: a pilot study. *J Lab Clin Med*. 1996;127:223-228.
48. Vahdat L, Kyriakos P, Lange D, et al. Reduction of paclitaxel-induced peripheral neuropathy with glutamine. *Clin Cancer Res*. 2001;7:1192-1197.
49. Wang W, Lin J, Lin T, et al. Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients. *Oncologist*. 2007;12:312-319.
50. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clin Proc*. 2010;85:752-758.
51. Deeb KK, Trump DL, Johnson CS. Vitamin D signaling pathways in cancer: potential for anticancer therapeutics. *Nat Rev Cancer*. 2007;7:684-700.
52. Rheem DS, Baylink DJ, Olafsson S, Jackson CS, Walter MH. Prevention of colorectal cancer with vitamin D. *Scand J Gastroenterol*. 2010;45:775-784.
53. Davis CD, Hartmuller V, Freedman M, et al. Vitamin D and cancer: current dilemmas and future needs. *Nutr Rev*. 2007;65(8 pt 2):S71-S74.
54. Jenab M, Bueno-de-Mesquita HB, Ferrari P, et al. Association between pre-diagnostic circulating vitamin D concentration and risk of colorectal cancer in European populations: a nested case-control study. *BMJ*. 2010;340:b5500.
55. Grant WB. Ecological studies of the UVB-vitamin D-cancer hypothesis. *Anticancer Res*. 2012;32:223-236.
56. Ali MM, Vaidya V. Vitamin D and cancer. *J Cancer Res Ther*. 2007;3:225-230.
57. Fleet JC, DeSmet M, Johnson R, Li Y. Vitamin D and cancer: a review of molecular mechanisms. *Biochem J*. 2012;441:61-76.
58. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr*. 2007;85:1586-1591.
59. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the US Preventive Services Task Force. *Ann Intern Med*. 2011;155:827-838.

60. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2011;96:1911-1930.
61. Institute of Medicine. *2011 Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011.
62. Garland CF, French CB, Baggerly LL, Heaney RP. Vitamin D supplement doses and serum 25-hydroxyvitamin D in the range associated with cancer prevention. *Anticancer Res*. 2011;31:617-622.
63. Natural Standard. *Vitamin D* (Professional Monograph). www.naturalstandard.com. Accessed April 8, 2012.
64. Wasser SP. Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. *Appl Microbiol Biotechnol*. 2002;60:258-274.
65. Sullivan R, Smith JE, Rowan NJ. Medicinal mushrooms and cancer therapy: translating a traditional practice into western medicine. *Perspect Biol Med*. 2006;49:159-170.
66. Deng G, Lin H, Seidman A, et al. A phase I/II trial of polysaccharide extract from *Grifola frondosa* (Maitake mushroom) in breast cancer patients: immunological effects. *J Cancer Res Clin Oncol*. 2009;135:1215-1221.
67. Konno S. Synergistic potentiation of D-fraction with vitamin C as possible alternative approach for cancer therapy. *Int J Gen Med*. 2009;2:91-108.
68. Stamets P. Potentiation of cell-mediated host defense using fruitbodies and mycelia of medicinal mushrooms. *Int J Med Mushrooms*. 2003;5:179-191.
69. Konno S, Aynehchi S, Dolin DJ, Schwartz AM, Choudhury MS, Tazaki H. Anticancer and hypoglycemic effects of polysaccharides in edible and medicinal maitake mushroom *Grifola frondosa* (Dicks.:Fr.) S.F. Gray. *Int J Med Mushrooms*. 2002; 4:185-195.
70. Soares R, Meireles M, Rocha A, et al. Maitake (D fraction) mushroom extract induces apoptosis in breast cancer cells by BAK-1 gene activation. *J Med Food*. 2011;14: 563-572.
71. Natural Standard. *Maitake mushroom* (Professional Monograph). http://www.naturalstandard.com. Accessed April 8, 2012.
72. Sala-Vila A, Calder PC. Update on the relationship of fish intake with prostate, breast, and colorectal cancers. *Crit Rev Food Sci Nutr*. 2011;51:855-871.
73. West NJ, Clark SK, Phillips RK, et al. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. *Gut*. 2010;59:918-925.
74. Murphy RA, Mourtzakis M, Mazurak VC. n-3 polyunsaturated fatty acids: the potential role for supplementation in cancer. *Curr Opin Clin Nutr Metab Care*. 2012;15: 246-251.
75. Ries A, Trottenberg P, Elsner F, et al. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: an EPCRC cachexia guidelines project. *Palliat Med*. 2011;26:294-304.
76. Murphy RA, Mourtzakis M, Chu QS, Baracos VE, Reiman T, Mazurak VC. Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. *Cancer*. 2011;117:1775-1782.
77. van der Meij BS, Langius JA, Smit EF, et al. Oral nutritional supplements containing (n-3) polyunsaturated fatty acids affect the nutritional status of patients with stage III non-small cell lung cancer during multimodality treatment. *J Nutr*. 2010;140:1774-1780.
78. Calder PC. Fatty acids and inflammation: the cutting edge between food and pharma. Eur J Pharmacol. (suppl 1): S50-S58.
79. Aronson WJ, Kobayashi N, Barnard RJ. Phase II prospective randomized trial of a low-fat diet with fish oil supplementation in men undergoing radical prostatectomy. *Cancer Prev Res (Phila)*. 2011;4:2062-2071.
80. Frattaroli J, Weidner G, Dnistrian AM, et al. Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology*. 2008;72:1319-1323.
81. Higashihara E, Itomura M, Terachi T, et al. Effects of eicosapentaenoic acid on biochemical failure after radical prostatectomy for prostate cancer. *In Vivo*. 2010;24:561-565.
82. Shaikh IA, Brown I, Wahle KW, Heys SD. Enhancing cytotoxic therapies for breast and prostate cancers with polyunsaturated fatty acids. *Nutr Cancer*. 2010;62:284-296.
83. Murphy RA, Mourtzakis M, Chu QS, Baracos VE, Reiman T, Mazurak VC. Supplementation with fish oil increases first-line chemotherapy efficacy in patients with advanced nonsmall cell lung cancer. *Cancer*. 2011;117:3774-3780.
84. Bonatto SJ, Oliveira HH, Nunes EA, et al. Fish oil supplementation improves neutrophil function during cancer chemotherapy. *Lipids*. 2012;47:383-389.
85. Zhang Y, Gu Y, Guo T, Li Y, Cai H. Perioperative immunonutrition for gastrointestinal cancer: a systematic review of randomized controlled trials. *Surg Oncol*. 2012;21: e87-e95.
86. Stableforth WD, Thomas S, Lewis SJ. A systematic review of the role of immunonutrition in patients undergoing surgery for head and neck cancer. *Int J Oral Maxillofac Surg*. 2009;38:103-110.
87. Kepler CK, Huang RC, Meredith D, Kim JH, Sharma AK. Omega-3 and fish oil supplements do not cause increased bleeding during spinal decompression surgery. *J Spinal Disord Tech*. 2012;25:129-132.
88. Salisbury AC, Harris WS, Amin AP, Reid KJ, O'Keefe JH Jr, Spertus JA. Relation between red blood cell omega-3 fatty acid index and bleeding during acute myocardial infarction. *Am J Cardiol*. 2012;109:13-18.
89. Khan N, Muktar H. Multitargeted therapy of cancer by green tea polyphenols. *Cancer Lett*. 2008;269:269-280.

90. Khan N, Muktar H. Cancer and metastasis: prevention and treatment by green tea. *Cancer Metastasis Rev*. 2010;29:435-445.
91. Liang G, Tang A, Lin X, et al. Green tea catechins augment the antitumor activity of doxorubicin in an in vivo mouse model for chemoresistant liver cancer. *Int J Oncol*. 2010;37:111-123.
92. Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. *Cancer Res*. 2006;66:1234-1240.
93. Jatoi A, Ellison N, Burch PA, et al. A phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. *Cancer*. 2003;97:1442-1446.
94. Nguyen MM, Ahmann FR, Nagle RB, et al. Randomized, double-blind, placebo-controlled trial of polyphenon E in prostate cancer patients before prostatectomy: evaluation of potential chemopreventive activities. *Cancer Prev Res (Phila)*. 2012;5:290-298.
95. McLarty J, Bigelow RL, Smith M, Elmajian D, Ankem M, Cardelli JA. Tea polyphenols decrease serum levels of prostate-specific antigen, hepatocyte growth factor, and vascular endothelial growth factor in prostate cancer patients and inhibit production of hepatocyte growth factor and vascular endothelial growth factor in vitro. *Cancer Prev Res (Phila)*. 2009;2:673-682.
96. Lee UL, Choi SW. The chemopreventive properties and therapeutic modulation of green tea polyphenols in oral squamous cell carcinoma. *ISRN Oncol*. 2011;2011:403707.
97. Stendell-Hollis NR, Thomson CA, Thompson PA, Bea JW, Cussler EC, Hakim IA. Green tea improves metabolic biomarkers, not weight or body composition: a pilot study in overweight breast cancer survivors. *J Hum Nutr Diet*. 2010;23:590-600.
98. Shanafelt TD, Call TG, Zent CS, et al. Phase I trial of daily oral Polyphenon E in patients with asymptomatic Rai stage 0 to II chronic lymphocytic leukemia. *J Clin Oncol*. 2009;27:3808-3814.
99. Schönthal AH. Adverse effects of concentrated green tea extracts. *Mol Nutr Food Res*. 2011;55:874-885.
100. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005;165:1095-1106.
101. Golden EB, Lam PY, Kardosh A, et al. Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors. *Blood*. 2009;113:5927-5937.
102. Bannerman B, Xu L, Jones M, et al. Preclinical evaluation of the antitumor activity of bortezomib in combination with vitamin C or with epigallocatechin gallate, a component of green tea. *Cancer Chemother Pharmacol*. 2011;68:1145-1154.
103. Donovan JL, Chavin KD, Devane CL, et al. Green tea (*Camellia sinensis*) extract does not alter cytochrome p450 3A4 or 2D6 activity in healthy volunteers. *Drug Metab Dispos*. 2004;32:906-908.
104. Lin L, Wang MN, Tsai TH. Food-drug interaction of (-)-epigallotcatechin-3-gallate on the pharmacokinetics of irinotecan and the metabolite SN-38. *Chem Biol Interact*. 2008;174:177-182.
105. Mirkov S, Komoroski BJ, Ramírez J, et al. Effects of green tea compounds on irinotecan metabolism. *Drug Metab Dispos*. 2007;35:228-233.
106. Ge J, Tan BX, Chen Y, et al. Interaction of green tea polyphenol epigallocatechin-3-gallate with sunitinib: potential risk of diminished sunitinib bioavailability. *J Mol Med (Berl)*. 2011;89:595-602.
107. Shin SC, Choi JS. Effects of epigallocatechin gallate on the oral bioavailability and pharmacokinetics of tamoxifen and its main metabolite, 4-hydroxytamoxifen, in rats. *Anticancer Drugs*. 2009;20:584-588.
108. Kroll DJ, Shaw HS, Oberlies NH. Milk thistle nomenclature: why it matters in cancer research and pharmacokinetic studies. *Integr Cancer Ther*. 2007;6:110-119.
109. Tamayo C, Diamond S. Review of clinical trials evaluating safety and efficacy of milk thistle (*Silybum marianum [L.] Gaertn*.). *Integr Cancer Ther*. 2007;6:146-157.
110. Enjalbert F, Rapior S, Nouguier-Soule J, Guillon S, Amouroux N, Cabot C. Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol*. 2002;40:715-757.
111. Hruby K, Csomos G, Fuhrmann M, Thaler H. Chemotherapy of *Amanita phalloides* poisoning with intravenous silibinin. *HumToxicol*. 1983;2:183-195.
112. Grossman M, Hoerman R, Weiss M, et al. 52-year old man with biopsy-confirmed hepatocellular carcinoma resolved spontaneously. *Am J Gastroenterol*. 1995;90:1500-1503.
113. Invernizzi R, Bernuzzi S, Ciani D, Ascari E. Silymarine during maintenance therapy of acute promyelocytic leukemia. *Haematologica*. 1993;78:340-341.
114. McBride A, Augustin KM, Nobbe J, Westervelt P. *Silybum marianum* (milk thistle) in the management and prevention of hepatotoxicity in a patient undergoing reinduction therapy for acute myelogenous leukemia. *J Oncol Pharm Pract*. 2012; 18:360-365.
115. Flaig TW, Gustafson DL, Su LJ, et al. A phase I and pharmacokinetic study of silybin-phytosome in prostate cancer patients. *Invest New Drugs*. 2007;25:139-146.
116. Hoh C, Boocock D, Marczylo T, et al. Pilot study of oral silibinin, a putative chemopreventive agent, in colorectal cancer patients: silibinin levels in plasma, colorectum, and liver and their pharmacodynamic consequences. *Clin Cancer Res*. 2006;12:2944-2950.
117. van Erp NP, Baker SD, Zhao M, et al. Effect of milk thistle (*Silybum marianum*) on the pharmacokinetics of irinotecan. *Clin Cancer Res*. 2005;11:7800-7806.

118. Ladas EJ, Kroll DJ, Oberlies NH, et al. A randomized, controlled, double-blind, pilot study of milk thistle for the treatment of hepatotoxicity in childhood acute lymphoblastic leukemia (ALL). *Cancer*. 2010;116:506-513.
119. Vidlar A, Vostalova J, Ulrichova J, et al. The safety and efficacy of a silymarin and selenium combination in men after radical prostatectomy: a six month placebo-controlled double-blind clinical trial. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2010;154:239-244.
120. McCulloch M, See C, Shu XJ, et al. Astragalus-based Chinese herbs and platinum-based chemotherapy for advanced non-small-cell lung cancer: meta-analysis of randomized trials. *J Clin Oncol*. 2006;24:419-430.
121. Tang W. *Chinese Drugs of Plant Origin*. Berlin, Germany: Springer-Verlag; 1992.
122. Qun L, Luo Q, Zhang ZY, et al. Effects of astragalus on IL-2/IL-2R system in patients with maintained hemodialysis. *Clin Nephrol*. 1999;52:333-334.
123. Chu DT, Lepe-Zuniga J, Wong WL, LaPushin R, Mavligit GM. Fractionated extract of *Astragalus membranaceus*, a Chinese medicinal herb, potentiates LAK cell cytotoxicity generated by a low dose of recombinant interleukin-2. *J Clin Lab Immunol*. 1988;26:183-187.
124. Cho WC, Leung KN. In vitro and in vivo anti-tumor effects of *Astragalus membranaceus. Cancer Lett*. 2007;252: 43-54.
125. Yu L, Lu Y, Li J, Wang H. Identification of a gene associated with astragalus and angelica's renal protective effects by silver staining mRNA differential display. *Chin Med J (Engl)*. 2002;115:923-927.
126. Cui R, He J, Wang B, et al. Suppressive effect of *Astragalus membranaceus Bunge* on chemical hepatocarcinogenesis in rats. *Cancer Chemother Pharmacol*. 2003;51:75-80.
127. Auyeung KK, Woo PK, Law PC, Ko JK. Astragalus saponins modulate cell invasiveness and angiogenesis in human gastric adenocarcinoma cells. *J Ethnopharmacol*. 2012;141:635-641.
128. Wu P, Dugoua JJ, Eyawo O, Mills EJ. Traditional Chinese medicines in the treatment of hepatocellular cancers: a systematic review and meta-analysis. *J Exp Clin Cancer Res*. 2009;28:112.
129. Taixiang W, Munro AJ, Guanjian L. Chinese medical herbs for chemotherapy side effects in colorectal cancer patients. *Cochrane Database Syst Rev*. 2005(1):CD004540. doi:10.1002/14651858.CD004540.pub2.
130. Chu DT, Wong WL, Mavligit GM. Immunotherapy with Chinese medicinal herbs. I. Immune restoration of local xenogeneic graft-versus-host reaction in cancer patients by fractionated *Astragalus membranaceus* in vitro. *J Clin Lab Immunol*. 1988;25:119-123.
131. Upton R. Astragalus root: analytical, quality control and therapeutic monograph. *American Herbal Pharmacopoeia*. 1999;1:1-25.
132. Shi D, Xiao X, Wang J, et al. Melatonin suppresses proinflammatory mediators in lipopolysaccharide-stimulates CRL 1999 cells via targeting MAPK, NF-kB, c/EBPbeta and p300 signaling. *J Pineal Res*. 2012;53:154-165.
133. Greene MW. Circadian rhythms and tumor growth. *Cancer Lett*. 2012;318:115-123.
134. Kryger MH. The burden of chronic insomnia on society. *Managed Care*. 2006;15(9 suppl 6):1-5, 17.
135. Zhadnova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU. Melatonin treatment for age-related insomnia. *J Clin Endocrinol Metab*. 2001;86:4727-4730.
136. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst*. 2001;93:1557-1562.
137. Schernhammer ES, Laden F, Speizer FE, et al. Night-shift work and risk of colorectal cancer in the Nurse's Health Study. *J Natl Cancer Inst*. 2003;95:825-828.
138. Fonken LK, Nelson RJ. Illuminating the deleterious effects of light at night. *F1000 Rep Med*. 2011;3:18.
139. Sanchez-Barcelo EJ, Mediavilla MD, Alonso-Gonzalez C, Reiter RJ. Melatonin uses in oncology: breast cancer prevention and reduction of side effects of chemotherapy and radiation. *Expert Opin Investig Drugs*. 2012;21:819-831.
140. Knower KC, Tp SQ, Takagi K, et al. Melatonin suppresses aromatase expression and activity in breast cancer associated fibroblasts. *Breast Cancer Res Treat*. 2012;132:765-771.
141. Molis TM, Spriggs LL, Jupiter Y, Hill SM. Melatonin modulation of estrogen-regulated proteins, growth factors, and proto-oncogens in human breast cancer. *J Pineal Res*. 1995;18:93-103.
142. Wang YM, Jin BZ, Ai F, et al. The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumors: a meta-analysis of randomized controlled trials. *Cancer Chemother Pharmacol*. 2012;69:1213-1220.
143. Seely D, Wu P, Fritz H, et al. Melatonin as adjuvant cancer care with and without chemotherapy: a systematic review and meta-analysis of randomized trials. *Integr Cancer Ther*. 2012;11:293-303.
144. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev*. 2002;2:CD001520. doi:10.1002/14651858.CD001520.
145. Cagnacci A, Arangino S, Renzi A, et al. Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women. *Clin Endocrinol (Oxf)*. 2001;54:339-346.
146. Hartter S, Grozinger M, Weigmann H, et al. Increased bioavailability of oral melatonin after fluvoxamine coadministration. *Clin Pharmacol Ther*. 2000;67:1-6.
147. Lissoni P, Barni S, Mandala M, et al. Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solic tumor patients with poor clinical status. *Eur J Cancer*. 1999;35:1688-1692.

148. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA*. 2012;307:1959-1969.
149. Elahi B, Nikfar S, Derakhshani S, et al. On the benefit of probiotics in the management of pouchitis in patients underwent ileal pouch anal anastomosis: a meta-analysis of controlled clinical trials. *Dig Dis Sci*. 2007;53:1278-1284.
150. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotheraphy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology*. 2000;119:305-309.
151. Sazawal S, Hiremath G, Dhingra U, et al. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. *Lancet Infect Dis*. 2006;6:374-382.
152. Simren M, Syrous A, Lindh A, Abrahamsson H. Effects of *Lactobacillus plantarum 299v* on symptoms and rectal sensitivity in patients with irritable bowel syndrome (IBS): a randomized, double-blind controlled trial. *Gastroenterology*. 2006;130(suppl 2):A600.
153. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. *Am J Gastroenterol*. 2006;101:1581-1590.
154. Qamar A, Aboudola S, Warny M, et al. *Saccromyces boulardii* stimulates intestinal immunoglobulin A immune response to *Clostridium difficile* toxin A in mice. *Infect Immun*. 2001;69:2762-2765.
155. McFarland LV, Surawicz CM, Greenberg RN, et al. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. *JAMA*. 1994;271:1913-1918.
156. Tong JL, Ran ZH, Shen J, et al. Meta-analysis: the effect of supplementation with probiotics on eradication rates and adverse events during Helicobacter pylori eradication therapy. *Aliment Pharmacol Ther*. 2007;25:155-168.
157. Hawrelak JA, Whitten DL, Myers SP. Is *Lactobacillus rhamnosus GG* effective in preventing the onset of antibiotic -associated diarrhoea: a systematic review. *Digestion*. 2005;72:51-56.
158. Cremonini F, Di Caro S, Nista EC, et al. Metaanalysis: the effect of probiotic administration on antibiotic-associated diarrhoea. *Aliment Pharmacol Ther*. 2002;16:1461-1467.
159. Johnston BC, Supina AL, Vohra S. Probiotics for pediatric antibiotic-associated diarrhea: a meta-analysis of randomized placebo-controlled trials. *CMAJ*. 2006;175:377-383.
160. Pozo-Olano JD, Warram JH, Gomez RG, Cavazos MG. Effect of a Lactobacillus preparation on traveller's diarrhea. *Gastroenterology*. 1978;74:829-830.
161. Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. *PLoS One*. 2012;7:e34938. doi:10.1371/journal.pone.0034938
162. Osterlund P, Ruotsalainen T, Korpela R, et al. *Lactobacillus* supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. *Br J Cancer*. 2007;97:1028-1034.
163. Urbancsek H, Kazar T, Mezes I, Neumann K. Results of a double-blind, randomized study to evaluate the efficacy and safety of Antibiophilus in patients with radiation-induced diarrhoea. *Eur J Gastroenterol Hepatol*. 2001;13:391-396.
164. Delia P, Sansotta G, Donato V, et al. Prevention of radiation-induced diarrhea with the use of VSL#3, a new high-potency probiotic preparation. *Am J Gastroenterol*. 2002;97:2150-2152.
165. Delia P, Sansotta G, Donato V, et al. Use of probiotics for prevention of radiation-induced diarrhea. *World J Gastroenterol*. 2007;13:912-915.
166. Chitapanarux I, Chitapanarux T, Traisathit P. Randomized controlled trial of live *lactobacillus acidophilus* plus *bifidobacterium bifidum* in prophylaxis of diarrhea during radiotherapy in cervical cancer patients. *Radiat Oncol*. 20105;5:31.
167. Giralt J, Regadera JP, Verges R, et al. Effects of probiotic *Lactobacillus casei DN-114 001* in prevention of radiation-induced diarrhea: results from multicenter, randomized, placebo-controlled nutritional trial. *Int J Radiat Oncol Biol Phys*. 2008;71:1213-1219.
168. Fuccio L, Guido A, Eusebi LH, et al. Effects of probiotics for the prevention and treatment of radiation-induced diarrhea. *J Clin Gastroenterol*. 2009;43:506-513.
169. Visich KL, Yeo TP. The prophylactic use of probiotics in the prevention of radiation therapy-induced diarrhea. *Clin J Oncol Nurs*. 2010;14:467-473.
170. Mego M, Ebringer L, Drgona L, et al. Prevention of febrile neutropenia in cancer patients by probiotic strain *Enterococcus faecium M-74*. Pilot study phase I. *Neoplasma*. 2005;52:159-164.
171. Muñoz P, Bouza E, Cuenca-Estrella M, et al. *Saccharomyces cerevisiae* fungemia: an emerging infectious disease. *Clin Infect Dis*. 2005;40:1625-1634.
172. Bailey JR, Probert CSJ, Cogan TA. Identification and characterisation of an iron-responsive candidate probiotic. *PLoS One*. 2011;6:e26507.