



Safety Considerations When Managing Dietary Supplements in Cancer Care



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Lecture Outline

1. Introduction
2. Definitions
 - Dietary supplements
 - integrative oncology
3. Resources
4. Health Systems and Health Behavior Considerations
5. Herb/Drug, Mechanism, and Nutrient/Drug Interactions
6. Radiation, Surgical, and Anti-Coagulant Considerations

Introduction

- Bachelor of Science in Nutritional Sciences (BS)
 - The Pennsylvania State University
- Master of Science in Research (MS)
 - National University of Natural Medicine
- Doctorate of Naturopathic Medicine (ND)
 - National University of Natural Medicine
- Clinical Residency- Integrative Oncology
 - Cancer Treatment Centers of America
- Postdoctoral Research Fellow in Complementary and Integrative Medicine
 - University of North Carolina
- Physician, Integrative Oncology
 - Vermont Wellness Medicine and Integrative Oncology

Definition: Dietary Supplement

Dietary Supplement: A product that is intended to supplement the diet. A dietary supplement contains one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals, amino acids, and other substances) or their components; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is identified on the front label of the product as being a dietary supplement.

- NIH, Office of Dietary Supplements



Definition: Integrative Oncology

"Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment."¹




Integrative Oncology
Fundamentals

1. Patient Safety
2. Managing OTC Supplements, Natural Products, Exercise, M/B Approaches
3. Supporting Quality of Life and Symptom Reduction
4. Evidence-Based



Integrative Oncology Resources



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Society for Integrative Oncology

- <https://integrativeonc.org/>

UNC-Integrative Medicine- Yoga, Massage, Acupuncture

- <https://unclineberger.org/patientcare/support/ccsp/integrative-medicine>

The ASCO Post-Integrative Oncology

- <http://www.ascopost.com/topics/supportive-care/integrative-oncology/>

Foundations of Mindfulness Courses at UNC

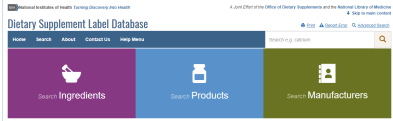
- <https://www.med.unc.edu/phyrehab/bim/mindfulness-program/mindfulness-course-schedule/>

Health Systems and Health Behavior Considerations

Health Systems Issues

The National Institutes of Health- Office of Dietary Supplements

- Dietary Supplements Label Database
 - Contains label information for approximately 76,000 dietary supplements available on the U.S. Market
 - Studies indicate the prevalence of dietary supplement use in cancer care reaches as high as 73%?




Health Systems Issues

Who is trained and available to manage all these dietary supplements and OTC products?

Oncologists?	Homeopaths?
Pharmacists?	Ayurvedic Practitioners?
Family Physicians?	Chiropractors?
Functional Medicine MDs or DOs?	Massage Therapists?
Nurse Practitioners or Physician Assistants?	Nutritionists?
Nurses?	Life and Wellness Coaches?
Naturopathic Doctors?	Mind/Body Therapists?
Chinese Medicine Practitioners?	Physical or Exercise Therapists?
Acupuncturists?	The supplement sales representative at the local health food store?
Herbalists?	

Health System Issues

- Lack in Number of Qualified Practitioners**
 - There are less than 6,000 NDs in North America and <200 who specialize in supportive cancer care.
- Lack of Quality Research Evidence**
 - Inability to set standards of care
- Lack of Insurance Coverage**
 - Prevents patients from seeking qualified practitioners due to expense
- Lack of Quality Products/Availability of Products**
 - Limited regulations and standardization of products
 - Highest quality products only available to licensed practitioners



Variations in Supplement Production

Dietary Supplement regulation began with the passage of the Dietary Supplements Health and Education Act (DSHEA) in 1994, which initiated regulatory measures such as Good Manufacturing Processes (GMPs)

However, there are a lot of variables to consider in the production and processing of dietary supplements that make this a very complex and heterogeneous procedure among suppliers and producers, such as:

- What is the soil quality used for growing herbs?
 - Harvesting at the correct time of year?
 - Using the correct part of the plant?
 - Are the plants sprayed with pesticides?
 - Are the final products tested for pesticides? heavy metals?
 - fillers and allergens (wheat, dairy, gluten, soy, nuts, binders, egg proteins)?
 - Do you account for variations in the level of active constituents?
- What is the therapeutic dose? Variations in research dosing?
 - How do you account for the mechanism of action with tens or hundreds of active constituents in 1 product?
 - How do you account for low bioavailability of certain supplement products?
 - Which form of vitamins and minerals are you using? Is this the best form for the intended purpose?

Supplement Quality and Safety

Curcumin Extract 700 mg 60 vcaps

Dietary Supplement

Recommendations: 1-2 capsules twice daily, or as directed by your healthcare professional.

Supplement Facts

Serving Size: 2 vegetarian capsules

Servings Per Container: 30

Amount Per Serving:

Curcuma longa Rhizome Extract 1400 mg
(total Curcuminoids min. 85-92% by HPLC)

Black Pepper Fruit/Berry Extract 90% 15 mg
(Bioperine® piperine)

Other Ingredients: Vegetable Cellulose Capsule, Magnesium Silicate, Ascorbyl Palmitate, Cellulose and Silica.

Warning: If pregnant, consult your physician before taking. Keep out of reach of children. Use only if safety seal is intact. Store sealed in a cool dry place.

Excludes: Coatings, Binders, Gluten (wheat, rye, barley), Milk/Dairy (casein, whey), Soy Protein, Egg Protein, Sugar.



Health Behavior Challenges

Patient Disclosure of Natural Product Use

There are numerous studies available from all over the world indicating patients choose not to disclose their natural products use to their oncologist.³

There are many different reasons why this might be:

- The oncologist never asked
- Fear the oncologist might tell the patient to stop
- Fear of ridicule or embarrassment
- Fear the oncologist will treat the patient differently or stop the conventional treatment



Poll Question #1

Poll: Why is a lack of standardization in the production of dietary supplements a health system safety concern?

- It could lead to the consumption of impurities such as heavy metals, fillers, allergens, etc.
- It makes it hard to track adverse events
- It could lead to variations in active constituents and effectiveness
- All of the above

Herb/Drug, Mechanism, and Nutrient/Drug Interactions

Herb/Drug Interactions

Herb/Drug Interaction: the combination of the two products (an herb and a pharmaceutical) taken at the same time, or around the same time, causes a change in the clearance of either product from the body.

The body mainly uses pathways in the liver to clear herbal and pharmaceutical products, known as the CYP proteins (Cytochrome P enzymes). There are several different pathways, such as CYP1A1, CYP1B1, CYP2D6 or the most common CYP3A4.

Herbs and drugs can speed up these pathways (an inducer) or slow down these pathways (inhibitor), which can effect how fast a substance is cleared from the body.



Herb/Drug Interactions

Therefore, if someone is using a chemotherapy and combines it with an herb that slows down the clearance of the chemotherapy from the body (inhibits the pathway), what could possibly happen?

- The chemotherapy could build up in the body and increase the toxicity or side effects.

If someone is using a chemotherapy and combines it with an herb that speeds up the clearance of the chemotherapy from the body (an inducer), what could possibly happen?

- The chemotherapy could leave the body too quickly and be less effective at killing cancer cells.

Herb/Drug Interactions- Clinical Management

For patients insistent on continuing their herbal medicine with chemotherapy, it is challenging to find a "happy medium," so everyone is satisfied

Clinical Approaches:

1. Holding an herb known to have a potential interaction for 48 hours prior to, during, and for 48 hours after receiving chemotherapy
 - Only works for infusions, and not daily chemotherapy.
2. Rule of 5 Half-Lives
 - Multiply the terminal half-life of a drug and herb by 5 to ensure 97% of each medicine is eliminated

Example: Doxorubicin and Green Tea

- Doxorubicin terminal elimination half-life: 20-48 hours, x 5 = 100 hours (4.2 days) – 240 hours (10 days)⁴
- EGCG terminal elimination half-life: 3.4 hours, x 5 = 17 hours⁵

Herb/Drug Interactions- Clinical Management

A patient with breast cancer was prescribed 60 mg/m² Doxorubicin infusion every 21 days, and would also like to take her green tea extract. There is a known herb/drug interaction via CYP3A4.

When can she "safely" take her green tea extract?



Answer: Days 11-20 (Stop 24 Hours Prior to Next Infusion)

Folate Content of Food and Multivitamins

The RDA for folate in adults is **400 mcg** daily

Mean dietary intakes of folate (including food folate and folic acid from fortified foods) range from **454 to 652 mcg DFE per day** in U.S. adults.⁹

Supplement Facts

Supplement Facts	Amount Per Serving	% Daily Value
Vitamin A (as retinyl acetate)	5000 IU	100%
Vitamin C (as ascorbic acid)	60 mg	100%
Vitamin D (as cholecalciferol)	400 IU	100%
Vitamin E (as alpha-tocopheryl acetate)	30 IU	100%
Thiamin (as thiamine mononitrate)	15 mg	100%
Riboflavin	17 mg	100%
Niacin (as niacinamide)	30 mg	100%
Vitamin B ₆ (as pyridoxine hydrochloride)	25 mg	100%
Folate (as folic acid)	400 mcg	100%
Vitamin B ₁₂ (as cyanocobalamin)	6 mcg	100%
Biotin	30 mcg	100%
Hydroxyethyl Cellulose	100 mg	0%
Hydroxyethyl Cellulose	100 mg	0%



Should we hold multivitamin supplementation during capecitabine (and 5FU) administration?

Mechanism Interactions

Natural products and pharmaceuticals can have the same or opposite physiological mechanism, causing a potential interaction. The interaction could theoretically decrease the effectiveness of the pharmaceutical, or increase side effects.

Example:

- Immunotherapy and Natural Immune Stimulants
- Stem Cell Transplants and Natural Immune Stimulants

Mechanism Interactions- Example

Nivolumab and High Dose Melatonin

Nivolumab: a human immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by blocking ligands PD-L1 and PD-L2 from binding to the PD-1 receptor. This upregulates T-cell cytotoxicity.¹⁰ *"Takes the brakes off of the immune system"*

Potential Adverse Reaction: Potentially fatal autoimmune disorders

Melatonin (20 mg): may increase T helper 17 (Th17) cell (a subset of T cells that regulate tumorigenesis, inflammation, and autoimmunity) differentiation¹¹; antigen presentation to T cells, and production of cytokines interleukin-10¹², interleukin-1, and TNF-alpha.¹³ This results in T cell proliferation.

Would taking Melatonin and Nivolumab together increase the risk of autoimmune side effects?

OR

Would taking Melatonin and Nivolumab together increase T-cell cytotoxicity towards tumor cells?

Natural Immune Stimulants and Hematological Malignancies

Natural immune stimulants, such as high dose melatonin, medicinal mushrooms, and certain herbal products (Astragalus) are known to stimulate the immune system and increase T-cell cytotoxicity.²⁵⁻²⁶

It is unknown if stimulating the immune system has a negative impact on someone with a hematological malignancy.

Until more research data is available, caution should be taken regarding the supplementation of natural immune stimulants with hematological malignancies.

Estrogenic Herbs and Hormone Dependent Cancers

- The growth of certain cancers, such as breast or ovarian cancer, may be stimulated by exposure to endogenous or exogenous estrogen.²⁷
- Therefore, we don't want any added estrogen exposure for someone with a estrogen-regulated cancer.
- Phytoestrogenic herbal products:
 - Soy, Flaxseed, Alfalfa, Red Clover, Ginseng (Siberian, Not Eleuthero) Resveratrol, Red Raspberry Leaf, Dong quai (Angelica sinensis), Ginkgo, Fenugreek, Hops, Burdock, Indian Rhubarb, Fermented Wheat Germ/Grass, Moringa, Licorice, Sage (Salvia officinalis), Red Sage, Calendula (Orally), Milk Thistle (Aerial Parts), Deer Antler Fuzz, Wild Yam, False Unicorn Root (Chamaelirium luteum) Cramp Bark (Viburnum opulus), Maca Root (Lepidium peruvianum)

Boron and Sex Hormones

Effect of dietary boron on mineral, estrogen, and testosterone metabolism in postmenopausal women.
 Researcher: David G. Miller MD, PhD, JD
 Author information
 Abstract
 A study was done to examine the effects of aluminum, magnesium, and boron on major mineral metabolism in postmenopausal women. The communication describes some of the effects of dietary boron on 12 women between the ages of 48 and 52 housed in a metabolic unit. A daily supplementation of 3 mg/day markedly affected several aspects of mineral metabolism of these women compared to a low boron diet.

"Boron supplementation markedly elevated the serum concentrations of 17 beta-estradiol"²⁸

Supplement Facts	Amount Per Serving	% Daily Value
Boron	3 mg	100%
Aluminum	10 mg	100%
Magnesium	100 mg	100%
Calcium	100 mg	100%
Phosphorus	100 mg	100%
Sodium	100 mg	100%
Potassium	100 mg	100%
Iron	100 mg	100%
Zinc	100 mg	100%
Copper	100 mg	100%
Manganese	100 mg	100%
Selenium	100 mg	100%
Chromium	100 mg	100%
Molybdenum	100 mg	100%
Vitamin A	100 mg	100%
Vitamin B1	100 mg	100%
Vitamin B2	100 mg	100%
Vitamin B3	100 mg	100%
Vitamin B6	100 mg	100%
Vitamin B12	100 mg	100%
Vitamin C	100 mg	100%
Vitamin D	100 mg	100%
Vitamin E	100 mg	100%
Vitamin K	100 mg	100%
Other Ingredients		



Directly Harmful Practices

Apricot Seeds (aka Amygdalin, Laetrile)

- A common "alternative," cancer treatment
- Has been studied a few decades ago for a potential anti-cancer effect
- The theory is Amygdalin is metabolized only by cancer cells, and releases cyanide to kill the cancer cell.
- However, data indicates the Amygdalin does not specifically effect only cancer cells, but is metabolized by all cells in the body, which can lead to cyanide poisoning.

Additional questionable products/practices include internal consumption of hydrogen peroxide, ozone, Kratom, insulin-potentiated chemotherapy, experimental procedures.

Poll Question #2

Poll: Goldenseal (*Hydrastis canadensis*) **inhibits** cytochrome P450 3A4. Paclitaxel is a major **substrate** of cytochrome P450 3A4. What is a potential outcome of taking these medicines at the same time?

- Decreased side effects of Paclitaxel
- Increased side effects of Goldenseal
- Increased side effects of Paclitaxel

Radiation, Surgical, and Anti-coagulant Considerations

Radiation Oncology Considerations

Avoiding High Dose Antioxidant Supplementation

N-Acetyl Cysteine (NAC) and Alpha Lipoic Acid (ALA)

- In-vitro study found a delayed radio-protective effect after 24 hours in cells exposed to 2 Gy of radiation due to NAC and other thiol-containing drugs.²⁹
- NAC also blocks the benefit of radiosensitizing agents in vitro.^{30,31}

Coenzyme Q10 > 300 mg daily

- Mouse models indicate CoQ10 can cause a lower specific growth delay in mice receiving single dose tumor irradiation + CoQ10.³²

Vitamin A in Renal Radiation

- Rat models have found all-trans retinoic acid exacerbated radiation nephropathy, with potential mechanism of action being the inhibition of renal nitric oxide activity by Vitamin A.³³



Surgical Oncology Considerations

There is a potential for dietary supplements to interfere with the medications and procedures involved in surgical oncology.

It is important to consider herb/drug considerations with anesthesia.

There are several herbal products with the potential to effect blood coagulation, including (but not limited to):

- Ephedra (Ma-huang), Feverfew, Fish Oil, Garlic, Ginger, Ginkgo (Ginkgo biloba), Ginseng, Goldenseal, Kava-Kava, Licorice, Hypericum (St. John's wort), Valerian, Vitamin E

General Recommendations:

- Discontinue all herbal products, and products with known anti-coagulant effect or herb/drug interactions **1 week** before surgery
- Discontinue all other dietary supplements **24 hours** before surgery

Anti-Coagulant Considerations

For any patient on anti-coagulant medication, it is important to consider herbal and natural products that also have a potential anti-coagulant effect. The most common natural products with anti-coagulant effect are:



Fish Oil
Garlic
Turmeric
Ginger
Cayenne
Vitamin E

Cinnamon
Ginkgo
Grape Seed Extract
Dong quai/Ginseng
Feverfew
Bromelain



Additional Resources

- 1. Natural Medicine Comprehensive Database
- <https://naturalmedicines.therapeuticresearch.com/>
- 2. National Center for Complementary and Integrative Health (NCCIH)
- <https://nccih.nih.gov/>
- 3. NIH-Office of Dietary Supplements
- <https://ods.od.nih.gov/>



Poll #3

Poll: A potential adverse effect of Ipilimumab is an autoimmune reaction. Melatonin and Ipilimumab share a similar mechanism of action by stimulating the immune system. What is a theoretical outcome due to this similar mechanism?

- Increased risk for an autoimmune disease
- Decreased risk for an autoimmune disease
- Decreased effectiveness of Melatonin

Questions

Any Questions?



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