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INTEGRATIVE CARE (C LAMMERSFELD, SECTION EDITOR)

The Use of Dietary Supplements in Oncology

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Abstract The use of dietary supplements among patients affected by cancer is extensive, with an estimated 20-90 % of patients using these products. Their use of these products is often not shared with the treating physician. This is because patients perceive or believe that their physicians are indifferent or negative toward the use of dietary supplements. As a result, patients may obtain information about dietary supplements from unreliable sources, exposing themselves to unnecessary risks. Since there are limited scientific data on the efficacy and safety of many dietary supplements, advising patients about when to use them during the course of illness is a clinical challenge. Improving the communication process between the health care team and their patients in this area is critical. We describe a practical patient-centered approach to managing dietary supplement use in cancer care. This approach makes use of all available scientific data relating to the safety and efficacy of these supplements combined with how to have an open, patient-centered discussion with patients about their needs and expectations.

Keywords Complementary medicine · Alternative medicine · Cancer care · Nutritional supplements · Dietary supplements · Patient–physician communication

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Introduction

A dietary supplement, as defined by the Dietary Supplement Health and Education Act, is a product that is intended to supplement the diet and contains one or more dietary ingredients, including vitamins, minerals, herbs or other botanicals, amino acids, and certain other substances [1] .

Globally, the use of dietary supplements was estimated in 2012 as exceeding $96 billion in sales [2]. Among the US adult population, this use is quite extensive, and in 2012 was one third of the global consumption, with $32.5 billion in sales [3]. Over 40 % of the US population used supplements in 1988–1994, and over half of the population used them in 2003–2006 [4].

As a result of this, increased federal funds were directed to research on dietary supplements to determine their health effects, safety, and efficacy. A portfolio analysis across the National Institutes of Health (NIH) and the Office of Dietary Supplements for fiscal years 2009–2011 indicated that the total NIH research budget for dietary supplements for fiscal years 2009-2011 was $855 million. Of this amount, the National Cancer Institute dedicated $188 million and the National Center for Complementary and Alternative Medicine dedicated $99 million [3].

Despite the limited knowledge of dietary supplements in cancer care, many studies have confirmed that most patients undergoing cancer therapy use self-selected forms of complementary and integrative medicine (CIM) [5, 6]. Nearly half of cancer patients in the USA report using at least one CIM treatment modality after their initial diagnosis and as many as 91 % report using at least one CIM treatment modality during chemotherapy and radiotherapy [7•].

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Dietary supplements are one of the easiest and most accessible modes of CIM therapies that patients use. Previous reports estimated that these products are used by 20-55 % of cancer patients [8–11]. In more recent reports of women with breast cancer undergoing treatment and up to 9 years after diagnosis, dietary supplement use ranged from 67 to 87 % [12, 13].

What Is the Evidence?

Even though the NIH supports substantial research of dietary supplements, the current knowledge of the effectiveness of these dietary supplements in cancer care is limited, and only a few benefits have been proven in clinical trials. A recent report from the US Preventive Services Task Force concludes that the current evidence is insufficient to assess the balance of benefits and harms from the use of multivitamins and single or paired nutrient supplements, except for β-carotene and vitamin E, for which the findings are negative, for the prevention of cancer [14]. On the other hand, in an article by one of the medical officers of the US Preventive Services Task Force, it was mentioned that with the exception of β-carotene and vitamin E, for which there is compelling evidence of harm, there is little reason to discourage people from taking vitamin supplements [15].

Some reports suggest a benefit from dietary supplement use. One of these recent reports reviewed the efficacy of dietary supplements for treatment-related toxicity and quality-of-life outcomes. The report authors found a number of high-quality studies examining the effects of dietary supplements on treatment-related toxicities. This is an issue that is commonly raised by cancer patients who wish to take dietary supplements. Their report suggests that in conditions such as neuropathy, mucositis, and diarrhea, there is a clinical benefit of integrating dietary supplements into conventional cancer care [7•].

Other reports suggest the possibility of a benefit in cancer care, such as the integration of curcumin as a chemosensitizer and radiosensitizer for treating tumors, and a chemoprotector and radioprotector for normal organs [16], the use of glutamine for the prevention of chemotherapy-induced peripheral neuropathy [17], the use of fish oil to improve chemotherapy clinical response in patients with lung cancer [18], the use of milk thistle to reduce chemotherapy-related hepatotoxicity in children with acute lymphoblastic leukemia [19], and the use of other substances [20•].

The Clinical Practice Committee of the Society of Integrative Oncology tried to address this dietary supplement use by patients affected by cancer in a different way. It identified that physicians need some basic information related to dietary supplements that are known to be safe and have indications of clinical efficacy. The Clinical Practice Committee surveyed clinicians with extensive experience in consulting cancer patients about dietary supplement use in leading cancer centers. They all agreed on a list of ten supplements that physicians can further discuss and share with their patients [20•].

This report included information on the mechanism of action of each dietary supplement, its safety, and its side effects, interactions with medications if known, and possible dosage. This information is summarized in Table 1.

Communication

Patients often do not report their use of dietary supplements to their provider [21, 22]. This gap in communication may result from patients' perception that their physicians are indifferent or negative toward the use of dietary supplements [23], or the perception that physicians emphasize scientific studies and evidence-based medicine, rather than a patient's preferences.

Clinicians need to understand why patients with cancer use dietary supplements in the first place. Patients tend to use dietary supplements in anticipation of psychological support or because they want to do everything possible to feel hopeful, get more control in decision making, enhance the immune system, use less toxic treatments, or reduce side effects and possible toxicity of conventional treatments. In fact, most patients choose to use dietary supplements to improve their quality of life rather than seeking a cure for their disease [24].

Communication is crucial in establishing trust with the patient, gathering information, addressing patient emotions and needs, and assisting patients in making decisions about care [25]. Patients of physicians who involve them in treatment decisions during office visits have better health outcomes and decreased psychological distress than patients of those physicians who do not [26].

The failure of physicians to communicate effectively with patients using dietary supplements may result in the loss of trust within the therapeutic relationship, and in the selection by patients of harmful, useless, or ineffective and costly nonconventional therapies when effective therapies may exist. Poor communication may also lead to a diminishment of patient autonomy and self-efficacy, and thereby diminish the self-healing response [23].

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 who has 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 compassion. Particularly when the physician is faced with unfamiliar information from a CIM field, he or she may feel "de-skilled." Being forced outside one's zone of comfort and

Table 1 Selected dietary supplements in oncology (adapted from [20])

Dietary supplement	Mechanism of action	Safety and side effects	Interactions	Dose/dosage
Curcumin	Can inhibit tumor initiation, promotion, invasion, angiogenesis and metastasis. Has been shown to interfere with multiple cell signaling pathways, including inhibition of NF-κB. Chemosensitizer and radiosensitizer	GRAS. Might cause some GI symptoms in high doses. Caution with gall bladder disease	Cyclophosphamide, camptothecin, anticoagulants	500 mg to 3 g
Glutamine	Reduces cytokine production and improves the GI tract mucosal barrier. Used to treat chemotherapeutic toxicities such as oral mucositis and chemotherapy-induced peripheral neuropathy	Minimal side effects. Caution in patients with hepatic and renal impairment	Decreases the effectiveness of lactulose. May interact with antiseizure medications	5–30 g/day
Vitamin D	Antiproliferative effects, can activate apoptotic pathways, and can inhibit angiogenesis	Generally safe with few side effects, most commonly GI	No reported interactions with antineoplastic agents	Measurement of serum 25-hydroxyvitamin D level should guide dosing
Maitake mushrooms	Biologic response modifier, providing T-cell-dependent immune enhancement and activation that enhance antitumor effect	GRAS. No reported side effects	Caution with hypoglycemic agents—careful monitoring of glucose levels in patients with diabetes. Owing to immune-modulating effects, caution in lymphoproliferative disorders and patients receiving immunomodulatory therapies. There is some concern that maitake mushroom might increase the anticoagulant effects of warfarin	A safe and effective dose has not been established. For type 2 diabetes, 1–1.5 g of maitake mushroom polysaccharides daily has been used
Fish oil	Reduces inflammation through changes in membrane fluidity, cell signaling, and production of anti-inflammatory eicosanoids and resolvins. These effects may retard cancer progression	Bloating, loose stools, fishy aftertaste, and eructations are the most commonly observed side effects (enteric coating of capsules reduces them). Fish oil may increase bleeding time, although observational studies of patients using fish oil before surgery have resulted in clinical concerns	Anticoagulant/antiplatelet drugs—caution and monitoring are suggested (especially at doses higher than 3 g daily). Chemotherapy-induced thrombocytopenia—owing to the risk of increased bleeding tendency, consider holding fish oil administration during chemotherapy with platelet levels below 50,000. Antihypertensive drugs—fish oil has hypotensive effects and may accentuate the effect of antihypertensive medications	2-3 g/day in clinical studies
Green tea	Has pro-apoptotic effects, inhibition of NF-κB and other signaling molecules, antimetastatic and prooxidative and antioxidative effects	Likely to be safe when consumed as a beverage in moderate amounts. Caffeine-related side effects are observed, including increased gastric acidity, effects on blood glucose levels, and elevated catecholamine levels	May antagonize warfarin, also has antiplatelet activity. EGCG could inhibit activity of bortezomib in multiple myeloma consider caution. EGCG inhibits P-glycoprotein and may cause interaction with irinotecan or verapamil. A case study and a laboratory study suggest a possible interaction between green tea and sunitinib. Green tea may	The commonly used dose of green tea is based on the amount typically consumed in Asian countries, which is about 3 cups per day, providing 240–320 mg of polyphenols

Table 1 (continued)

Dietary supplement	Mechanism of action	Safety and side effects	Interactions	Dose/dosage
			increase tamoxifen bioavailability. Green tea appears to reduce absorption of non-heme iron from foods	
Milk thistle	Silymarin, the active constituent of the milk thistle seed, seems to cause an alteration of the outer hepatocyte cell membrane that prevents toxin penetration. It also stimulates nucleolar polymerase A, resulting in increased ribosomal protein synthesis, which can stimulate liver regeneration and the formation of new hepatocytes	Orally, milk thistle is usually well tolerated. It can cause an occasional laxative effect	Preliminary research in an animal model suggests that milk thistle might increase plasma levels of tamoxifen	There is no clear recommendation for milk thistle dosage. An average of 200–400 mg/day in divided doses has been used in most of the studies investigating silymarin
Astragalus membranaceus	The polysaccharides in astragalus were found to potentiate the immune-mediated antitumor activity of interleukin-2, improve lymphocyte responses, enhance natural killer cell activity, and increase phagocytosis, perhaps by regulating tumor necrosis factor production	Astragalus is well tolerated. Adverse effects have not been reported	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	It is unclear what the optimal dose is. Traditionally, astragalus powder at 1–28 g/day is used
Melatonin	Stimulation of apoptosis, upregulation of antioxidant enzymes, suppression of tumor and endothelial growth factors, downregulation of pro-oxidative enzymes	Melatonin can be used safely with a beneficial effect and without adverse impact on conventional cancer therapy outcomes	Melatonin may theoretically affect glucose tolerance and anticoagulant pharmacology. Caffeine, alcohol, NSAIDs, beta-blockers, benzodiazepines, diuretics, and calcium channel blockers endogenously suppress melatonin production	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
Probiotics	Live microorganisms which, when administered in adequate amounts, are intended have immune-modulating properties. The main use of probiotics in cancer care is in the treatment of intestinal toxicity during both chemotherapy and radiotherapy	There are no known safety issues with most probiotic bacteria at appropriate doses	No known clear interactions with conventional cancer treatments and probiotic species. Caution about taking iron supplements simultaneously with probiotics	In the case of chemotherapy-induced diarrhea, a dose of 10×10^9–20×10^9 cells of *Lactobacillus rhamnosus* GG

EGCG epigallocatechin gallate, *GI* gastrointestinal, *GRAS* generally regarded as safe, *NF-κB* nuclear factor κB

competence can lead to defensiveness and a breakdown in communication with the patient [27•].

Communication between clinicians and patients is an interactive process, not a concise, focused dialogue of questions and answers. The patient–clinician dialogue involves not just "words"; it also involves the "voice." The ways in which one expresses oneself—using a soft or loud voice, slow or fast speech, and verbal and nonverbal cues—are all connected and are part of communication between two people. Communication can relate to previous visits, family and caregiver involvement, other health care providers, and personal and professional experiences of the clinician and the patient. Family, employment, emotions, desires and wants, hidden wishes and concerns, where one finds meaning in life, health beliefs, and social, religious, and spiritual issues are all part of effective communication [28].

The physician who is receptive to patient inquiries and is aware of subtle, nonverbal messages can create an environment of safety in which a patient feels and is protected [29].

Clinicians must use a sensitive approach in communication with the patient who has an interest in the use of dietary supplements. This approach uses effective communication skills and experience in attentive listening.

A communication approach that fosters a collaborative relationship that includes adequate information exchange, empathy and compassion, responding to emotional needs, and managing uncertainty can lead to informed decisions about dietary supplement use [28].

Strategy To Address a Patient's Use of Dietary Supplements

The optimal approach to discussing dietary supplement use is meeting uncertainty with facts about safety, efficacy, and expectations. Subsequently, a mutually informed decision can be made about the patient's care [22, 28, 30, 31].

We believe that asking the right questions, particularly when final answers are not available, will lead to improved patient–physician communication and a rational strategy to address patients' needs and expectations in the face of uncertainty [22].

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, some suggest that we need not discourage the patient from using

Table 2 Useful and reliable resources related to dietary supplements

Subscription databases	Free resources
Natural Medicines Comprehensive Database: http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=&s=ND	CAM on PubMed: http://nccam.nih.gov/research/camonpubmed(searches journal literature in PubMed, pre-filtered to CAM topics)
Natural Standard: http://www.naturalstandard.com/	MedlinePlus pages
Alt Health Watch (articles on CAM topics): http://www.ebscohost.com/academic/alt-healthwatch	Herbs and supplements: http://www.nlm.nih.gov/medlineplus/druginfo/herb_All.html
HerbMedPro: http://cms.herbalgram.org/herbmedpro/overview.html?targetPage=http://cms.herbalgram.org/herbmedpro/index.html	CAM: http://www.nlm.nih.gov/medlineplus/complementaryandalternativemedicine.html
	Cancer alternative therapies: http://www.nlm.nih.gov/medlineplus/canceralternativetherapies.html
	Dietary supplements: http://www.nlm.nih.gov/medlineplus/dietarysupplements.html
	NCCAM: http://nccam.nih.gov/
	NCCAM—for health providers: http://nccam.nih.gov/health/providers
	NCCAM—cancer and complementary health approaches : http://nccam.nih.gov/health/cancer/camcancer.htm
	Memorial Sloan Kettering Cancer Center—herbs, botanicals, and other products: http://www.mskcc.org/cancer-care/integrative-medicine/about-herbs-botanicals-other-products
	National Cancer Institute—CAM: http://www.cancer.gov/cancertopics/cam
	National Cancer Institute Office of Cancer Complementary and Alternative Medicine: http://cam.cancer.gov/cam/
	Integrative Oncology Consultants: http://www.moshefrenkelmd.com
	CAM-Cancer: http://www.cam-cancer.org/CAM-Summaries

CAM complementary and alternative medicine, *NCCAM* National Center for Complementary and Alternative Medicine

those supplements despite the limited evidence [7•, 20•, 22]. One cannot overlook the patient perspective in this equation.

Patients frequently see consumption of natural products as an avenue they can use to empower themselves, attempt to take control of their health, and increase their quality of life [32, 33]. 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 [33].

If their physician is not a responsive and reliable source of information, patients obtain and collect information on dietary 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 [34].

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 physician.

As in other fields of medicine, physicians need to approach dietary supplement use in cancer in a systematic way. Most of the scientific data in the medical literature to support the use of dietary supplements cannot be considered as proof of efficacy, but the current findings can be considered as clinical clues. Such clues can provide a basis for honest and open discussion with the patient regarding potential benefit or harm, including economic considerations. When physicians use a patient-centered approach, they can promote informed decision making by the patient, and this can lead to patients collaborating better and more effectively with the physician [22, 27•, 28–32, 35]

Patients can be given appropriate information from reliable sources about dietary supplements such as mentioned in Table 2, or can use peer-reviewed documents such as the 2009 guidelines of the Society of Integrative Oncology [35]. For many physicians, dietary supplement information is not readily available, and this is the point where other members of the treatment team can help out, such as nurses, pharmacists, and dieticians who have expertise in exploring these options of care further. This improves care for patients and their families [27•].

An objective and balanced discussion of the findings from this search will lead to trust and improve the delicate relationship needed in this communication process. This discussion is crucial to building a treatment plan that patients and their caregivers are actively involved with, is personalized, safe, and evidenced based [30].

For most busy practitioners , we suggest familiarity with the commonest dietary supplements and basic information related to these (summarized in Table 1). Such discussion might not be a comprehensive overview of the topic, yet it is still important, as it conveys to the patient that the physician is interested in the patient's concerns and needs.

Conclusions

The use of dietary supplements among patients affected by cancer is extensive. It is also controversial. With the increased use of such supplements by cancer patients, physicians need a rational approach to advise and communicate with patients as well as to monitor their use of the supplements. A practical patient-centered approach, as we describe, may help physicians address the challenges of dietary supplement use. Our responsibility is to make use of all available scientific data relating to the safety and efficacy of these supplements, but not be limited by it, in cases in which the data are conflicting or inconclusive. A physician can disagree with a patient's choices while compassionately engaging and supporting the patient in fulfillment of the physician's roles of caring, comforting, and healing, even if cure is not possible.

Compliance with Ethics Guidelines

Conflict of Interest Moshe Frenkel and Victor Sierpina declare that they have no conflict of interest

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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