Review of Complementary and Alternative Medicine and Selected Nutraceuticals: Background for a Pilot Study on Nutrigenomic Intervention in Patients with Advanced Cancer

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ABSTRACT
As commonly defined, complementary and alternative medicine (CAM) is a broad category that includes biologically based practices, mind-body medicine, manipulative and body-based practices, and energy medicine as well as complete medical systems such as naturopathy, homeopathy, Ayurvedic medicine, and traditional Chinese medicine. Several CAM methodologies show promise for the treatment of chronic conditions such as depression and pain disorders or have demonstrated effects upon the immune response in experimental studies. There is growing interest in the use of integrative medicine—the combination of CAM methodologies with a conventional medical approach—for the optimization of treatment of various cancers.

The Ohio State University Center for Integrative Medicine has developed a specialized nutrigenomic protocol for integrative cancer care. The center uses a comprehensive nutritional and medical evaluation, including a panel of proinflammatory molecules and physiologic parameters, to guide a program of individualized dietary interventions. Dietary supplementation is a current focus of study, including: (1) Omega-3 fatty acids and B vitamins, which are thought to play important roles in immunomodulation; (2) Magnesium oxide, which has been shown to decrease inflammation and improve insulin resistance and lipid profiles; and (3) Cinnamon extract, which reportedly decreases serum glucose levels. This article presents a brief overview of CAM and integrative medicine and a discussion of the relevant nutraceuticals. (Altern Ther Health Med. 2012;18(2):26-34.)

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Biologically based practices include botanicals, animal-derived extracts, vitamins and minerals, fatty acids, amino acids, pre- and probiotics, whole diets, and functional foods. The use of dietary supplements, especially vitamins and minerals, has grown considerably in the past two decades, primarily as a way to improve general health but also as a means to treat specific illnesses. Functional foods are usual parts of the diet that may contain biologically active components (such as polyphenols, phytoestrogens, fish oils, and carotenoids) that provide additional health benefits beyond basic nutrition. In contrast to some of the other modalities, a large quantity of data is available from clinical studies (mainly phase II) of supplements containing single chemical constituents (eg, vitamins...
and minerals). For example, vitamins C, E, and coenzyme Q10 have shown disappointing results for the prevention or treatment of cancer and cardiovascular disease, despite positive results from early observational studies. In contrast, a Cochrane review that assessed the use of cranberry products vs placebo for prevention of urinary tract infection (UTI) demonstrated that the use of cranberry products significantly decreased the incidence of UTI at 12 months, particularly in women with recurrent UTIs. Many other dietary supplements are currently being studied in clinical trials.

HERBAL MEDICINE

Herbal medicine has existed for thousands of years, having its basis in the Ayurvedic and traditional Chinese medicine systems. Two well-known longitudinal studies from Harvard in the 1990s demonstrated increasing use of self-prescribed herbal medicines in the general population of the United States (2.5% in 1990, 12.1% in 1997) and increasing consultation of herbal-medicine practitioners during the same period. Common motivations for using herbal medicines are promotion of well-being, prevention of future illness, or treatment of a life-threatening condition, whereas surveys show that disappointment with conventional medicine is not a primary motivation for use of alternative therapies. The stereotypical user of herbal medicines is female, affluent, college-educated, middle-aged, and likely to be using conventional medicines as well. Herbal medicines are generally perceived to be safe and effective and to provide the user with some control over his or her treatment.

Although many traditional herbal medicines have been used over hundreds or thousands of years, few medicines have proven effective in placebo-controlled randomized trials. Those herbal medicines proven to be effective include Ginkgo biloba as treatment for dementia or intermittent claudication, St John's wort (Hypericum perforatum) as therapy for mild to moderate depression, kava (Piper methysticum) as an herbal anxiolytic, and horse chestnut (Aesculus hippocastanum) seed as a treatment for chronic venous insufficiency. Other herbal medicines have doubtful efficacy (such as Asian ginseng for any indication) or no clinically relevant efficacy (such as evening primrose oil and garlic).

Many herbal medicines have important adverse effects or may cause herb-drug interactions. For example, ginkgo potentiates antiplatelet drugs, and St John’s wort induces cytochrome P450, affecting metabolism of other drugs. Licorice acts as a mineralocorticoid and may lead to potassium loss and to sodium and water retention, especially when used with antihypertensive medications. Other herbal medicines have direct adverse effects upon organ systems. Perhaps the most well-known example is the ephedra species, which can cause heart and circulatory problems or death. Importantly, all herbal medicines are contraindicated in pregnant or lactating women due to a lack of reliable data regarding teratogenicity. Furthermore, important safety concerns exist regarding preparation of herbal medicines. Botanical substitution is common (active ingredients may be underdosed), and multiple contaminants such as other plants, microorganisms and microbial toxins, pesticides, fumigation agents, and heavy metals have been found in some herbal medicines. In the United States, the Dietary Supplement Health and Education Act regulates herbal medicines as dietary supplements, and thus, they are not under the same rigorous control as medications.

HOMEOPATHY

Homeopathy is a whole medical system whose principles were originally outlined by Hahnemann in his "Essay on the New Curative Principle" (1796). Two basic scientific tenets define homeopathy: the Principle of Similars and the Principle of Dilutions. The Principle of Similars states that remedies retain biologic activity when serially diluted by shaking, which extracts the vital nature of the substance in a process known as "potentization." Although low concentrations of many substances have biologic activity, preparations with a dilution of the active substance below the limit of molecular dilution (ie, less than Avogadro's number) are more problematic. This principle is the most controversial and has led many to reject homeopathy as a valid treatment modality.

The philosophical tenet underlying homeopathy is that the body possesses a close mind-body connection and self-healing potential. Illness is viewed as an imbalance in one's vital force. A correctly prescribed remedy restores balance to the body. In classic homeopathy, homeopathic preparations are prescribed according to an extremely detailed characterization of symptoms obtained from the patient. The symptoms evoked by common remedies given repeatedly to healthy volunteers have been recorded in a process known as a "proving" (similar to a Phase I pharmacologic study but with the goal of cataloguing side effects of each remedy). These symptoms are catalogued in Materia Medica, the homeopathic book on pharmacology. A Repertory is a cross-reference tool that the practitioner uses to find a group of remedies closely corresponding to the symptom complex with which the patient is presenting. Remedies are most effective when chosen based on the total set of symptoms presented (not necessarily based on the disease); thus, practitioners may treat 2 patients with the same diagnosis with different potencies.

Clinical homeopathy (homeotherapeutics) uses the prescription of preparations combining several remedies in lower potencies (so-called combination remedies) to treat symptomatic variations of a condition, and thus, it is more similar to conventional drug therapy. A few single-remedy preparations are reportedly successful for prophylaxis and relief of acute cold and influenza. Some positive studies show the efficacy of homeopathy for select conditions such as asthma and allergic rhinitis; however, many studies of homeopathic remedies are of low methodological quality, often due to a lack of validated outcome measures or small sample sizes. Although homeopathy may be one of the most difficult alternative-treatment methodologies for Western biocentrists to accept, it also may be one of the most frequently used complementary therapies worldwide.

MIND-BODY MEDICINE (MBM)

Mind-body medicine (MBM) focuses on ways in which health is affected by emotional, mental, social, spiritual, and behavioral fac-
Mind-body medicine can address many common complaints about health care by affording greater control in treatment, less expensive alternatives, methods for maintaining wellness, and effective options for treatment of chronic illnesses. Some examples of mind-body therapies are meditation, hypnosis, guided imagery, relaxation therapy, biofeedback, yoga, tai chi, qigong, and spiritual healing. Mainstream treatment has incorporated cognitive-behavioral therapies and group support, once considered to be forms of CAM.

Mind-body medicine may be especially helpful for chronic-pain disorders, anxiety, and insomnia and may be effective in the treatment of coronary artery disease. Guided imagery is a therapist-directed technique that uses the power of suggestion and imagery to harness specific biological effects that may not be accessible normally to the conscious mind. Reviews show that imagery, usually in conjunction with a psychological intervention, may reduce morbidity and prolong survival in cancer patients. Furthermore, modest evidence suggests that guided imagery has positive effects on surgical and cancer-treatment outcomes. Similarly, moderate evidence supports hypnosis for the treatment of acute- and chronic-pain conditions, including surgery.

Researchers have studied the effects of behavioral therapies upon immune parameters in some detail. For example, Keiel glutathione S-transferase (GST) and granulocyte-macrophage colony-stimulating factor (GM-CSF) in peripheral blood mononuclear cells (PBMCs) in patients with colorectal cancer. Importantly, several surveys have shown that patients in general believe that chiropractic works for them, and they are very likely to be satisfied with the treatment received.

Research into potential mechanisms for the effectiveness of manipulative and body-based practices is ongoing. Animal studies suggest that manipulation of the spine evokes changes in the output of proprioceptive afferent neurons in paraspinal tissue, in turn altering the outflow to the autonomic nervous system. Some studies suggest that massage can alter chemical and immune parameters, such as levels of substance P, serotonin, and cortisol; natural killer (NK) cell number; and CD4+ T-cell count. These studies require replication. Both spinal manipulation and massage present relatively few risks to patients. Interestingly, despite the relative lack of information regarding long-term effects, dosing, or cost-effectiveness, the majority of patients has high levels of satisfaction with both chiropractic and massage therapy.

TRADITIONAL CHINESE MEDICINE (TCM)

According to the National Institutes of Health and the World Health Organization, traditional Chinese medicine (TCM) originated approximately 3000 years ago. Yin and yang are fundamental concepts representing opposites in nature. It is believed that the body is traversed by a system of channels (known as meridians) that carries vital energy (qi), blood, and fluid. The goal of diagnosis and treatment is to detect the internal imbalance by its external manifes-
CAM and Nutrigenomics

Researchers report that spiritual-healing techniques claim to be able to palpate energy fields and/or perceive auras of colors around the body, layers of which indicate the physical, emotional, mental, relational, and spiritual conditions of the person. Practitioners administer treatment by the laying-on of hands while holding in mind a mental intent, meditative focus, or prayer for healing. The mechanism of action of energy therapy is unknown but may include: (1) unblocking the patient’s own energies, (2) projection of the practitioner’s energy, (3) channeling of energies from nature, or (4) interventions of spiritual agents. The use of these practices remains controversial because the existence of the biofield and beneficial effects of therapy cannot be demonstrated biophysically. Multiple studies, however, have shown that spiritual-healing practices can be effective for pain, anxiety, depression, AIDS, hypertension, and wound healing, among others, and spiritual healing has no known side effects or interactions with other treatments, making it an excellent therapy of first choice.

NATUROPATHY

Naturopathy is another whole medical system that incorporates many CAM modalities. It is loosely defined as the use of natural methods to approach health and illness. The nature cure consisting of medicinal herbs, exercise, and water originated in the 1800s in Germany and was most popular in the United States in the 1920s and 1930s. The unifying principles of naturopathy include (1) the healing power of nature (Vis Medicatrix Naturae), (2) identification and treatment of causes (Tolle causam), (3) do no harm (Primum non nocere), (4) doctor as teacher (Docere), (5) treatment of the whole person, and (6) prevention. Primary modalities of treatment include diet modification and supplementation, herbal and homeopathic medicine, hydrotherapy, physical medicine (therapeutic massage and joint manipulation), and lifestyle counseling. Much of the evidence supporting naturopathy is empirical, and although individual modalities used by naturopathic physicians can be validated (eg, nutritional approaches), naturopathy itself is difficult to study since the methods of healing may differ among patients. Few states have legislation regarding the practice of naturopathy, and in states without legislation, no specific educational requirements exist for naturopathic physicians.

ENERGY MEDICINE

Energy medicine is based on the perception of patients and therapists that subtle biological energies surround and permeate the human body. Spiritual awareness (ie, the sense of being part of something that is wiser and larger than oneself) is an important component of energy medicine and is thought to be especially helpful when facing serious or terminal illness. As previously stated on the NCCAM website, energy medicine encompasses the use of measurable sources of energy such as sound, light, magnetism, and lasers as well as biofields or vital energy, known by various names such as qi, doshas, and homeopathic resonance. Magnetic therapy, music therapy, and high-intensity light therapy for seasonal affective disorder are among the more familiar types of energy medicine. Practices that involve manipulation of vital energy include Reiki, qi qong, healing touch, and intercessory prayer. Researchers report that prayer healing can be effective even from miles away. Practitioners of spiritual-healing techniques claim to be able to palpate energy fields and/or perceive auras of colors around the body, layers of which indicate the physical, emotional, mental, relational,
Steinsbekk et al studied 1406 patients from a total-population survey. Among patients who presently have or previously had cancer, 16.1% visited a CAM practitioner in the previous 12 months as compared to 12.8% for the total population. The likelihood of consulting a CAM practitioner increased among those having a university degree, having lower perceived global health, and having a health complaint within the last 12 months.

The use of dietary supplements in particular is important among cancer patients due to the potential of some supplements to interact with other therapies. In a study of 827 cancer survivors from the American Cancer Society's longitudinal Study of Cancer Survivors-I, 573 patients (69.3%) reported the use of dietary supplements after receiving their cancer diagnosis. Again, female gender and higher educational levels were associated with dietary-supplement use. The most common reasons patients cited for using supplements included "something they could do to help themselves" (56.2%) and "to boost their immune system" (51.1%).

SELECTED NUTRACEUTICALS

Nutrigenomics is a personalized approach to food, nutrition, and health that involves tailoring food to the individual genotype. It is now known that many bioactive food components may either increase the risk of or protect against cardiovascular disease and the development of cancer. In particular, it is thought that substances that can reduce chronic inflammation may potentially reduce the risk of cancer. Included in this group are amino acids such as arginine and glutamine; carbohydrates such as the beta-glucans, which appear to act as biological-response modifiers; lipids, especially omega-3 fatty acids; minerals such as zinc, iron, and selenium; vitamins such as the antioxidant vitamins C and E; carotenoids; polyphenols such as curcumin; phenyl isothiocyanates; and pre- and probiotics. Chronic hyperinsulinemia such as occurs with the consumption of a high glycemic-index diet may increase the risk of cancer.

At the Ohio State University Center for Integrative Medicine, a specialized nutrigenomic protocol for integrative cancer care has been developed. This protocol includes comprehensive nutritional and medical evaluation, a program of individualized dietary interventions guided by levels of proinflammatory molecules and other physiologic parameters, community-education classes, and periodic assessments. A current focus of study is dietary supplementation with omega-3 fatty acids, magnesium oxide, high-dose B-complex vitamins, and cinnamon for patients with advanced or metastatic cancers. Omega-3 fatty acids and B vitamins were chosen due to their important roles in immunomodulation. Studies have shown that magnesium oxide decreases inflammation as well as improves insulin resistance and serum lipid profiles. Finally, the intake of cinnamon extracts reportedly decreases serum glucose levels. Each supplement is discussed in more detail below.

Omega-3 (n-3) Polyunsaturated Fatty Acids

Omega-3 (n-3) polyunsaturated fatty acids (PUFAs) are fatty acids in which the first double bond resides in a position three carbon atoms from the methyl terminal. The precursor to omega-3 PUFAs, α-linolenic acid, cannot be synthesized in the human body; thus, omega-3 PUFAs must be ingested either by intake of plant sources or of eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), found in marine sources and available as supplements. The Western diet, typically high in omega-6 PUFAs and low in omega-3 PUFAs, is thought to contribute to cardiovascular disease, inflammation, and cancer. In a recent review, researchers reported that intake of omega-3 PUFAs is beneficial to reduce multiple cardiometabolic risk factors. It reduces the risk of coronary heart disease; decreases triglycerides, blood pressure, and inflammatory markers; improves endothelial function; prevents certain cardiac arrhythmias; reduces platelet aggregation and vasoconstriction; enhances fibrinolysis and reduces fibrin formation; and decreases the risk of microalbuminuria and sudden cardiac death. Similarly, a review of the literature and of the FDA's guidelines for the use of omega-3 PUFAs suggests that omega-3 PUFAs significantly reduce coronary mortality and sudden death in patients without prior cardiovascular disease and reduce all-cause and cardiac mortality when used as secondary prevention.

In addition to the beneficial cardiovascular effects associated with omega-3 PUFAs, several studies have demonstrated immunomodulatory effects. In general, omega-6 PUFAs such as arachidonic acid are proinflammatory, whereas omega-3 PUFAs inhibit inflammation. This inhibition occurs both by inhibiting the formation of the omega-6-PUFA-derived pro-inflammatory eicosanoids and by forming potent anti-inflammatory mediators, resolvins and protectins. Resolvins and protectins suppress the activity of nuclear transcription factors and decrease production of proinflammatory factors such as COX-2, TNF-α, and IL-1β. Awareness of these effects is important because the oral administration of EPA and DHA can alter the composition of human immune cells, typically high in arachadonic acid, leading to a change in the expression pattern of eicosanoids. This change in turn affects phagocytosis, T-cell signaling, and antigen presentation capability. In a group of healthy human volunteers consuming either an anti-inflammatory blend rich in PUFAs including alpha-linoleic acid, EPA, stearidonic acid, and gamma-linolenic acid (group A) or an inflammatory fat blend containing arachidonic acid (group B) for 2 weeks, researchers observed significantly increased plasma concentrations of EPA and alpha-linoleic acid in group A. After ex vivo lipopolysaccharide stimulation, release of PGE2 and leukotriene B4 were significantly decreased in group A, whereas PGE2 and IL-10 concentrations were significantly increased in group B. These results demonstrate an immunomodulatory effect of low-dose dietary PUFA supplementation.

A recent study of 42 patients who underwent radical resection of colorectal cancer with an indication for postoperative total parental nutrition compared supplementation with soybean oil or a combination of soybean oil and omega-3 fish oil. Patients in the omega-3 group had significantly lower levels of IL-6 and higher ratios of CD4+/CD8+ cells after completion of the supplementation than patients in the control group, again suggesting that omega-3 oils may diminish or otherwise modulate the immune response. Importantly, omega-3 PUFAs may have effects on processes contributing to carcinogenesis. Omega-3 PUFAs are natural ligands for peroxisome proliferator receptor activator (PPAR) gamma, a mediator known to affect cell proliferation, survival, and differentiation. In vitro studies have shown that Omega-3 PUFAs inhibit cell proliferation and induce apoptosis in cancer cells. Some studies have
demonstrated decreased risk of prostate, colon, and breast cancer with consumption of a diet high in omega-3 PUFAs, leading to the use of omega-3 PUFAs for cancer prevention and treatment, as well as for nutritional support of cancer patients to reduce weight loss and modulate the immune system. Finally, omega-3 PUFAs appear to have a beneficial effect on tumor cachexia. A recent literature review showed that administration of omega-3 PUFAs (EPA and DHA) oral supplements to patients with advanced cancer led to increased weight and appetite, improved quality of life, and reduced postsurgical morbidity. Supplementation is indicated in patients with cancers of the upper digestive tract and pancreas.

Fish oil has generally regarded as safe (GRAS) status (FDA) at doses up to 3 g per day. Higher doses may impair blood clotting, increase LDL levels, or impair glucose control and may be associated with impairment of the immune response, particularly in patients who are immunosuppressed. A moderate risk of interaction with antihypertensive drugs (enhancement of antihypertensive effect) and a minor risk of interaction with anticoagulant or antiplatelet drugs (risk of bleeding) exist. In a randomized, placebo-controlled trial with 84 schizophrenic patients given 2 g per day of EPA or placebo, in addition to prescribed antipsychotic medications, the EPA group showed a significant increase in bleeding time and body mass index. Common side effects of fish oil include fishy taste, belching, heartburn, nausea, and diarrhea.

**Magnesium Oxide**

Magnesium has multiple roles in cardiovascular function, energy metabolism, insulin signaling, release of neurotransmitters, and endothelial cell function. Studies have shown that increased dietary intake of magnesium (Mg) confers benefits such as improved insulin resistance and serum lipid profiles as well as decreased inflammation, endothelial dysfunction, oxidative stress, and platelet aggregation. Experimental magnesium deficiency in rats induces an inflammatory syndrome consisting of leukocyte and macrophage activation, release of inflammatory cytokines and acute phase proteins, and excess production of free radicals. In addition, multiple studies have found an association between magnesium intake and colorectal cancer risk.

Total magnesium intake in the East Asian population, which has a low overall risk of colorectal cancer, does not differ from that in the US population, but in the US population, the ratio of calcium to magnesium intake is higher. A study of 688 patients with adenoma, 210 with hyperplastic polyps, and 1306 polyp-free controls from the Tennessee Colorectal Polyp Study linked total Mg consumption to a decreased risk of colorectal adenoma, especially in those patients with low ratio of calcium to magnesium (Ca:Mg) intake. In addition, those patients with a common polymorphism in the transient receptor potential melastatin 7 (TRMP7) gene, which is essential for magnesium absorption, had an increased risk of adenomatous and hyperplastic polyps, and the polymorphism appeared to interact with the ratio of calcium to magnesium intake. Participants who had the polymorphism and consumed diets with a high Ca:Mg intake ratio had a higher risk of adenoma and hyperplastic polyps than subjects who did not have the polymorphism. The Netherlands Cohort Study on Diet and Cancer found significant inverse trends in risks of colon and proximal colon cancer across increasing quintiles of magnesium intake in overweight subjects. Similarly, in a cohort of women aged 55 to 69, the hazard ratios of colorectal cancer declined across increasing quintiles of magnesium intake.

Researchers have not documented hypermagnesemia from intake of dietary magnesium in the absence of intestinal or renal disease. The Food and Nutrition Board of the National Institute of Medicine has established tolerable upper limits for magnesium supplementation (adults, including pregnant or nursing women, 350 mg daily). The development of hypermagnesemia is rare in individuals with normal renal function, even with excessive supplementation, but may occur in patients with renal insufficiency. The most common side effect of excessive magnesium supplementation is diarrhea, sometimes accompanied by nausea and cramping. At serum magnesium concentrations greater than 2 to 3.5 mmol per liter, neurologic and cardiac symptoms such as muscle weakness, breathing difficulty, and cardiac arrest may ensue.

**B-Complex Vitamins**

The B vitamins and folate are related through one-carbon metabolism and together with methionine have an important role in DNA methylation, synthesis, and repair. In addition, adequate intake of vitamins B6, B12, folate, vitamins C and E, selenium, zinc, copper, and iron all support a T1 inflammatory-mediated immune response, leading to elaboration of proinflammatory cytokines; intake of vitamins A and D support a T2 cytokine-mediated anti-inflammatory cytokine response.

Many observational studies have supported the impact of dietary factors on the incidence of colorectal cancer. Data from the case-control arm of the Melbourne Colorectal Cancer Study, comparing 715 incident cases with 727 matched controls, suggest that folate, methionine, and vitamins B6 and B12 together with the antioxidants selenium and vitamins C and E, lead to lower colorectal cancer (CRC) risk. Similarly, a large Scottish case-control study designed to investigate the association between dietary and supplementary intake of vitamin B12 and CRC, found an inverse dose-dependent association between CRC and dietary B12 (OR = 0.77) and CRC and total B12 (OR = 0.86). Furthermore, in a prospective study of dietary folate and vitamin B and colon cancer according to microsatellite (MSI) instability and KRAS mutational status, Scherhammer et al concluded that high vitamin B12 intake was inversely associated with colon cancers, regardless of MSI or KRAS status. Recent advances in the understanding of the biology of CRC carcinogenesis highlight the importance of epigenetic modifications such as DNA methylation. Micronutrients such as folic acid and selenium may have a direct influence on DNA methylation, and thus have therapeutic potential as nutraceuticals.

The vitamin-B-complex formulation that the Center for Integrative Medicine employs in its program contains thiamin 100 mg (vitamin B1), riboflavin 100 mg (B2), niacin 100 mg (B3), pantothenic acid 100 mg (B5), pyridoxine 100 mg (B6), biotin 100 mcg (B7), folic acid 400 mcg (B9), and cyanocobalamin 100 mcg (B12).

**Thiamine**

This vitamin is relatively nontoxic even at high doses, with no tolerable upper level of intake established. Rare cases of dermatitis or other hypersensitivity have been reported.

**Riboflavin**

This vitamin is likewise very safe, with insufficient...
data reported to establish an upper intake level (UL) in adults. Large oral doses (400 mg) have been reported to cause diarrhea and polyuria.82

**Niacin.** This vitamin has a number of well-known toxicities, the most common of which is prostaglandin-mediated flushing, itching, and headache at doses of greater than 30 mg per day.83 Premedication with aspirin can alleviate these symptoms.84 Gastrointestinal symptoms are more common with time-release preparations.82 The most serious adverse effect is hepatotoxicity, manifested by jaundice and elevated transaminases. At doses greater than 3 g per day, fulminant hepatitis has been reported.82,85 Impaired glucose tolerance and increased hepatic output of glucose has been reported, although a meta-analysis of 10 randomized, controlled trials conducted on patients with recent-onset, insulin-dependent diabetes mellitus (DM) did not show significant adverse effects.82,84 Other potential adverse effects of niacin administration include elevated plasma uric acid; tachycardia, arrhythmia, and syncope in hypertensive patients on medication; and elevated plasma homocysteine levels.82

**Pantothenic Acid.** Use of this vitamin is considered to be very safe, having insufficient data to establish UL.82

**Pyridoxine.** Sensory neuropathy may be observed at doses of 500 mg per day (the UL is 100 mg/d).82

**Biotin.** This vitamin is reported to be safe in humans. There is insufficient data to establish UL.82

**Folic acid.** This vitamin is well-tolerated at doses of less than 1 mg per day (the UL). At doses of greater than 5 mg per day, abdominal cramps, diarrhea, and rash may develop, while at doses of greater than 15 mg per day, irritability and increased frequency of seizures may occur.82

**Cobalamin.** This vitamin is considered to be very safe. No UL is established.82

**CINNAMON EXTRACT, GLYCEMIC LOAD, AND CANCER RISK**

It has been suggested that consumption of a high glycemic index (GI) or glycemic load (GL) diet may lead to chronic hyperinsulinenia, which is thought to increase the risk of cancer.51,85 In a meta-analysis examining five studies of GI or GL intake in relation to endometrial cancer risk, Mulholland et al observed an increased risk of endometrial cancer with high GL consumption, which was further increased in obese women.55 Other studies have suggested that high GI intake is also associated with increased risk of esophageal adenocarcinoma86 and thyroid87 cancers, and a meta-analysis performed to explore the association between GI and GL and cancer risk further supports a direct association between high GI and GL intake and colorectal and endometrial cancers.88 Epidemiologic data suggests that patients with metabolic syndrome have an elevated risk of colon cancer, possibly due to the effect of hyperinsulinenia on concentrations of insulin-like growth factor.89 Determinants examined in relation to the risk of colon cancer or adenoma included obesity, abdominal fat distribution, physical inactivity, type 2 diabetes, hypertension, hypertryglyceridemia, hyperglycemia, low HDL cholesterol, and markers of hyperinsulinenia (insulin and C-peptide levels). In a retrospective review of 652 patients with type 2 diabetes mellitus who were diagnosed with adenomatous polyps, poorly controlled diabetes (HbA1c ≥ 7.5%) predicted a greater prevalence of right-sided polyps, more advanced lesions, and a greater number of polyps.90 The Risk Factors and Life Expectancy Project studied more than 37,000 patients over a period of 7 years. This study was important because it demonstrated that patients with high blood glucose and metabolic abnormalities linked to insulin resistance had a significantly increased risk of colorectal-cancer mortality as compared to patients who did not have this cluster of metabolic abnormalities.91

Although researchers have not as yet definitively proven the effectiveness of dietary supplementation with cinnamon (Cinnamomum cassia),92,93 several studies have reported modest effects in lowering blood glucose levels after cinnamon supplementation.94 Anderson et al reported that consumption of 1 to 6 g of cinnamon daily for 40 days reduced mean fasting serum glucose, TAG, total cholesterol, and LDL-cholesterol in subjects with type 2 DM.95

The literature suggests some possible mechanisms for the effect of cinnamon on glucose levels. In vitro studies have shown that cinnamon increases the expression of PPARs γ and α (transcriptional factors known to be involved in the regulation of insulin resistance and adipogenesis) and their target genes in 3T3-L1 adipocytes.96 Additionally, Cao et al have demonstrated that cinnamon polyphenol extract can regulate anti- and proinflammatory and glucose-transporter gene expression in mouse macrophages.97

Both common and cassia cinnamon are generally safe when ingested in amounts commonly found in food.92 Three randomized, controlled trials employing cassia cinnamon at intakes of up to 6 g per day for 40 days,97 1.5 g per day for 6 weeks,98 and 3 g per day for 4 months,98 respectively, demonstrated no significant adverse effects. The most common adverse effect from common or cassia cinnamon ingestion, as described in several case reports and case series, is contact irritation or allergic reaction involving skin or mucus membranes, eg, contact dermatitis and stomatitis.99

**CONCLUSION**

There is growing interest regarding the integration of elements of complementary and alternative medicine into conventional medical treatments. In particular, integrative medicine is a current area of research interest for the multidisciplinary treatment of cancer patients. Researchers have studied various biologically-based practices extensively, especially the use of specific vitamins and minerals. There is less good-quality evidence supporting the use of herbal medicine and homeopathy, yet these modalities continue to be used widely by patients. The use of mind-body-medicine modalities may be helpful for certain chronic conditions and is a current focus of study, particularly with regard to its potential effect upon immune parameters. Other potential sources of alternative approaches to healing include manipulative and body-based practices such as chiropractic and massage; traditional Chinese medicine including acupuncture; naturopathy; and energy medicine. Nutrigenomics is a personalized approach that involves tailoring nutrition to the individual genotype in hopes of effecting disease prevention. In particular, it is thought that reduction of the extent of chronic inflammation may reduce the risk of cancer development.
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