Fullscript

Supplements for integrative oncology

A CLINICAL GUIDE FOR PRACTITIONERS

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At Fullscript, we believe that dietary supplements are core to an integrative treatment plan.

From nutraceuticals to botanicals to multi-ingredient formulations, there's no shortage of options for Integrative oncologists interested in recommending supplements, and the industry continues to innovate at an incredible pace.

Integrative oncology has been defined as 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".

An increasing number of oncologists are choosing to integrate dietary supplements into their patients' treatment plans, and 75% of cancer patients report seeking dietary supplement advice from their healthcare professionals. However, with thousands of products available through Fullscript, it can be difficult to know where to start.

As healthcare practitioners, it's also critical that we remain well-informed about all the options available to us so that we can best support our patients. Whether your practice specializes in medical, surgical or radiation oncology, nutritional supplementation can improve patient health outcomes when used in conjunction with your standard modes of treatment.

We hope this kit provides you with the initial information needed to comfortably use dietary supplements in your practice. Our world-class customer success team is always available to answer questions, or connect you with our integrative medical advisory team for guidance on product selection and protocol development.

In health,

Dr. Alex Keller, ND
Medical Director
Fullscript

Supplements 101

Regardless of your experience level, the supplement landscape can easily become overwhelming.

Supplements are typically divided into two key categories:

Nutrients

also known as Nutraceuticals or Orthomolecular Medicine

Botanicals

also known as Herbal Medicine or Phytotherapy

Each category is meant to support underlying excesses or deficiencies, with the ultimate goal of bringing the body back into balance. Where it can become complicated is in understanding the different uses and dosing of specific extracts, chelates, preparations, and more. Despite the complexities, integrative oncologists may recommend a variety of dietary supplement products for their clients, including vitamins and minerals, probiotics, essential fatty acids, botanicals, and several others. In the Fullscript catalog alone, there are over 15,000 unique products to filter through and understand.

Common supplement types

The following table outlines several common supplement types and some of their key functions.

Supplement type	Description	Key functions	Examples
Enzymes	Proteins that act as catalysts (increase the rate) of chemical reactions in the body	Break down carbohydrates, lipids, and proteins; degrade potentially harmful substances	Amylase Nattokinase Lactase Lipase Protease Serrapeptase
Fiber	Complex carbohydrates indigestible by humans	Supports digestion (improves regularity of bowel movements), provides a source of energy for gut bacteria, reduces cholesterol	Guar gum Pectin Psyllium husk
Greens	Products containing one or more green plant ingredients, including algae, fruit, grasses, and vegetables	Provide antioxidants, vitamins, minerals, and anti-inflammatory properties	Alfalfa Barley grass Chlorella Spirulina

Supplement type	Description	Key functions	Examples
Herbs (also called botanical medicine, phytotherapeutics, or medicinal herbs)	Plants used in herbal medicine for their therapeutic properties and health effects; parts used include the root, rhizome, bark, stem, leaves, seeds, flowers, and fruit	Exert therapeutic actions (e.g., analgesic, anti-bacterial, anti-inflammatory, improve insulin sensitivity) through active components	Ashwagandha (*Withania somnifera)* Garlic (*Allium sativum*) St. John's wort (*Hypericum perforatum*) Turmeric (*Curcuma longa*)
Medicinal mushrooms	Edible fungi that possess a variety of therapeutic properties and health effects	May induce anti-inflammatory, anti-microbial, and/or immunomodulating effects	Chaga (*Inonotus obliquus*) Lion's mane (*Hericium erinaceus*) Reishi (*Ganoderma lingzhi*) Turkey tail (*Coriolus versicolor*)
Minerals	Elements required in small amounts from the diet	Contribute to a variety of bodily functions including fluid balance, nerve transmission, muscle function, bone development, and blood pressure regulation	Macrominerals (e.g., calcium, magnesium, potassium) Microminerals (e.g., iron, selenium, zinc)
Omega fatty acids	Fatty acids containing one or more double bonds between carbons within the fatty acid chain, making them unsaturated	Contribute to energy storage, endocrine function, immune function, and cellular structure	Omega-3 fatty acids (e.g., EPA, DHA) Omega-6 fatty acids (e.g., LA, GLA)
Probiotics	Live microorganisms that, when administered in adequate amounts, confer a health benefit to the host	Inhibit the growth of pathogens in the gut; support gastrointestinal health, immune function, and nutrient absorption	*Bifidobacterium longum* *Lactobacillus acidophilus* *Saccharomyces boulardii*
Protein	Large molecules consisting of amino acids; essential as structural components in the body	Builds/repairs muscle and other tissues; synthesizes DNA, hormones, enzymes, and neurotransmitters	Amino acids (e.g., l-carnitine, l-glutamine) Enzymes Protein powder
Vitamins	Organic compounds required in small amounts from the diet	Contribute to a variety of bodily functions including vision, energy production, bone metabolism, immune function, metabolism, and blood coagulation	Fat-soluble vitamins (e.g., A, D, E, K) Water-soluble vitamins (e.g., B, C)

Nutrients

For this guide, we'll define nutrients as ingredients that would otherwise be found in food, including vitamins, minerals, phytochemicals and antioxidants.

What are nutrients?

In order to sustain life and wellness, the human body requires a careful balance of a broad range of nutrients, categorized as macronutrients and micronutrients.

Macronutrients constitute the major food groups of carbohydrates, fats and proteins. They are required in large amounts, used primarily for energy production and tissue growth, but also play crucial roles in maintaining musculoskeletal function.

Micronutrients are required in trace amounts and include vitamins and minerals. Phytonutrients, such as anthocyanin found in blueberries or resveratrol found in grapes, are also often classified as micronutrients.

How do nutrients work?

Macronutrients are the caloric basis for our daily energy need, but also provide the building blocks of tissue development, fiber for our microbiota, cholesterol for hormone production, and more.

Micronutrients are not relevant for energy and instead contribute to tissue development, hormone and neurotransmitter production, brain function, immune function, and more.

Common examples of nutritional supplements

Dietary supplements can provide a wide array of nutrients in condensed form, allowing users to target specific deficiencies or upregulate certain pathways that require those nutrients in abundance.

Some common examples include:

- **Whey protein isolate**
- **Omega-3 fatty acids**
- **Calcium**
- **B vitamins**

For a detailed review of the key dietary nutrients, visit **www.fullscript.com/hcp**

Botanicals

For this guide, botanicals are defined as therapeutic plant extracts not otherwise intended as food, including whole plant extracts and specific phytochemical extracts.

What are botanicals?

Considered the original pharmacy, records of humanity using botanical extracts therapeutically date back to the beginning of recorded history. More recently, botanical medicine has served as the inspiration for numerous pharmaceutical interventions and continues to reveal its purposes via modern research.

For the integrative practitioner, botanical medicine is essential, normally eliciting far fewer and less significant adverse effects than pharmaceutical interventions. A growing body of research shows that if used in correct dosages, certain botanical extracts are in fact more effective than pharmaceutical equivalents, and often more cost effective as well.

How do botanicals work?

Botanical medicine has as broad a pharmacopeia as modern pharmaceuticals. Given their capacity to interact with virtually every bodily system and tissue, there are literally thousands of therapeutic uses for botanicals. Although there is a vast amount of literature on the traditional use of botanical medicine, there is only a scant amount of modern research relative to modern pharmaceutical interventions. As a result, it becomes somewhat challenging to compare most botanicals with pharmaceuticals regarding clinical outcomes. However, according to a recent World Health Organization report, this landscape is rapidly evolving.

For a review of the various uses and existing clinical research supporting botanical medicine, visit **www.fullscript.com/hcp**.

Examples of botanical ingredients

Botanical medicine can provide an abundance of therapeutic effects, allowing everyone, from the skilled practitioner to the common layperson, to apply these therapies effectively.

Some common examples include:

- **Garlic (*Allium sativum*) –** immune function, cardiovascular function
- **Goldenseal (*Hydrastis canadensis*) –** lowers blood sugar, decreases trglycerides, antimicrobial
- **Turmeric (*Curcuma longa*) –** improves inflammation and outcomes of inflammatory conditions

Note: The form of extract is very important in botanical medicine. Plants contain a variety of therapeutic chemicals, differing in their use and extraction process. Practitioners should not only understand the existing clinical research and how to dose these extracts for therapeutic purposes, but also to prevent harm.

Supplement quality standards

Working with high-quality dietary supplements is crucial for clinical outcomes – but what does high-quality even mean?

There are a few key factors to assess when selecting the products you work with:

- **Ingredient sourcing**
- **Ingredient absorption**
- **Product manufacturing**

Ingredient sourcing & absorption

The source of ingredients when working with both simple and complex patient cases is the first step in determining whether you will have a high-quality end product. If working with nutrients, one might question whether the ingredient is naturally derived or synthetically produced. If the latter, this will have an effect on absorption and/or cause side effects.

For the purpose of this introductory resource, let's consider iron. There are various forms of iron found in dietary supplements. Three examples include:

- **Ferrous fumarate**
- **Ferrous bisglycinate**
- **Heme iron**

Ferrous fumarate is the iron salt from fumaric acid, which is found naturally in certain mushrooms and moss species, but is typically synthetically manufactured from malic acid in apples. Ferrous fumarate is one of the most common iron-based ingredients in dietary supplements due to its affordability, but it is also often shown to be associated with constipation.

Ferrous bisglycinate is an iron chelate, meaning it is manufactured to bind one molecule of ferrous iron to two molecules of the amino acid glycine. The patented version of ferrous bisglycinate is known as Ferrochel. Absorption of iron bisglycinate is widely thought to be superior to ferrous fumarate, therefore causing less constipation. Iron chelates normally price in the mid-range of iron ingredients.

Heme iron is derived mainly from hemoglobin and myoglobin in animal tissue. It is absorbed more efficiently than non-heme iron, at a rate of 15% - 35%, depending on the person's current iron saturation levels. Heme iron, although typically the most expensive form of supplementary iron and not vegan-friendly, is considered the best absorbed form of iron.

Similar examples exist for most supplement ingredients, so please take the time to review the ingredient summaries at **www.fullscript.com/hcp** to learn more about the wide variety of options available.

Product manufacturing

Supplement product manufacturing standards vary widely in the United States. However, as of 2007, all United States supplement manufacturers are required to comply with FDA-mandated Current Good Manufacturing Practice (CGMP) guidelines. Typically, CGMP standards are considered the baseline to "ensure the quality of the dietary supplement and to ensure that the dietary supplement is packaged and labeled as specified in the master manufacturing record."

Under CGMP requirements, manufacturers are required to qualify and verify ingredient and/or product properties using valid testing and analysis equipment. This is done to produce a certificate of analysis that identifies identity, strength, quality and purity to help reduce the risk of product adulteration. Certain companies will publish the analyses of their batches for public transparency and to build trust within the industry.

Beyond CGMP, many supplement manufacturers will elect to apply voluntary third-party certification to their manufacturing or ingredient-sourcing standards.

See the chart on the next page for some common examples of third-party certifications.

At Fullscript, we believe quality is uniquely defined by each individual user. As a result, **we allow practitioners to curate a catalog that best suits the needs of their patients.**

In our catalog's advanced search tool, you will find several of these third-party certifications that can be used for filtering when selecting products.

You can also learn more about each of the various certifications at **www.fullscript.com/hcp**

These are some of the numerous third-party certifications you will find in the Fullscript catalog. Note that specific certifications can be applied for different reasons, so it's important to understand and determine which quality assurances are most significant for your clinical needs.

Certification Mark	Organization	Description
	**NSF cGMP**	The Good Manufacturing Practices (GMP) registration program from the NSF provides an independent audit for manufacturers of raw materials, ingredients, and supplements, as well as distributors, warehousing and packaging firms. The program verifies a company's commitment to current GMP standards for processes, procedures, and documentation of a product's identity, strength, composition, quality, and purity.
	**National Sanitation Foundation (NSF) Certified for Sport®**	NSF Certified for Sport is a third-party certification program designed specifically for sports supplements to ensure products do not contain unsafe levels of contaminants, prohibited substances, and masking agents.
	**USDA Organic**	The National Organic Program (NOP), a program housed within the United States Department of Agriculture (USDA), is responsible for developing national standards for production, labeling, and enforcement of all USDA organic products.
	**Fair Trade**	Fair Trade Certified, a third-party certification based on social, environmental, and economic standards, ensures that products are grown, harvested, manufactured, and traded in ways that improve lives and protect the environment.
	**The Non-GMO Project**	The Non-GMO Project is a non-profit organization offering a third-party non-GMO verification program that aims to support sources and practices that effectively minimize GMO risk to the supply chain.
	**Gluten-Free Certification Organization (GFCO)**	GFCO is an industry program of the Gluten Intolerance Group (GIG), a non-profit organization that offers third-party certification to manufacturers of gluten-free products, including dietary supplements.
	**Vegan Action**	Vegan Action, a non-profit organization, offers third-party certification to verify vegan claims, ensure that animals and animal-by products have not been used in the formulation or manufacturing of products, and ensure that products have not been tested on animals.
	**Star-K**	STAR-K certification programs ensure that food and ingredients meet all kosher requirements. This verifies inspection of ingredients, manufacturing processes and products comply with the Jewish Code.

How to read a supplement label

Supplement Facts

Serving Size 2 Capsules
Servings Per Container 30

	Amount Per Serving	% Daily Value
Vitamin C	500mg	834%*
Zinc	20mg	199%*
Beta Glucans	300mg	†
Echinachea purpurea Standardized to 4% alkylamides (4 mg)	100mg	†
Proprietary blend	500mg	
Echinacea angustifolia (leaf)		†
Allium sativum (bulb)		†
Withania somnifera (root)		†
Ganoderma lucidum (aerial parts)		†
Rhodiola rosea (root)		†
Andrographis paniculata (aerial parts)		†

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

The "Supplement Facts" title is an indicator that the product is marketed for sale in the U.S. and is an FDA standard.

The serving size, and sometimes the number of servings per container, will be included to help you compare more easily between products.

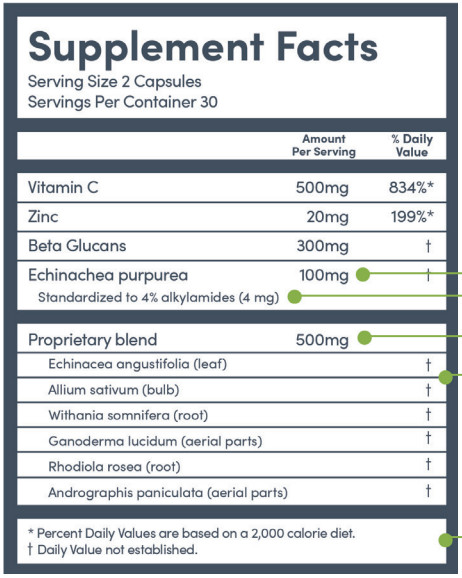
Make sure the serving sizes match when comparing supplements to get an accurate comparison between the products.

Vitamins and minerals will always show the dose in both weight and % daily value to help you understand how you're hitting your dietary requirements.

Many supplements will have doses that exceed the recommended daily value.

Dietary supplement ingredients that are not vitamins or minerals will not have a % daily value as they are not essential ingredients in the diet.

Dietary supplements are regulated by the FDA, and all labels must follow a consistent format to make it easier for consumers to understand supplements. There are some tricks to understanding dietary supplement labels well, so be sure to pay attention to the following points when you're evaluating your supplements.



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Withania somnifera (root)		†
Ganoderma lucidum (aerial parts)		†
Rhodiola rosea (root)		†
Andrographis paniculata (aerial parts)		†

* Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value not established.

Herbs will sometimes have additional information listed in the supplement facts panel. You might see ratio numbers (i.e. 4:1) that designate how much raw material of the herb (fresh or dried herb) went into making the supplement version of the herb.

Herbs might have a standardization amount that corresponds to how much of an active ingredient is present in the herbal supplement. The dose of the active ingredient is often listed, but not always.

Proprietary blends are common in dietary supplements. Only the total amount of the proprietary blend in a serving needs to be listed on a supplement, which means that you don't get all of the information about every ingredient that is in the blend.

Ingredients in a proprietary blend are listed in order from most to least. This is similar to how food ingredients are listed on nutrition facts panels that you find on prepared foods.

The daily value percent is established against a 2,000 calorie diet. While this is the standard calorie amount across most labels, it's always important to scale your requirements based on the calorie intake that you need to reach your health goals.

Evidence-based decision support

Evidence-based decision support (EBDS) is a clinical decision support system that provides practitioners the efficient means of combining relevant scientific evidence, patients' values and preferences, and clinical judgment to develop clinical treatment plans using the best therapeutic interventions available.

The purpose of EBDS in the context of integrative medicine is to help practitioners make decisions about supplements to discover best practices according to available research.

Why is EBDS important?

The foundation of clinical practice is the ability to research effectively, consolidate information, and apply the information with the individual patient and their case in an efficient manner. Researching and consolidating information can take effort and time that many practitioners don't have.EBDS makes researching, staying up-to-date, limiting errors, and selecting appropriate products easier than ever.

Rating scales for EBDS

In order to establish an evidence-based decision support system, it was necessary to first determine a rating scale for the evidence that would be used. Not all evidence is equal and practitioners should know exactly what kind of evidence is being referenced with regard to specific ingredients.

The following rating scale was established to clearly prioritize meta-analyses and systematic reviews of human trials, followed by randomized, double-blind, placebo-controlled (RDBPC) human trials, which collectively represent the first three tiers. Thereafter, non-RDBPC human trials, animal trials, and theoretical research are ranked in succession, respectively.

Overall, Fullscript emphasizes tiers A through D in the development of content and protocols, but the ranking will also be clearly identified for practitioner reference.

Class	Qualifying studies	Minimum requirements
A	Systematic review or meta-analysis of human trials	
B	Human RDBPC	$\geq$ 2 studies and/or 1 study with $\geq$ 50 subjects
C	Human RDBPC or RCT	1 study < 50 subjects
D	Human trials or In-vivo animal trials	
E	In-vitro studies	
F	Theoretical based on biochemistry/physiology/ pharmacokinetics	

RDBPC = Randomized Double-Blind Placebo Controlled *RCT = Randomized Controlled Trials*

Curcumin *[Ker-cue-min]*

A plant chemical found in turmeric root (Curcuma longa). It can be used to make curries, teas, and other drinks, mustard sauces, cheese, butter, and chips. It is also used as a colorant and as a preservative.

Main medical uses

It is commonly used in the treatment of inflammation, in the treatment of metabolic syndrome, and as an antioxidant in the protection against cardiac diseases. Research also demonstrates its potential use in treating type II diabetes.

Adverse effects

It is considered safe and non-toxic with good tolerability. Diarrhea, headaches, rash, or yellow stool may occur. However, the prevalence of these adverse effects was not dose-dependent between doses of 1,000-12,000 mg. Curcumin use has also been associated with nausea.

Associated depletions & interactions

It has been shown to be a strong inhibitor of CYP3A4, CYP2C9, CYP2D6, and CYP1A2 and may, therefore, interact with pharmaceuticals that are metabolized by these cytochromes. It may interact with caffeine, talinolol, & iron.

Mechanism of action & metabolism

It has limited bioavailability and is quickly metabolized. Phase I hepatic metabolism reduces the compound's double bonds through alcohol dehydrogenase in liver microsomes. Phase II metabolism also rapidly conjugates curcumin into glucuronides and sulfates. Curcumin may be excreted unchanged or as conjugates in urine.

Licensed ingredients

Ingredient	Formulation	Bioavailability & Safety	Indication & Outcome	Class
Unformulated	No formulation	2g produced no change to bioavailability in humans	**MetSyn:** ↓LDL, TG	A
			↓BMI, WC, BF%	B
			↑ HDL, ↓ LDL	B
BCM-95®	Micronized curcumin in turmeric essential oils	↑ 7x bioavailability	**Depression:** ↓ symptoms	A
Curcumin-Bioperine®	Combined w/ piperine	↑ 21x bioavailability	**Oxidative Stress:** ↓ malondialdehyde	A
			MetSyn: ↑ HDL, ↓LDL, non-HDL, Total-C, TG, lipoprotein(a)	B

C3 Complex®	95% concentration combination of three curcuminoids	Long-term safety profile up to 12,000 mg daily	**Dementia:** Insufficient evidence	A
Longvida®	Solid lipid particle structure with improved solubility	↑ 100x bioavailability	**Cognition/Mood:** ↑ attention, memory, fatigue, calmness, contentedness, ↓LDL and total cholesterol	B
			Endothelial Function: ↑ nitric oxide, blood flow ↓ oxidative stress	C
Meriva®	Micronized curcumin in turmeric essential oils	↑ 29x bioavailability	**Osteo-Muscular Pain:** ↓ pain, ↑ physical function	B
Theracurmin®	Highly dispersible, water-soluble & low aggregability	↑ 27x bioavailability	↓ osteoarthritis pain	B
			↑ attention & memory	C
			↓ AT-LDL	C

Dosing & administration

Condition	Dosing & Administration	Outcome	Class
Arthritis	Curcumin: 1000 mg per day	↓ Joint pain	A
Metabolic Syndrome	Curcumin extract: 630 mg 3x daily for 12 weeks	↑ HDL-C ↓ LDL-C, TG	B
	Turmeric: 2.4 g per day for 4 weeks	↓ BMI, WC, BF%	B
Non-Alcoholic Fatty Liver Disease	Curcumin formulation: 500 mg per day	↓ Liver fat content, BMI, TC, LDL-C, TG, aspartate aminotransferase, alanine aminotransferase, glucose, and HBA1C	B
Type II Diabetes	Nano-micelle curcumin: 80 mg per day for 3 months	↓ HBA1C, FBG, TG, BMI	B
	Turmeric: 2 g per day for 1 month w/ metformin	↓ HBA1C, FBG, LDL-C, non-HDL-C and LDL/HDL ratio, hsCRP, lipid peroxidation, MDA ↑total antioxidant status	B
	Curcumin: 150 mg, 2x per day for 8 weeks	↑ Endothelial function ↓ Malondialdehyde, ET-1, IL-6 and TNFalpha	B
Osteoarthritis	Curcumin: 180 mg per day	↓ Knee pain	B
Rheumatoid Arthritis	Curcumin: 500 mg per day	↓ Tenderness and swelling	C
Peptic Ulcer	Turmeric: 600 mg 5x per day for 4 weeks	↓ Ulcer prevalence, abdominal pain and discomfort	C

Drug-nutrient interactions

Developing individualized treatment plans that combine pharmaceuticals with supplements can easily become complicated. The following charts allow for quick reference when working with the most common pharmaceuticals.

The information provided in the following charts is based on a review of literature available at the time of publication. While the content is considered to be accurate at the time of publication, new or updated research released after the publication date may impact the accuracy of the information. Please use clinical discretion when consulting this resource and refer to the online resources for the most recent versions.

Pharmaceutical	Class of drug	Nutrient	Interaction	Class
Acetaminophen/ Hydrocodone Vicodin, Norco	**Pain** Narcotic, anti-Inflammatory	Caffeine	Increases analgesic effects	A
			Increases absorption	B
			Increases elimination of drug	C
		Alcohol	Increases risk of hepatotoxicity	B
			Induces CYP2E1	C
Albuterol Ventolin, Proventil	**Breathing** Bronchodilator	None	No significant interactions confirmed	N/A
Amlopidine Norvasc	**Blood Pressure** Calcium channel blocker	Grapefruit juice	Inhibits CYP3A4; slightly increases plasma concentration of drug	C
Atorvastatin Lipitor	**Cholesterol** Statin	Grapefruit juice	Increases serum atorvastatin;	B
			Induces CYP3A4; increases plasma concentration of atorvastatin acid and atorvastatin lactone	C
		St. John's Wort	Increases LDL and total cholesterol	C
Gabapentin Neurontin, Neuraptine	**Neuropathy, Pain**	Alcohol	Gabapentin is safe to use in treatment of alcohol dependency; reduces symptoms of alcohol withdrawal	A
		Cannabis	Gabapentin reduces symptoms of cannabis withdrawal	B
Insulin Glargine Injection Lantus Solostar	**Diabetes** Insulin analogue	None	Potentially significant theoretical interaction	F
			See the white paper for further details	

Levothyroxine Levothroid, Synthroid	**Thyroid** Synthetic Thyroxine	Calcium	Decreases absorption of drug; increases TSH	B
		Vitamin C	Increases absorption of drug; decreases TSH	B
		Coffee	Decreases absorption of drug	C
		Grapefruit juice	Inhibits OATP1A2; slightly decreases absorption of drug	C
Lisinopril Prinivil, Zestril	**Blood Pressure** ACE Inhibitor	None	No significant interactions confirmed	N/A
Metformin Glucophage XL, Gluformin	**Diabetes (biguanide)** Hepatic glucose reducer	Berberine (300 mg)	Improves insulin sensitivity; decreases HOMA-IR, total cholesterol, LDL	B
		Alcohol (>7 drinks/week)	Increases effect of drug; increases lactic acidosis and lactate production	C
Metoprolol Lopressor, Toprol-XL	**Blood Pressure** Beta-blocker	None	No significant interactions confirmed	N/A
Omeprazole Prilosec, Zegerid	**Acid-Reflux** Proton pump inhibitor	St. John's Wort	Induces CYP2C19 and CYP3A4; decreases effectiveness of drug	C
		Grapefruit juice	Inhibits CYP3A4; inhibits metabolism of drug	C
Rosuvastatin Crestor	**Cholesterol** Statin	Grapefruit juice	Inhibits OATP2B1; reduces bioavailability of drug	C
		EGCG	Significantly reduces systemic exposure of drug	C

Our interaction and depletion sheets are developed using A through C quality evidence.

For more information about the Fullscript evidence rating scale, please refer to page 18, or see the full white paper at

www.fullscript.com/hcp

Drug-nutrient depletions

Pharmaceutical	Class of drug	Nutrients depleted	Recommended dosage	Class
Acetaminophen/ Hydrocodone Vicodin, Norco	**Pain** Narcotic, Anti-Inflammatory	Glutathione	NAC - FDA approved protocol **Loading phase:** 0.14 to 0.16 g/kg up to 17 doses. **Maintenance:** 0.069 to 0.083 g/kg	B
Albuterol Ventolin, Proventil	**Breathing** Bronchodilator	No significant depletions confirmed. See white paper for details.	N/A	N/A
Amlopidine Norvasc	**Blood Pressure** Calcium Channel Blocker	No significant depletions confirmed	N/A	N/A
Atorvastatin Lipitor	**Cholesterol** Statin	Coenzyme Q10	50-200 mg/day	B
Gabapentin Neurontin, Neuraptine	**Neuropathy, Pain**	Folic Acid	400 mcg/day	B
Insulin Glargine Injection Lantus Solostar	**Diabetes** Insulin analogue	Magnesium	336 mg/day for 3 months	B
Levothyroxine Levothroid, Synthroid	**Thyroid** Synthetic Thyroxine	No significant depletions confirmed	N/A	N/A
Lisinopril Prinivil, Zestril	**Blood Pressure** ACE Inhibitor	Zinc	11 mg/day for men and 8 mg/day for women	A
Metformin Glucophage XL, Gluformin	**Diabetes (biguanide)** Hepatic Glucose Reducer	Vitamin B12 Folic Acid	1000 mcg/day sublingual 5 mg/day	B B
Metoprolol Lopressor, Toprol-XL	**Blood Pressure** Beta-blocker	No significant depletions confirmed. See white paper for details.	N/A	N/A
Omeprazole Prilosec, Zegerid	**Acid-Reflux** Proton Pump Inhibitor	Magnesium Vitamin B12 Calcium Iron	250-300 mg/day 1000-2000 mcg/day 500-1000 mg elemental calcium (carbonate, citrate) 3x/day 105–210 mg/day elemental iron	A C C C
Rosuvastatin Crestor	**Cholesterol** Statin	Coenzyme Q10	50-200 mg/day	A

Dietary considerations in integrative oncology

It is estimated that approximately one third of all cancer-related deaths in the United States may be attributed to diet. Research suggests that two dietary patterns, the Mediterranean Diet and the Ketogenic Diet, may assist with the prevention and management of various cancers.

The Mediterranean Diet (MD)

The MD reduces intake of meat and dairy products, and focuses on the consumption of fruits, vegetables, fish, whole-grain cereals, and polyunsaturated fats.

The MD may play a role in cancer prevention by regulating pro- and anti-inflammatory cytokines, increasing cellular autophagy, and reducing arachidonic acid, prostaglandins, leukotrienes, nitric oxide, angiogenesis, cancer cell proliferation, and oxidative stress.

Compliance with the MD has been associated with decreased general rates of cancer, particularly in the digestive and colorectal tracts. The MD may also decrease the risk of bladder cancer, breast cancer endometrial cancer, and prostate cancer. It has also been shown to reduce the risk for lung cancer, especially in smokers, and skin cancer, particularly melanoma and basal cell carcinomas, in women.

The Keto Diet (KD)

The KD involves significantly reducing the consumption of carbohydrates, while increasing the consumption of healthy fats. By restricting the body's use of glucose as a primary energy source, the KD mimics a fasting state and induces ketosis in which ketone bodies become the primary source of energy through fatty acid oxidation. While normal cells can utilize ketones as an alternative source of energy, tumor cells cannot.

Anti-cancer mechanisms beyond the alteration of glucose metabolism in cancer cells may also occur with the KD. For example, it has been suggested that the increase in serum β-hydroxybutyrate from the KD may prevent cancer proliferation. Other preclinical studies show that the KD may increase tumor cell sensitivity to radiation. The KD, when combined with high daily doses of vitamin D3, may also lead to modulation of breast cancer indicators, including increased expression of progesterone receptors and reduced expression of epidermal growth factor receptors.

The KD may reduce fatigue in patients not receiving chemotherapy treatment, as well as improve physical functioning, starchy-food cravings, insulin sensitivity, visceral fat content, and lean mass profile in ovarian or endometrial cancer. The diet has also been suggested as an option for concurrent antineoplastic therapies in malignant glioma. It is for these reasons that the KD has been theorized as a possible adjunctive therapeutic strategy in integrative oncology.

It is important to note that compliance to the KD may be required for at least three to four weeks in order to observe improvements. Further, adherence to the KD may prove difficult for some patients undergoing concurrent radiation and chemotherapy. However, regular counselling from a dietitian, provision of ketogenic-adherent meals, and access to cooking classes are suggested strategies to improve compliance to the KD during therapy.

Developing protocols

Protocol development in integrative oncology requires careful consideration. Patients require individualized care, and what works for one patient may not work for another.

As a result, the Fullscript Integrative Medical Advisory team advises using an evidence-informed approach to protocol development. To simplify this process for practitioners, we have assembled a sampling of evidence-based standardized protocols that practitioners can use as a foundation when developing individualized protocols.

To establish these protocols, we applied the **Rating Scale** found on page 13 of this booklet to discern the rigor of evidence supporting a specific nutrient's therapeutic effect.

The following protocols were developed using only A through D-quality evidence. These are categorized as follows:

Class	Type	Studies
A	Systematic review or meta-analysis of human trials	N/A
B	Human RDBPC	≥ 2 studies and/ or 1 study with ≥ 50 subjects
C	Human RDBPC or RCT	1 study < 50 subjects
D	Human trials or In-vivo animal trials	

Please refer to the complete **Rating Scale** for further information.

For more protocols and a complete listing of the literature reviewed, visit our Integrative Clinical Education Hub at

www.fullscript.com/hcp

Disclaimer

The ingredients included in these protocols are based on a review of existing clinical research, with a priority placed on systematic reviews and meta-analyses, classified as A in the Rating Scale.

These protocols are intended to form a foundation for developing individualized treatment plans. Clinician discretion is highly advised, as ingredients can vary in safety and effectiveness, depending on the needs of the individual patient.

Oral mucositis

induced by chemotherapy, radiotherapy, or surgery

Zinc

40 mg zinc lozenges, 30 minutes preoperatively

50–220 mg zinc sulfate, three times per day, 14 days from the first day of chemotherapy

- A single dose of zinc lozenge before operation decreased the incidence of postoperative sore throat both immediately and up to 4 hours after 1
- In leukemia patients undergoing chemotherapy, zinc sulfate supplementation has demonstrated a decrease in severity and incidence of oral mucositis
- Zinc sulfate supplementation demonstrated a decrease in xerostomia and pain in chemotherapy-treated patients
- Zinc supplementation administered in conjunction with radiotherapy in oral cancer patients decreased the severity and development of oral mucositis

L-glutamine

2-10 g, swish and swallow 3 times per day, throughout the chemoradiotherapy course and for 14 additional days

- L-glutamine supplementation reduced the duration and severity of chemotherapy-induced stomatitis
- L-glutamine supplementation demonstrated a reduction in the Oral Mucositis Assessment Scale ulceration score, as well as a carryover effect to a second round of chemotherapy treatment

Honey

15–20 ml, swish and swallow 15 min before and after radiotherapy treatment and before bed, for 6 weeks

- In head and neck cancer patients, honey has shown to delay the onset of oral mucositis, as well as decrease interruptions and weight loss
- Increased healing and decreased pain were observed within three days of honey paste application. Within five days, honey application decreased oral wounds and bleeding
- Honey was shown to be effective in reducing oral mucositis in head and neck cancer patients receiving external beam radiation therapy
- Honey has been shown to reduce the occurence of Grade 3 and 4 oral mucositis in patients receiving radiation therapy

Vitamin E

Topical vitamin E paste, two days before each cycle of chemotherapy to 20 days after completion of each cycle

Vitamin E oil, before every session of radiotherapy (fraction of 2 Gy) and eight to 12 hours after each radiotherapy session over the five to seven-week treatment period

- Chemotherapy-Related Oral Mucositis (ChROM) in children was improved when topical vitamin E was applied
- Vitamin E reduced the incidence of oral mucositis induced by radiotherapy in patients with oropharynx and oral cavity cancers
- Topical Vitamin E performed better on oral mucositis than Vitamin E systemic administration

Cachexia

Omega-3 fatty acids

300mg, once per day, minimum 6 weeks

- Fish oil or marine phospholipids have been shown to stabilize weight and appetite in pancreatic cancer patients
- Patients with unresectable pancreatic and bile duct cancer improved cachexia status through omega-3 fatty acid supplementation
- Significantly decreased resting energy expenditure, increased skeletal muscle mass and lean body mass, and improved chemotherapy tolerance and prognosis were observed with fish oil supplementation in cancer patients experiencing cachexia; no changes were observed in serum CRP levels

Melatonin

20 mg, once per day in the evening, minimum 21 days

- Melatonin has shown to reduce the frequency of neuropathy, myelosuppression, and cancer related cachexia
- The concomitant administration of melatonin with chemotherapy has been shown to improve survival time and reduce chemotherapeutic toxicity in non-small cell lung cancer patients
- A decrease in TNF concentrations was observed in neoplastic cachexia patients, and therefore may be an effective treatment for cachexia

Other ingredient considerations

Beta-hydroxyl beta-methyl butyrate (HMB), L-glutamine, and L-arginine

Proprietary blend: 14 g of beta-hydroxy-beta-methylbutyrate, L-glutamine, L-arginine, once per day, minimum 4 weeks

- The combination of HMB, L-glutamine, and arginine has been shown to be effective in increasing fat-free mass in Stage IV cancer patients

L-glutamine

10g, 8 hours before radiation therapy (66 Gy in 2-Gy fractions)

- L-glutamine prevented weight loss and decreased the incidence and severity of acute radiation-induced esophagitis

L-carnitine

4g, once per day, minimum 12 weeks

- L-carnitine supplementation was associated with an increase in body-mass-index and improved nutritional status (body cell mass, body fat) and quality of life parameters

Nausea

Ginger

1.2 g of standardized ginger extract, once per day, during the first three cycles of chemotherapy

160 mg of standardized ginger extract, once per day, starting from the day after cisplatin administration

10 mg standardized to 6-gingerol, twice per day for 12 weeks

500 mg, twice per day, 5 days before and 5 days after chemotherapy in addition to routine antiemetic drugs, such as dexamethasone, metoclopramide, and aprepitant (DMA) capsules

- Ginger is associated with reduced chemotherapy-induced nausea and cancer-related fatigue
- Functional Living Index nausea score was improved by ginger in females cancer patients and head and neck cancer patients receiving a high dose of cisplatin
- Ginger improved appetite score, FACT-G score (quality of life indicator), complete response (CR) rate (defined as no emesis or rescue treatment at any time), and grade 3 fatigue

Multi disciplinary approach to chemotherapy induced nausea

Vitamin B6 plus acupuncture point PC6

- Vitamin B6 injection and acupuncture point PC6 was shown to reduce emesis episodes and increase the number of emesis-free days in cancer patients undergoing chemotherapy

Radiotherapy-induced diarrhea

Lactobacillus acidophilus LAC-361 & *Bifidobacterium longum* BB-536

Proprietary blend: 1.3 billion CFU, twice per day, minimum 60 days

- A reduction in radiation therapy-induced diarrhea (grade 2, 3, 4) was demonstrated in patients with pelvic cancers, with or without operation, prior to radiation therapy
- Probiotics have also been shown to reduce radiation-induced diarrhea in abdominal cancers

Summary

The ingredients included in these protocols are based on a review of existing clinical research, with a priority placed on systematic reviews and meta-analyses, classified as A in the Rating Scale.

These protocols are intended to form a foundation for developing individualized treatment plans. Clinician discretion is still advised, as ingredients can vary in safety and effectiveness depending on the needs of the individual patient.

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