

# Health Professional's Guide *to* Dietary Supplements

Taylor C. Wallace, PHD, CFS, FACN, Editor

Foreword and Introduction by  
Johanna T. Dwyer, DSc, RD and Joseph M. Betz, PhD

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# Foreword

**M**ORE THAN HALF OF US ADULTS USE DIETARY SUPPLEMENTS, AND NUTRIENT-CONTAINING supplements are by far the most popular. Depending on their nature and dose, the ingredients in supplements have positive, negative, or no health effects. Therefore, health professionals must be able to provide counsel about dietary supplement use, knowing that individual products may vary in their strength and chemical composition and therefore in their bioactive properties. These properties, along with the integrity of the manufacturing processes used (eg, purity and proper ingredient identification), will determine safety and efficacy.

Supplements differ from foods and drugs in important ways that may affect the metabolism of the nutrients and bioactives they contain, and they are also regulated differently than foods. The dissemination of objective and reliable sources of information on dietary supplement science is critical to make evidence-based clinical practice a reality. We applaud the editor and contributors for producing this resource, which furthers those efforts. The *Health Professional's Guide to Dietary Supplements* provides a desktop reference with much of this information in a single ready-to-use format.

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# Preface

**D**IETARY SUPPLEMENTS PLAY AN IMPORTANT ROLE IN THE GROWING NUTRITION INDUSTRY worldwide. A dietary supplement is defined in the United States as a product that is intended to supplement the diet that may contain one or more dietary ingredients, such as a vitamin or a mineral, an herb or other botanicals, an amino acid, a dietary substance for use by humans to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of the preceding ingredients.<sup>1</sup> The safety and efficacy of dietary supplements differ from product to product, and many gaps in knowledge still exist. While many products have extensive research portfolios demonstrating their safety and health-promoting effects, other products lack even small human clinical trials. Regardless of the extent of available research, consumers widely report using dietary supplements to “improve” or “maintain” health.<sup>2</sup> The mainstream use and availability of dietary supplements by over 52% of consumers and 63% of older adults<sup>3</sup> creates an enormous need for a balanced and credible go-to scientific resource of reliable information for health professionals, written by top experts.

This guide provides health professionals with a quick reference for over 100 commonly used dietary supplements. While it would be nearly impossible to cover all existing botanical and nutrient supplements, we utilized data from the National Health and Nutrition Examination Survey, the *Nutrition Business Journal*, and the Council for Responsible Nutrition to determine the supplements used most by consumers in the United States.

Since 2018, it has been of the utmost pleasure to serve as Editor-in-Chief of the *Journal of Dietary Supplements*. The Journal’s rigorous and scholarly scientific standards are reflected in its internationally recognized and diverse group of subject matter experts who serve on the Editorial Board.<sup>4</sup> It is my hope that this book, along with the Journal, will be indispensable assets for researchers and health professionals seeking up-to-date information on dietary supplements for years to come. The Journal’s endorsement of the *Health Professional’s Guide to Dietary Supplements* is a tribute to the hard work of hundreds of talented individuals who made significant intellectual contributions to this work.

I am proud to have been able to lead the development of this comprehensive guide and hope you will check out the other nutrition resources, including more titles in the Health Professional’s Guide series, that the Academy of Nutrition and Dietetics offers to nutrition and health professionals.

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# Acknowledgments

THIS GUIDE FOR CLINICIANS WOULD NOT HAVE BEEN POSSIBLE WITHOUT THE SCIENTIFIC expertise of the many authors and peer reviewers who dedicated their time to ensuring each chapter is reflective of current science. In addition to my editorial review, each chapter in this textbook was peer-reviewed by at least two subject matter experts to ensure the utmost quality. Please refer to page 641 for a complete list of reviewers. Thank you to Betsy Hornick, MS, RDN, at the Academy of Nutrition and Dietetics for assisting in the planning, organization, and development of the book, and to Christina West for her editorial services. I am forever grateful to Drs Johanna T. Dwyer and Joseph M. Betz at the National Institutes of Health Office of Dietary Supplements for assembling a comprehensive Introduction for the book that addresses many of the common questions health professionals have about dietary supplements and highlights the extensive government resources available for both consumers and health professionals. I am also honored to currently serve as the Editor-in-Chief of *Journal of Dietary Supplements*, and I am humbled by the Journal's endorsement of this work. This book is dedicated to the great internal team and external network of accomplished researchers that have together helped grow Think Healthy Group beyond my wildest dreams. It is through innovative research, collaborative efforts, and strong scientific societies like the Academy of Nutrition and Dietetics that nutrition and food science will achieve both a healthier population and planet.

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# About the Editor

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Dr Wallace is an Advisory Board Member and regular contributor to Forbes Health, as well as a regular guest commentator on national news outlets such as ABC, CBS, and NBC and daytime TV shows such as *The Doctors*, *The Good Dish*, *The Doctor Oz Show*, and *The Tamron Hall Show*. He also operates a popular blog and online e-learning site for health professionals and consumers ([www.drwallace.com](http://www.drwallace.com)). Dr Wallace is a Fellow of the American College of Nutrition and has received numerous awards, notably the Charles A. Regus Award for original research and innovation in the field of nutrition. Currently, he serves as the Editor-in-Chief of *Journal of Dietary Supplements*, Deputy Editor-in-Chief of *Journal of the American College of Nutrition*, and Nutrition Section Editor of *Annals of Medicine*. To date, he has edited eight academic textbooks and published over 100 peer-reviewed manuscripts and book chapters. His cookbook, *Sizzling Science*, has sold over 15,000 copies since its publication in 2019. In 2021, the Governor of Kentucky bestowed Dr Wallace the title of Kentucky Colonel, the State's highest civilian honor, for his work in the fields of nutrition and food science. The *Huffington Post* recently recognized Dr Wallace as “the nation’s premier food and nutrition guru.”



# What You Need to Know About Dietary Supplements and Where to Find It

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## Dietary Supplement Products

This chapter addresses some common questions about what dietary supplement products are, how they differ from foods, what they contain, who uses them, and how they are regulated. Readers are encouraged to consult the objective and reliable federal resources included in this chapter for additional information on safety, efficacy, and quality of dietary supplements, including those covered in this desk reference.

### *What Are Dietary Supplements?*

A dietary supplement is defined as a product intended to supplement the diet that contains one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals, amino acids, enzymes, and other substances) or their constituents and is taken by mouth as a pill, capsule, tablet, powder, or liquid. A product is easily identified as a supplement because the package's front panel must contain the words "dietary supplement" and the label will display the Supplement Facts panel.

In the United States, dietary supplements are regulated as a special category of food. The Dietary Supplement Health and Education Act of 1994 defined dietary supplements and their regulation.<sup>1</sup> However, the products that are defined as dietary supplements and their regulations differ from country to country.<sup>2</sup> Many products defined as dietary supplements in the United States that contain nutrients are called natural health products (NHPs) in Canada or food supplements in the European Union. In other countries, some products containing bioactives considered to be supplement ingredients in the United States may not be allowed at all, whereas others are regulated more rigorously as medicines or drugs.

### *How Do Dietary Supplements Differ From Foods and Drugs?*

Supplements differ from foods and beverages. Although foods usually have a nutritional purpose and some supplements (like vitamin pills) do as well, many supplements (eg, botanicals like St John's wort or *Ginkgo biloba*) do not. Supplements often contain much larger and more concentrated amounts of nutrients and other bioactives in different matrixes, and they often have few or no calories compared with conventional food

sources of the same nutrients. Some supplement products often resemble drugs. Although supplement products may be regarded as having medicine-like properties, in the United States they are regulated as a category of food. They also differ in the conditions under which they are used, often providing concentrated nutrients or bioactive extracts in a bolus and consumed as part of a meal, on an empty stomach, or with other supplements or medications. These characteristics of supplements affect their absorption, distribution, metabolism, and excretion.

Unlike drugs, *dietary supplements are not intended to treat, diagnose, prevent, or cure diseases*. That means supplements should not make claims such as “reduces pain” or “treats heart disease.” These types of claims can only be made for drugs, not dietary supplements, unless the US Food and Drug Administration (FDA) has authorized a health claim (eg, calcium with vitamin D supplements for prevention of osteoporosis).

## ***What Can Labels Tell You About Dietary Supplements?***

According to the FDA, supplement labels are required to list the name of the dietary supplement; the amount of the supplement; its nutrition labeling (how a serving compares to nutrient needs as displayed in the Supplement Facts panel); the list of ingredients, and the name of the manufacturer, packer, or distributor along with place of business.<sup>3</sup> The label may also include health-related claims with appropriate disclaimers.

### **Ingredients**

Ingredients are listed on supplement labels in the Supplement Facts panel and in an ingredients list. Because supplements are foods, they must contain a nutrition label. The nutrition label for a supplement product is called a Supplement Facts panel. Labels must also provide an ingredients list. Components that are sources of dietary ingredients may be listed within the Supplement Facts panel—for example, “Calcium (as calcium carbonate).” When ingredients are listed this way, they do not have to be listed again in the ingredient statement (also called an ingredients list). Ingredients not listed in the Supplement Facts panel or those that are not considered to be dietary ingredients, such as excipients (eg, inactive substances like fillers, preservatives, and coloring agents that serve as the vehicle for the active substance), are also listed there. The amount of active ingredient (called the dietary ingredient) per serving must be listed in the Supplement Facts panel. For nutrients, the amount of each nutrient listed is the net amount of the active ingredient. For a mineral, for example, it is the amount of the element such as iron and *not* the amount of the source of the mineral (eg, ferrous sulfate).

The active constituents that are dietary ingredients but do not have an established Daily Value (DV), such as botanical extracts and glucosamine, must be listed, generally below the Supplement Facts panel in decreasing order of abundance and with an asterisk to indicate that there is no DV. Some supplements include “proprietary blends” that contain many different nutrients, herbs, amino acids, caffeine, extracts, and other constituents. Manufacturers are required to state the total amount of the blend on the Supplement Facts panel and the *names* of the ingredients in the blend in order from most to least abundant, but they do not have to state the amounts of the individual ingredients in these blends. This makes it difficult to determine the dose of each particular constituent in the blend. Botanical ingredients are required to be listed by the common and usual name of the plant as provided in the American Herbal Products Association’s *Herbs of Commerce*, and those not included in that source are listed by their Latin binomial name. The part of the plant

from which the botanical ingredient was derived (eg, root, leaf, seed, etc) must also be provided on supplement labels.

### Percentage of Daily Value

The percentage of daily value (%DV) is also provided in the Supplement Facts panel. The contents of dietary ingredients are stated by weight per serving and also by %DV based on the serving size stated on the label. Ingredients that have no established DV must still be listed, but an asterisk (explained below the panel as “no Daily Value established”) is provided in the DV column. For nutrients with a human nutritional requirement, the %DV is the percentage based on a 2,000-calorie diet that approximates the recommended daily intake for each nutrient.

### Serving Size

The Supplement Facts panel provides the serving size (eg, number of capsules, drops, or scoops per serving) recommended by the manufacturer. The instructions may direct the consumer to use more than one serving per day, so total daily exposure should take that information into account. To estimate how recommended amounts per day compare with nutrient needs, multiply the amounts by the number of servings suggested.

### Claims

In the United States, three types of claims are permitted but are not mandatory on dietary supplement labels: health claims, nutrient content claims, and structure/function claims. *Health claims* describe a relationship between a food, food component, or dietary supplement ingredient and the reduction of the risk of a disease or health-related condition. *Nutrient content claims* describe the relative amount of a nutrient or other dietary constituent in the product. *Structure/function claims* describe how a product may affect body organs or systems but cannot mention any specific disease. Although structure/function claims do not require premarket FDA approval, manufacturers are required to have substantiation data; if the claim is made on the label, it must also include a disclaimer that reads, “This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.”

A detailed discussion of the details of regulation is beyond the scope of this introduction. However, it is important to note that if promotional messages in the manufacturer’s accompanying literature, advertising, and other marketing efforts suggest that a supplement prevents, treats, cures, or diagnoses a disease, the FDA may regard these claims as extensions of labeling and issue warning letters. Such disease-related claims are only allowed on drugs and are not legal for supplements.

## *How Can You Evaluate and Compare Different Supplements?*

The easiest way to assess and compare the content of ingredients in supplements is to look at the product labels. A convenient and no-cost online resource is the National Institutes of Health (NIH) Dietary Supplement Label Database (DSLDB) (refer to Box 1 on page 4).<sup>4-6</sup> The DSLDB was developed and is maintained by the Office of Dietary Supplements (ODS). The database contains label information from more than 150,000 dietary supplement products available in the US marketplace. It captures an image of the label and all of the

## BOX 1

### Objective Sources of Information on Dietary Supplements

Name	Source	Information	Link
Dietary Supplement Ingredient Database (DSID)	US Department of Agriculture; Office of Dietary Supplements, National Institutes of Health	Reports national estimates of ingredient content, allowing for comparison of multivitamin and multimineral supplements for adults and children, over-the-counter prenatal supplements, and omega-3 fatty acid supplements. The DSID is intended primarily for research applications rather than for assessing content of individual products.	<a href="https://dsid.usda.nih.gov">https://dsid.usda.nih.gov</a>
Dietary Supplement Label Database (DSLDB)	US National Institutes of Health, Office of Dietary Supplements	Includes current and historical label information on products marketed in the US. The database allows for searching by products, brands, and ingredients. Products are categorized by 10 product types, 4 target groups, and 10 supplement forms.	<a href="https://dsldb.od.nih.gov">https://dsldb.od.nih.gov</a>
Government Accountability Office	US Congress	Produces occasional reports and testimonies related to dietary supplements and their cost, quality, safety and efficacy, and regulation.	<a href="http://www.gao.gov">www.gao.gov</a>
Human Performance Resource Center	Uniformed Services University of the Health Sciences, US Department of Defense	Provides information on supplements, particularly those used by warfighters and physically active individuals, such as ergogenic (performance-enhancing) aids, weight-loss supplements, testosterone precursors, boosters, and anabolics. Supplements are rated by potential benefit, if any, and safety risk.	<a href="http://www.hprc-online.org">www.hprc-online.org</a>
National Academy of Sciences	Food and Nutrition Board of the National Academy of Medicine	Includes several reports on dietary supplement safety and efficacy, their regulation, reviews of supplements for use in the armed forces, and monographs on Dietary Reference Intakes for nutrients.	<a href="http://www.nationalacademies.org/fnb/food-and-nutrition-board">www.nationalacademies.org/fnb/food-and-nutrition-board</a>
National Center for Complementary and Integrative Health	US National Institutes of Health	Provides fact sheets on herbs and botanicals and other nonnutrient natural products, including probiotics and prebiotics, hormones, enzymes, and other ingredients such as coenzyme Q10, methylsulfonylmethane, chondroitin, glucosamine, and complementary therapies.	<a href="http://www.nccih.nih.gov">www.nccih.nih.gov</a>
PubMed	National Library of Medicine	Compiles articles with citations from the Medline database and additional life science journals. Also includes links to full-text articles on journal websites and other related web resources.	<a href="https://pubmed.ncbi.nlm.nih.gov">https://pubmed.ncbi.nlm.nih.gov</a>

*Box continues*

## BOX 1 (CONTINUED)

Name	Source	Information	Link
Office of Dietary Supplements	US National Institutes of Health	Provides downloadable fact sheets on individual vitamins and minerals, multivitamin/multimineral supplements, weight-loss supplements, omega-3 fatty acids, and fish oil for patients and professionals. Also provides the DLSID and cosponsors the DSID.	<a href="https://ods.od.nih.gov">https://ods.od.nih.gov</a>

information on the label, including directions for use, health-related claims, supplement facts, ingredients, and any cautions. The DLSID can be used to compare the contents of two labels; to search for a particular supplement ingredient, manufacturer, or specific text on the label; or to search for a specific health-related claim.

Another database, which is most useful for researchers, is the US Department of Agriculture (USDA) Dietary Supplement Ingredient Database (DSID). This database was developed by the USDA Nutrient Data Laboratory in collaboration with the ODS and other federal agencies. The DSID summarizes the results of chemical analyses of common categories of dietary supplements and is available online. Refer to Box 1 for additional information on these databases and other authoritative sources of information about dietary supplements.

The DSID contains results of analytical determinations of ingredients in a nationally representative sample of the most popular types of supplement products. The latest version (DSID-4) reports national estimates of ingredient content in omega-3 fatty acid supplements and in nonprescription multivitamin/multimineral (MVM) supplements for adults, children, and pregnant individuals.

The DSID website also includes a feature that permits users to enter the label contents of a product of interest and obtain estimated amounts of the nutrients that have been derived from analytical results.<sup>7,8</sup> This feature is particularly useful to researchers because there may be differences between label values and analytically determined values for ingredients in supplement products. This is usually because dietary supplements are required to comply with label content claims for the entire shelf life of the product, so manufacturers may legally add ingredients to supplements in higher amounts than those declared on the label (consistent with safety) so that the minimum content is still present over time. This is especially true of more chemically labile nutrients like some vitamins. However, overages are not standardized among manufacturers. As a result, researchers may underestimate nutrient intakes from dietary supplements if they rely only on labeled amounts. Analyses summarized in the DSID also found that some ingredients were sometimes present at lower levels than those on the label. The analytical data permit statistically predicted estimates of ingredient amounts in various products, and estimates often differ from amounts listed on labels. The DSID is intended primarily for research applications. The data are appropriate for use in population studies of nutrient intake rather than for assessing the content of individual products.



## Dietary Supplement Use

### *Who Needs Dietary Supplements?*

For healthy humans who consume a well-balanced diet, there is no absolute need for any dietary supplement. The patterns recommended by the *Dietary Guidelines for Americans, 2020–2025* and the MyPlate eating guides provide an adequate diet from food alone for most age and life-stage groups. However, nutrient-containing supplements are an option to fill gaps in intakes for those who cannot properly process nutrients from food or do not or choose not to consume a variety of foods that meet their nutrient requirements in all respects. As noted, some dietary ingredients lack a recommended DV, and the need for supplements that contain botanical or other nonnutritive ingredients has not been established.

### *Who Uses Dietary Supplements?*

A study of National Health and Nutrition Examination Survey (NHANES) data reports that 58% of US adults aged 20 years and older have used any dietary supplement over the past 30 days, and use is higher among females (64%) than males (51%).\* The prevalence of use among adults of all ages is higher today than it was a decade ago. Overall use and multiple supplement use has increased with age in adults, and use is highest among females\* aged 60 years or older (80%).<sup>9</sup>

The most popular products continue to be vitamin mineral supplements in all age groups, followed by MVM, vitamin D, and omega-3 fatty acid supplements.<sup>9,10</sup> Most dietary supplement users tend to be individuals who practice healthier lifestyle habits and are likely to be in very good or excellent health, report moderate alcohol use, do not smoke, and exercise more frequently than nonusers. A much smaller group of supplement users are already ill and take supplements as complementary treatments along with conventional treatments or instead of them. In addition, a small number of people actually discontinue conventional medical care and replace it with supplements. These latter groups are of special concern because they may be taking supplements along with medications without checking with their health care provider, and interactions may occur, some of which can be serious. For example, 6% to 8% of adults with chronic kidney failure surveyed in the 1999–2008 NHANES used one or more of 37 herbs that are potentially harmful to patients with kidney disease because of supplement–drug interactions.<sup>11</sup>

### *Why Do People Use Dietary Supplements?*

The motivations for using dietary supplements are many and varied. Many individuals feel that taking a supplement provides additional “insurance” for promoting their health and preventing or warding off disease or nutritional deficiencies resulting from a poor diet. Others use supplements to maintain their health and wellness, and still others use them to help address various health conditions.<sup>12</sup>

In a recent NHANES analysis sponsored by the ODS, the most common reasons for supplement use were to “improve” (45%) or “maintain” (33%) overall health. Other reasons included “to ensure adequate intakes of essential nutrients” or were site-specific such as women’s\* use of calcium products for “bone health” (36%) or men’s\* use of supplements for “heart health or to lower cholesterol” (18%). Older adults (aged  $\geq 60$  years) were more likely than younger individuals to report motivations related to site- or condition-specific reasons like heart, bone and joint, and eye health.<sup>13</sup>

\* Study participants were described as females and males. Gender was not further specified.



## Efficacy of Dietary Supplements

Most people who took supplements did so on their own. In the NHANES survey just described, only 23% of respondents used supplements because of recommendations by their health care professional.<sup>13</sup> Others use supplements either because they are given to them by parents or partners, or because they are influenced by claims on product labels or what television personalities, athletes, or others say who testify to the supplement's effectiveness in advertisements or mass media.

### *Are Nutrient Supplements Effective?*

Evidence of supplement effectiveness is strongest for single nutrients in preventing or treating dietary deficiencies or other conditions that affect their absorption and metabolism.

#### Disease Prevention

Supplementation of diets with lacking nutrients is a useful public health preventive strategy for targeting groups with very high nutrient needs who are at high risk of deficiency due to growth, pregnancy, lactation, disease, age, or other reasons. Some supplement examples mentioned in the *Dietary Guidelines for Americans, 2020–2025* include folic acid for individuals capable of becoming pregnant, iron and folic acid for those who are pregnant, vitamin K to prevent hemorrhage in newborn infants, vitamin D and iron for breastfed infants, vitamin B12 for older adults, calcium/vitamin D for people who are postmenopausal and seniors, and iron for rapidly growing teenagers and menstruating people aged 19 through 50 years.

Supplements can also improve the dietary status of groups with deficient intakes who cannot or will not meet their nutrient needs through food alone. Gaps or shortfalls are particularly likely to arise for micronutrients not widely distributed naturally in foods, like vitamin D, vitamin B12, iodine, and vitamin K. For example, intakes of vitamin D, vitamin B12, choline, iron, and zinc may be low among individuals who follow a vegan or vegetarian diet unless they consume highly fortified foods or use dietary supplements. Older adults may benefit from vitamin B12 supplementation because B12 deficiency may develop in older individuals with age-related hypochlorhydria and/or a relative intrinsic factor deficiency.

Dietary supplements are also useful when micronutrient fortification cannot be used because large numbers of individuals cannot tolerate additional amounts of a nutrient, while others in the population need it. One example is iron and the use of iron supplements instead of fortification in countries where many people suffer from iron overload (hemochromatosis). Fortification of the food supply with iron is not an option in those countries because it would put too many individuals at risk. Use of iron supplements instead permits those who cannot tolerate high levels of iron to avoid them in their diets, whereas those such as pregnant individuals who have high iron needs can take iron supplements.

#### Disease Treatment

Some diseases affect nutrient absorption, distribution, and elimination, and nutrient-containing dietary supplements are an important adjunctive treatment for these diseases. Micronutrient supplements provide single or several nutrients in appropriate amounts without adding calories, which is helpful in many disease states. Health care providers should identify needs and provide patients with the correct types and supplement doses to take to provide the correct types and supplement doses needed.

Many gastrointestinal diseases have effects on nutrient absorption that sometimes require chronic supplementation with specific nutrients. These include restrictive malabsorptive bariatric surgery, celiac disease, Crohn's disease, and any major surgical resection of the gastrointestinal tract. For example, individuals who have undergone Roux-en-Y or gastric sleeve bariatric surgical procedures for the treatment of obesity need lifelong supplementation due to malabsorption of many fat- and water-soluble vitamins and minerals due to the surgery. Surgery and other procedures often require discontinuation of supplements for several days or a week before surgery because of their effects. For example, health care professionals should use vigilance for supplement use if patients require surgery and consume products, especially botanicals, that affect bleeding time.

Patients in the later stages of chronic kidney failure and those who receive dialysis also may require special vitamin and mineral supplements (such as vitamin B6, vitamin B12, folic acid and vitamin D, iron, and calcium) to help cope with the effects of the disease.

Individuals who have inborn errors of metabolism that involve vitamins, minerals, or other nutrients may find that special supplements formulated to treat their disease are lifesaving. Supplements may be needed for illnesses that require medications affecting nutrient needs. Potassium supplements may be helpful in counteracting the effects of certain diuretics. Calcium/vitamin D supplements are useful in slowing bone loss due to tamoxifen and other antiestrogens used in breast cancer treatment. MVM supplements in amounts approximating the Recommended Dietary Allowance (RDA) can help prevent deficiencies among individuals with chronic diseases that limit oral intake and appetite and among older and more frail persons.

MVM supplements are the most popular supplements used in the United States. Although they can help decrease nutrient inadequacies if (and only if) individuals are deficient to begin with, they also increase the risk of micronutrient excess.<sup>14</sup>

## *Are Nonnutrient Dietary Supplements Effective?*

Efficacy means that a product is certain to produce its intended effects. Nutrient supplements have beneficial effects in individuals who are deficient or have insufficient nutrient intake. Adding amounts in excess of the RDA will not result in extra benefits. In contrast with nutrient supplements, there is limited evidence showing that supplementation with botanicals or other nonnutrient constituents is required by the body or that they improve health, have other health benefits, or prevent, treat, or cure disease.

Clinicians and patients should be aware that although label statements (including structure/function claims) are required by law to be truthful and not misleading, dietary supplements marketed in the United States are not approved by the government as being effective before going to market. That is, even if a product label makes claims, such as “supports memory” or “enhances sexual performance,” it may not bring about these effects. Statements of nutritional support and structure/function claims are not necessarily based on rigorous clinical studies, and publicly available evidence that they are effective may be lacking. As opposed to structure/function claims, all health claims undergo premarket review by the FDA. Box 2 presents useful resources in the scientific literature that can be checked to assess evidence of dietary supplement efficacy.

## BOX 2

### Useful Resources for Assessing Evidence and Efficacy Related to Dietary Supplements

Resource	Link
<i>Systematic reviews</i>	
Cochrane Library: high-quality, independent systematic reviews of available evidence to inform health care decision-making	<a href="http://www.cochranelibrary.com">www.cochranelibrary.com</a>
Agency for Healthcare Research and Quality: systematic evidence reviews	<a href="http://www.ahrq.gov/research/index.html">www.ahrq.gov/research/index.html</a>
<i>Other evidence-based information</i>	
US National Institutes of Health Office of Dietary Supplements	<a href="https://ods.od.nih.gov">https://ods.od.nih.gov</a>
National Center for Complementary and Integrative Health	<a href="http://www.nccih.nih.gov">www.nccih.nih.gov</a>
National Cancer Institute Physician's Data Query (PDQ) on complementary and alternative medicine (CAM)	<a href="http://www.cancer.gov/about-cancer/treatment/cam">www.cancer.gov/about-cancer/treatment/cam</a>
CAM on PubMed: research articles or summaries on CAM in scientific journals	<a href="https://pubmed.ncbi.nlm.nih.gov">https://pubmed.ncbi.nlm.nih.gov</a>
PDQ Cancer Information for Health Professionals: cancer clinical trials	<a href="http://www.cancer.gov/publications/pdq">www.cancer.gov/publications/pdq</a>
National Library of Medicine MedlinePlus: provides credible health information from government agencies and health-related organizations	<a href="https://medlineplus.gov">https://medlineplus.gov</a>
Natural Products Alert (NAPRALERT): provides abstracts and articles on clinical and nonclinical studies of natural products, including their pharmacologic activity	<a href="https://pharmacognosy.pharmacy.uic.edu/napralert">https://pharmacognosy.pharmacy.uic.edu/napralert</a>
<i>Research and clinical trials</i>	
Computer Access to Research on Dietary Supplements (CARDS): provides access to a database of federally funded research projects involving dietary supplements, including details and a description of the research	<a href="https://ods.od.nih.gov/Research/CARDS_Database.aspx">https://ods.od.nih.gov/Research/CARDS_Database.aspx</a>
National Library of Medicine PubMed and PubMed Central	<a href="http://www.ncbi.nlm.nih.gov/pmc">www.ncbi.nlm.nih.gov/pmc</a>
ClinicalTrials.gov: provides a searchable database of privately and publicly funded clinical trials being conducted around the world	<a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>

# 5-Hydroxytryptophan (5-HTP)

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## Introduction

5-Hydroxytryptophan (5-HTP), or oxitriptan, is an amino acid created from tryptophan and a precursor to serotonin (5-hydroxytryptamine [5-HT]), a neurotransmitter/hormone. Figure 1 on page 24 shows the metabolic pathway in the brain, highlighting the relationship between serotonin and dopamine.<sup>1-3</sup> The enzymes performing these tasks are found in the raphe nuclei (midbrain), kidneys, adrenal glands, pineal gland (for melatonin production), and enterochromaffin cells of the gastrointestinal tract.<sup>2-5</sup> As such, considering its size, nearly 80% to 90% of 5-HTP and serotonin (hormone) are produced in the gastrointestinal tract.<sup>5</sup> 5-HTP is also used to make melatonin and 5-hydroxyindoleacetic acid (5-HIAA) further down the line, using a monoamine oxidase enzyme (MAO).

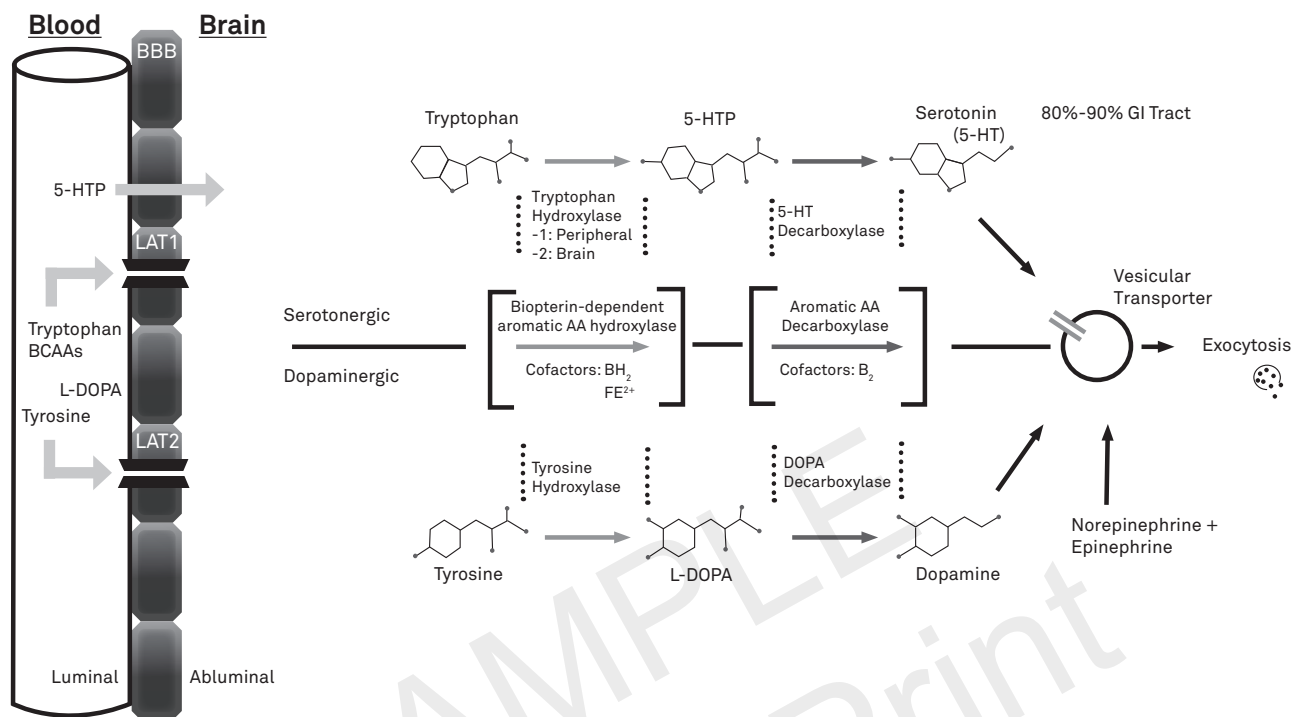
Stress, insulin resistance, and vitamin B6 or magnesium deficiency negatively affect 5-HTP metabolism, ultimately reducing serotonin levels.<sup>2,15</sup> Due to serotonin's link to mood, behavior (sexual and other), memory, pain, appetite, digestion, thermoregulation, sleep, and more, 5-HTP is often sought as a supplement for depression, anxiety, learning disabilities, and some neurological disorders.<sup>16,17</sup> Serotonin cannot cross into the brain, but 5-HTP and tryptophan can.<sup>17,18</sup> That said, 5-HTP is more ideal because it freely enters the brain, only becomes serotonin, and bypasses the rate-limiting enzyme tryptophan hydroxylase (TPH), whereas up to 95% of tryptophan is shunted away to become niacin (vitamin B3), or it can be blocked from entering the brain if there are larger concentrations of tyrosine or branched-chain amino acids (BCAAs) in the blood because they use the same entry point (LAT<sub>1</sub>, LAT<sub>2</sub>).<sup>17-19</sup>

Lastly, minor caution is generally suggested for 5-HTP supplementation. This was based on the international distribution of contaminated tryptophan supplements by one Japanese manufacturer, between 1980 and 1990, leading to the hospitalization of 1,500 people in the United States.<sup>11,12</sup> 5-HTP was linked by association but never confirmed. Still, related research dramatically declined as a result until the mid-2000s, which is why clinical trials have broad, limited evidence regarding the medical efficacy of 5-HTP use. While additional research is needed, existing data suggest possible therapeutic uses when the pathophysiology includes or relates to a serotonin deficit.

## Recommended (or Suggested) Intakes

The US Food and Drug Administration has only approved 5-HTP supplementation for people with BH<sub>4</sub> deficiency.<sup>1</sup> However, clinical trial doses range from 20 to 3,250 mg/d, and so Dietary Reference Intakes for 5-HTP do not currently exist. Despite the absence of adequate guidelines, 200 to 300 mg/d, divided into three or four smaller quantities to reduce the risk of nausea, is commonly used.<sup>2,15,20</sup> A study with children ages 3 to 17 years who were behaviorally at-risk, given 100 mg twice daily, led to greater feelings of agitation for 20% of participants, prompting a reduction of each dose to 50 mg.<sup>21</sup> To avoid nausea,

**Figure 1** Serotonergic and dopaminergic neurotransmitter production<sup>2,3,6-10</sup>



In the serotonin pathway, tryptophan hydroxylase converts tryptophan to 5-HTP, using iron ( $\text{Fe}^{2+}$ ) and tetrahydrobiopterin ( $\text{BH}_4$ ) as cofactors. 5-HT decarboxylase converts 5-HTP to 5-HT, with a pyridoxal phosphate (bioactive vitamin B6) coenzyme. Evidence suggests serotonergic and dopaminergic aromatic amino acid hydroxylase (AAAH; tryptophan, tyrosine) and decarboxylase (AAAD; 5-HT, DOPA) enzymes work in both pathways interchangeably.

Abbreviations: 5-Hydroxytryptophan, 5-HTP; AA, amino acid; BBB, blood-brain barrier; BCAA, branched-chain amino acid; GI, gastrointestinal; LAT, L-type amino acid transporter; L-DOPA, levodopa.

Birdsall<sup>17</sup> recommends 50 mg three times per day with meals; if the clinical response is inadequate after 2 weeks, titrate upward to 100 mg per dose and so on. For insomnia, 100 to 300 mg can be administered before bed. Hinz et al<sup>8</sup> discussed administering serotonin and dopamine precursors (5-HTP, tyrosine, levodopa) simultaneously to prevent competitive uptake into the brain, emphasizing it as an individualized process. Effective therapeutic ranges have been reported as daily intake up to 2,400 mg 5-HTP, 14,000 mg tyrosine, and 2,100 mg levodopa (L-DOPA), independently of one another.

## Excessive Intakes

Although a Tolerable Upper Intake Level (UL) has yet to be identified for 5-HTP, dose-related adverse events have been reported. Nausea and vomiting are among the most common, followed by diarrhea, abdominal pain, bloating, headache, anorexia (not nervous), and lethargy.<sup>15,22,23</sup> Previously, patients who received intravenous infusions of 200 mg or larger exhibited more severe adverse effects such as confusion and memory impairment; symptoms were significantly less prevalent with oral doses of equal or smaller amounts. A similar trend was reflected in isolated animal studies where doses of 100 to 200 mg/kg body weight induced serotonin syndrome, but 50 mg/kg body weight or less seemed fine. Of note, the authors deemed these results preliminary, considering the limited sample sizes.<sup>2</sup>

## Sources and Bioavailability

5-HTP can be found in minuscule amounts within *Griffonia simplicifolia* seeds, a West and Central African shrub used as an herbal supplement.<sup>2,24</sup> It is also available as an over-the-counter (OTC) supplement in many forms.<sup>8</sup> About 70% of any tolerable oral dose, bolus or split small amounts, is absorbed into circulation where it has a half-life of approximately 2 hours; this may be up to 4 hours if coadministered with an aromatic L-amino acid decarboxylase (AAAD) inhibitor.<sup>20,25-27</sup> This does not appear to be altered by the presence of competing amino acids (tyrosine or BCAA's). Use of an oral spray can enhance sublingual absorption.<sup>25</sup>

## Supplement Interactions

Drug-nutrient interactions do exist with antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs), wherein serotonin levels may spike and induce serotonin syndrome or related conditions.<sup>2</sup> To our knowledge, no human cases of serotonin syndrome related to 5-HTP supplementation have ever been documented, albeit manic episodes have occurred in combination with MAOIs.<sup>28</sup> Augmented neuroendocrine responses (prolactin, cortisol) have been seen with some antidepressants as well.<sup>2,22</sup> AAAD inhibitors (eg, carbidopa) increase 5-HTP in the blood by preventing the gastrointestinal tract from using it, giving them the potential to affect gut function and motility.<sup>26</sup> Greater 5-HTP bioavailability may not cause a spike in serotonin, but it does increase urinary 5-HIAA, which is a serotonin metabolite frequently used as a diagnostic marker for carcinoid syndrome and tumors due to their elevated serotonin metabolism. In these cases, research suggests using serum chromogranin A (CGA) instead.<sup>25,29</sup> Occasionally laboratories use 5-HTP to assess the potency of serotonin-altering drugs, known as the 5-HTP-induced behavioral syndrome test.<sup>30</sup> Nutrient-nutrient interactions may occur with unbalanced or isolated intake of 5-HTP and catecholamine precursors (tyrosine, L-DOPA), as they may compete with each other, altering serotonin or dopamine levels, respectively.<sup>6-10</sup> Finally, green tea polyphenols (catechins) are reported to inhibit enzymes of the AAAD class.<sup>31</sup>

## Health Promotion and Disease Prevention

In 1989, contaminated tryptophan supplements were traced to more than 95% of reported eosinophilia–myalgia syndrome (EMS) cases among 1,500 patients in the United States. EMS causes severe muscle pain (myalgia) and increased circulating eosinophils in the blood (eosinophilia). At least 37 deaths among these patients were attributable to EMS. 5-HTP was weakly linked to 10 cases in 1998, the assessment methods of which have since come under scrutiny; no additional related deaths have been reported.<sup>11,15</sup> Nevertheless, given that we cannot be certain whether the complications were biologic in nature, a toxic constituent, nutrient, or drug-induced, caution is advised.<sup>13,14</sup>

### *Depression*

Although 5-HTP is strongly advocated for managing clinical depression, the literature does not offer sufficient evidence for its use in this way. Experts argue that despite increased bioavailability from carbidopa, the improvements observed for depression have been no greater in magnitude than the average placebo effect (30% to 45%) after a 30-day treatment with reuptake inhibitors.<sup>8,32</sup> The authors of a 2019 systematic review and meta-analysis gave credence to this and concluded that the existing studies were weak, chiefly for a lack of placebo or control groups as well as poorly defined criteria for what constitutes depressive “diagnoses.”<sup>33</sup> Regardless, it is important to consider the ability of 5-HTP to



deplete catecholamine levels if the dose regimen is mismanaged or unbalanced, as this may exacerbate depressive states.<sup>8,32,34</sup> Due to the connected and variable nature of these mechanisms, health care professionals should note that these contraindications could apply to other conditions such as generalized anxiety disorder (GAD), attention-deficit/hyperactivity disorder (ADHD), or Parkinson disease.<sup>8</sup> More clinical research with larger sample sizes is warranted to determine the efficacy of 5-HTP in depression management.

### ***Anxiety and Panic Disorder***

Research regarding 5-HTP use for GAD is relatively inconclusive. Yet there is evidence suggesting 5-HTP helps manage panic attacks.<sup>35</sup> In a related study, children who ingested 2 mg/kg 5-HTP/d at bedtime demonstrated a 50% reduction in the occurrence of sleep terrors after 20 days, and this effect seemed to persist for most participants up to the 6-month end point.<sup>36</sup>

### ***Appetite Suppression and Weight Loss***

5-HTP is largely anecdotal in its association with weight loss, primarily for increased feelings of satiety, sometimes correlating with a decrease in BMI.<sup>25</sup> The weight loss reported, although significant statistically, usually averages between 1 and 2 kg.<sup>37</sup> The majority of research has been conducted with female\* individuals, and the observed weight loss seems to stem from decreased intake. The distinction between reduced intake related from greater satiety and not from suppressed appetite could possibly benefit patients undergoing treatment for binge eating or related disorders.

### ***Parkinson Disease***

In 2020, 5-HTP (50 mg/d) was evaluated over 4 weeks in a Phase IIa clinical trial of patients with Parkinson disease. The preliminary data indicated clinically relevant benefits for medication-related motor complications as well as comorbid depression, which affects up to 35% of all patients with Parkinson disease, including 17% who had major depressive disorder.<sup>24,34</sup> Recently, research advocates developing a slow-release form of 5-HTP to treat patients with neurological disorders, coupled with a proserotonergic medication, to thereby avoid a sudden spike in blood levels, rapid metabolism, and potential serotonin syndrome-like complications.<sup>27</sup>

### ***Addiction and Withdrawal Effects***

Experts believe that serotonin and subsequently 5-HTP play a larger role in patients with drug addiction and withdrawal, especially those involving opioids. For example, a 53-year-old female presented with refractory muscle spasms secondary to opioid withdrawal and was intolerant to the standard clonidine treatment. She was given a loading dose of 200 mg 5-HTP, followed by 100 mg nightly until her symptoms improved about 2 weeks later; at that point supplementation was discontinued with no adverse events.<sup>38</sup> In a related trial, 20 people who underwent treatment for alcohol were administered a combination of 5-HTP (5 mg), glutamine (150 mg), phenylalanine (300 mg), vitamin B6 (1 mg), calcium gluconate (50 mg), magnesium oxide (25 mg), and folic acid (0.01 mg) for 40 days. The

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\* Study participants were described as female. Gender was not further specified.

investigators reported that this combination helped alleviate most of the associated withdrawal symptoms except anxiety.<sup>39</sup>

## Autism Spectrum Disorder

A review from Patrick and Ames<sup>16</sup> discussed a link between the hormone action of vitamin D (calcitriol), serotonin, and development. They theorized that regularly, as well as prenatally, supplementing with vitamin D and serotonin precursors (tryptophan, 5-HTP) may impart a benefit for individuals with autism, with the potential to ameliorate some symptoms of the disorder, and maybe even act preventively.

## Other Conditions

Finally, 5-HTP is reported to help individuals with sleep issues<sup>40</sup> or conditions like cerebellar ataxia,<sup>41</sup> migraine and headache,<sup>42,43</sup> irritable bowel syndrome,<sup>23</sup> and menopause.<sup>44</sup> However, data are limited and researchers should undertake additional investigation to determine its efficacy.

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# Acai Berry

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## Introduction

Acai berry (*Euterpe oleracea*), also known as acai (ah-sigh-eeh), is the fruit of the acai palm. This tree is a member of the palm family and is native to parts of the central and northern South American tropics, notably the Brazilian Amazon. An acai berry (sometimes referred to as palm berry) is approximately the size of a blueberry but is darker purple or black and contains a large hard seed in the middle; thus, it is known as a drupe fruit. This berry is not sweet and not too bitter; it has a nutty beet flavor and is occasionally regarded as somewhat tasteless. Acai berry is very high in fiber, contains high amounts of other bioactive compounds, is a good source of calcium and vitamins A and E,<sup>1-4</sup> and has at least as much vitamin C as an orange.<sup>5</sup> Most individuals, except for those who live in the Amazon region, do not consume the raw acai fruit, as its shelf life is very unstable and only lasts about a day because of its very high monounsaturated fat content. Acai fruit (pulp/skin) is composed of 54.8% fat, 39.1% carbohydrates (84.7% of which is fiber), and 6.1% protein.<sup>6</sup> The dark color of acai comes from the abundant anthocyanin compounds found within the fruit.<sup>7</sup> Anthocyanins are a group of flavonoid pigments known to exert an effect on enzymatic function in favor of improved health and physiologic function.<sup>8,9</sup> Commonly referred to as a “functional food” or “ultimate super food,” acai berry has demonstrated abundant antioxidant properties. For example, acai berries have been shown to reduce free radical oxidation in vitro and have one of the highest superoxide (free radical) scavenging capacities of any fruit or vegetable.<sup>2,3,10-12</sup> In addition to its antioxidant capabilities, studies show that acai berry can improve blood glucose levels,<sup>12</sup> effects of neurodegenerative disease,<sup>13</sup> and anti-inflammatory capacities.<sup>14</sup>

Although research found that the acai berry has excellent antioxidant properties, one study showed that only 10% of its antioxidant abilities come from the anthocyanin compounds of the acai fruit, particularly against peroxy radicals and peroxy nitrite.<sup>10</sup> This lends support for other phytonutrient compounds, notably proanthocyanidins and other flavonoids<sup>6</sup> in the fruit, contributing to the total antioxidant ability of acai berry. To note, much of acai’s ability to attenuate free radical oxidation (ie, antioxidant scavenging) was shown in studies using in vitro cellular experiments and assays, which analyze the cellular activity of free radicals, reactive oxygen species (ROS) accumulation, and other ROS marker changes when different concentrations of acai are applied.<sup>1,3,10</sup> Data demonstrating the antioxidant and anti-inflammatory effectiveness of acai in in vivo trials are more limited, and researchers often study concentrations of the phytonutrient molecules or antioxidant enzymes within the blood or effects on other homeostatic blood markers (eg, cholesterol and blood pressure). Further research is needed to elucidate the actual mechanistic benefits of acai in human clinical research.

Regarding the quality and consumption of acai, two specific palm species produce fruit and are sold as acai: *Euterpe oleracea* and *Euterpe precatoria*. Some products labeled as acai may contain one or both species; according to the data, many of the aforementioned antioxidant and anti-inflammatory properties found in *E. precatoria* are found to at least the same degree as in *E. oleracea* or better.<sup>1,15</sup> In addition, a similar “palm fruit” named Jussara (*Euterpe edulis*) is not as widely available but has very similar

phytonutrient profiles to *E. oleracea*.<sup>16</sup> When choosing acai-based products, one should pay attention to the ingredients to ensure that the product contains one of these three palm species. In addition, the literature assessing the purity of various commercially available acai products indicates that not all products contain the same or adequate levels of anthocyanins. For example, data from 56 commercially available acai products reported values ranging from 0.004 to 80 mg/serving (0.74–336.7 mg/100 g), a 20,000-fold difference in anthocyanin quantity.<sup>17</sup> Given the requirement for acai to be sourced exclusively from the South American tropical region and the lack of quality control standards, regulators face challenges when determining the purity of the acai product being purchased. Until further regulation is enacted regarding either acai quality or product labeling, the potential health benefits of acai-containing supplements are limited and may vary.

Consuming raw or locally prepared acai presents a risk of *Trypanosoma cruzi* infection, the parasite that causes Chagas disease.<sup>18</sup> This parasite is localized to the Amazonian region, as the acai fruit has an extremely short shelf life and does not travel well in its raw form. Individuals should be aware of these risks when consuming raw acai food products, but not supplements. Acai consumed outside of this region is pasteurized, which eliminates the risk of *T. cruzi* infection.

## Recommended (or Suggested) Intakes

There are currently no guidelines for recommended intakes of acai in whole fruit, puree, or powder form. Currently, research has not shown sufficient scientific evidence to help experts determine the appropriate dosage range, as studies and manufacturer recommendations vary from 20 to 200 g acai pulp and from 2 to 6 g powder (1 tsp to 1 tbsp). Because of robust differences in the quality of acai-containing products and the desired profiles of the anthocyanins and other phytonutrients, better quality control in harvesting, manufacturing, processing, and product labeling is needed.<sup>17</sup>

## Excessive Intakes

Researchers have not identified a toxic level of acai pulp or powder. Daily intakes studied in rats have been as high as 40 g/kg with no adverse effects or toxicity.<sup>19,20</sup> Most doses reported within the literature indicate a weight of the commercially available or personally prepared extract, powder, or pulp. There are no known standards for upper limits or toxic levels of acai in any form.

## Sources and Bioavailability

The acai fruit is very unstable, with freshness lasting approximately 24 hours. As a result, the raw fruit is flash frozen on site and is typically sold as a frozen puree, in powder form, or even as supplemental pills outside of the native acai tropical region. Acai puree and powder forms may have a slightly different macronutrient composition, depending on the other ingredients added to the food product (water, sugar, etc). The acai fruit is commonly used in acai bowls, in which acai pulp or powder is mixed with other fruit and granola, and in smoothies blended with frozen berries.

Conflicting data exist indicating that not all sources of acai products (eg, purees and powders) contain the same quantity of phytochemicals, particularly anthocyanins. In one study, researchers analyzed 56 commercially available products (both supplement and food products) from the United States; they found that seven products had no detectable anthocyanins (all from supplement forms), and other anthocyanin quantities ranged widely.<sup>17</sup> The previous literature supports a relatively low bioavailability of anthocyanins (1%–7.5%), whether from the whole food or isolated form of acai,<sup>21,22</sup> which contributes to the potency of anthocyanins absorbed.

## Supplement Interactions

## Health Promotion and Disease Prevention

There are no known interactions of acai berry with medications. Individuals should consult their physician about using acai in high quantities.

### *Antioxidant and Anti-Inflammatory Effects*

A majority of the studies on acai are related to its antioxidant and anti-inflammatory capabilities.<sup>1,10,13,23</sup> Much of the acai research has been conducted using in vitro experiments to study downregulation of inflammatory pathways and cytokines and improvement of scavenging capabilities, messenger RNA, and protein expression of inflammatory markers.<sup>3,10,23,24</sup> One proposed reason why acai can exert these beneficial effects is its level of anthocyanin compounds, which are known to have an antioxidant effect with strong scavenging of free radical compounds that thereby lowers inflammation.<sup>3,10</sup> Reports indicate that acai's most abundant anthocyanin is cyanidin 3-glucoside, with up to 1,040 mg/L in fresh acai pulp.<sup>25</sup> ROS and antioxidant capacity were reported to increase threefold vs 2.3-fold after individuals consumed acai pulp and acai juice, respectively,<sup>26</sup> indicating a greater benefit from consuming the flesh of the fruit.<sup>2</sup> Animal studies have demonstrated an anti-inflammatory response to acai administration, which reduced the presence of inflammatory markers (eg, prostaglandins, interleukin-10) as well as inflammatory enzymes (eg, cyclooxygenase [COX]-2) in isolated cells and tissues from animals fed acai.<sup>27</sup> Limited studies using chronic ingestion of acai in human trials reported significantly reduced ROS and increased antioxidant enzymes,<sup>26</sup> as well as reduced inflammatory blood markers.<sup>11,26</sup> The ability of acai consumption to promote antioxidant capacity and reduce inflammation has tremendous potential, but more research, specifically human trials, is needed to elucidate the specific role and mechanisms of acai in human health and disease.<sup>1,13,28</sup>

### *Cardiovascular Disease and Comorbidities*

Studies evaluating the physiologic benefits of acai consumption show favorable outcomes such as reductions in cardiovascular disease (CVD) and related comorbidities.<sup>9,22,28,29</sup> One study reported lowering of total cholesterol (TC) and resting glucose (area under the curve) with 200 g acai puree for 30 days but demonstrated no change in resting blood pressure.<sup>12</sup> These findings are in contrast with another study, which showed no benefit of acai intake on glucose or lipid concentrations and only a reduction in inflammation.<sup>14</sup> However, another study demonstrated a decrease in TC in a healthy population consuming acai.<sup>11</sup> One study reported that acai fruit extract protects mice from a multitude of metabolic syndrome characteristics, especially when consuming a high-fat diet. For instance, mice in one study were fed acai extract in combination with a high-fat diet; they demonstrated reductions in body weight, glucose, fat deposition in the liver, and oxidative stress compared with mice consuming a high-fat diet without acai.<sup>30</sup> In response to acai consumption, in another study mice exhibited reduced atherosclerosis and dramatically reduced inflammation.<sup>31</sup> Additional long-term research is warranted using these specific parameters in human participants. It should be noted that oleic acid is the major fatty acid comprising 53.9% of the acai fatty acid profile, and there are plentiful reports in the literature on the numerous health benefits of oleic acid in the diet.<sup>30</sup> There is also a likelihood that the flavonoid composition of acai (namely, anthocyanins) contributes largely to its cardioprotective effects, similar to other anthocyanin-rich fruits.<sup>9,22,28,29</sup> As mentioned previously, the lack of quality control (stability, packaging) and necessary transportation (shipment) of acai-derived products could contribute to the mixed findings on acai in CVD-related research.<sup>17,25</sup>



Additional research is needed to establish recommendations on acai consumption to prevent or treat CVD and related comorbidities.

## Other Health Benefits

Emerging literature on acai for neuroprotective effects discusses its use in the potential treatment of progressive neurodegenerative diseases, such as Alzheimer disease and Parkinson disease, particularly through the antioxidant capabilities of the flavonoids found in the acai pulp.<sup>13</sup> In addition, there are data supporting the antitumorogenic properties of acai.<sup>4,19</sup> One recent study administered acai extract to rats with breast cancer and reported a reduced death rate, longer life span, and significantly reduced inflammatory and angiogenic state.<sup>27</sup> Another study demonstrated that acai antioxidants can enter human cells fully intact and scavenge free radicals at low doses; in addition, acai has the potential to inhibit both COX-1 and COX-2.<sup>3</sup> Similar research supports the use of acai pulp to reduce oxidative stress in cultured astrocytes.<sup>32</sup> Researchers have reported that acai alters the contents of red blood cells, increases erythropoietin expression in mice,<sup>24</sup> and provides potential benefits in kidney failure.<sup>33</sup>

In summary, research has shown that most of the proposed health benefits from acai consumption are primarily from anthocyanins and other flavonoid components. Additional research is needed before specific recommendations on acai use can be made. Exhaustive literature reviews specifically on the consumption of acai and similar anthocyanin-containing fruit and its effects on disease prevention and treatment have been published.<sup>19,22,28,29,33,34</sup>

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# Adenosine 5'-Triphosphate (ATP)

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## Introduction

Adenosine 5'-triphosphate (ATP), which supports the body's biochemical method of storing and transporting energy, is the primary molecule that provides the energy to drive many processes in living cells such as muscle contraction, neurotransmission, and cardiac function.<sup>1</sup> When ATP is utilized, it is broken down into adenosine-5' diphosphate (ADP) and inorganic phosphate (P). However, limited quantities of ATP are stored in cells. Once ATP is utilized (eg, to fuel muscle contraction), it must be quickly replenished. Multiple metabolic processes can recycle ADP and P back into ATP. Because the human body contains, on average, approximately 250 g ATP and ATP is continuously recycled, the human body turns over roughly its own weight in ATP each day.<sup>2</sup> In addition to its role as an intracellular energy source, ATP can also be released from the cells to act as a messenger to nearby cells; this process is known as ATP signaling.<sup>3</sup> It was first detected between nerve cells and muscle tissue, but ATP signaling is now known to influence a wide variety of cell types in the body. In addition, research has shown that extracellular ATP facilitates functions such as increased skeletal muscle calcium permeability, chloride efflux blocking, and vasodilation.<sup>4</sup>

## Recommended (or Suggested) Intakes

No recommended intakes currently exist for ATP, and there is limited nutrition education and training among health professionals, including dietitians, nurses, pharmacists, and physicians. Dietary Reference Intakes for ATP do not currently exist in the United States, Canada, or Europe, although ATP is an approved food ingredient in these regions. In the European Union, a European Food Safety Authority panel concluded that daily consumption of up to 400 mg ATP is safe, and a self-affirmed Generally Recognized as Safe panel concluded that a commercial form of ATP, PEAK ATP (TSI USA) or disodium ATP, is safe up to 800 mg/d.<sup>5</sup> The safety of PEAK ATP is well documented in both human and animal studies.<sup>6-11</sup> PEAK ATP is not genetically modified and is gluten-free, vegan, and vegetarian friendly, enabling its safe use among populations with dietary restrictions. Based on the existing research, the recommended dose of ATP is 400 mg (acute or daily supplementation) taken on an empty stomach with water. ATP should be taken as one serving approximately 30 to 60 minutes before exercise or approximately 20 to 30 minutes before breakfast on nontraining days or for nonsports applications.

## Groups at Risk for Inadequacy

Aging in humans is widely acknowledged to be accompanied by decreased ATP levels within the blood, skeletal muscle, and a variety of bodily ATP pools.<sup>12-17</sup> Mitochondrial dysfunction, which is associated with a decline in skeletal muscle mitochondrial ATP

synthesis, has been linked to the development of type 2 diabetes and an increased risk of cardiovascular issues.<sup>18,19</sup> ATP supplementation can prevent declines in ATP pools during times of increased energy needs.<sup>20</sup>

## Excessive Intakes

To date, researchers have not been able to identify a toxic level of supplemental ATP. One study investigating oral ATP administration (250, 1,250, or 5,000 mg/d) for 28 days showed no adverse effects or safety concerns.<sup>7</sup>

## Sources and Bioavailability

During the digestion of food, macronutrients (carbohydrates, fats, and proteins) are broken down and oxidized to provide chemical energy in the form of ATP.<sup>21</sup> Most cells use glucose for ATP synthesis. To produce ATP from glucose, three primary sets of reactions work in series: (1) glycolysis, which occurs in the cytosol; (2) the citric acid cycle, which takes place in the mitochondrial matrix; and (3) oxidative phosphorylation, which takes place in the inner mitochondrial membrane. The intermediate products of glycolysis and the citric acid cycle are used as sources of metabolic energy and to produce many of the small molecules used as raw materials for biosynthesis, including ATP. For oral supplementation, ATP is typically provided in its disodium salt form. Several studies have investigated the bioavailability of supplemental ATP under resting conditions and have not observed any significant increases in ATP levels.<sup>7-9</sup> However, supplementation with 400 mg ATP for 15 days resulted in increased blood levels of ATP (and its metabolites) 30 minutes after high-intensity exercise compared with placebo.<sup>20</sup> Therefore, researchers postulated that oral ATP absorption does not follow a classic absorption model (transported intact into the bloodstream); rather, it may work through an indirect mechanism supporting ATP resynthesis. The chronic ingestion of oral ATP acts to increase the capacity of erythrocytes to synthesize and thus sustain plasma ATP concentrations in response to hypoxic perturbations associated with high-intensity exercise. Researchers further suggest that ATP and its respective metabolites may stimulate intracellular ATP synthesis by interacting with specific ATP and adenosine receptors on cellular surfaces through a signaling effect.

## Supplement Interactions

Individuals are encouraged to follow the directions on product labels. Research has not shown that ATP interacts with medications or laboratory tests.

## Health Promotion and Disease Prevention

Oral supplementation with ATP disodium has demonstrated acute and long-term physiologic benefits, including improvements in muscular performance, body composition, and recovery and attenuated muscle breakdown and fatigue. ATP may also support cardiovascular health, recovery from surgery, and management of lower back pain.

### *Sports Nutrition*

Numerous studies demonstrate the benefits of acute and regular ATP supplementation on muscular performance. In one study of 27 healthy young men, acute supplementation with 225 mg ATP increased one-repetition maximum strength.<sup>8</sup> In another study, acute supplementation with 400 mg ATP significantly improved athletic performance in 11 recreationally trained men, resulting in more total weight lifted and greater oxygen consumption during exercise.<sup>22</sup> Benefits of prolonged supplementation with ATP on athletic performance and body composition have been observed in four different studies. One study investigated



the effect of twice-daily supplementation with 200 mg ATP for 15 days in 16 recreationally active men, and the researchers observed significantly improved leg muscle performance and decreased leg muscle fatigue.<sup>23</sup> In a second study with 400 mg ATP administered daily over 12 weeks to 21 resistance-trained men\*, a significant increase in lean body mass and muscle thickness was observed with ATP over training alone.<sup>10</sup> Significant increases in total strength and vertical jump power were also observed. A third study examined the effect of 15 days of supplementation with 400 mg ATP on repeated sprint performance in 42 resistance-trained men. In this study, ATP supplementation resulted in a significant increase in peak power observed in the Wingate Anaerobic Test in later bouts compared with baseline and prevented the decline in muscle excitability in later bouts.<sup>20</sup> In a fourth study, 14 days of supplementation with 225 mg ATP increased repetitions to fatigue and total lifting volume.<sup>8</sup> The use of ATP is not prohibited by the World Anti-Doping Agency.

### ***Blood Flow (Cardiovascular Health)***

The literature shows that ATP has cardiovascular benefits. In one study investigating the effects of ATP alone and combined with exercise, 12 healthy young adults were administered 400 mg ATP daily for 12 weeks.<sup>24</sup> ATP supplementation led to a significant increase in blood flow than was observed with exercise alone. In addition, ATP significantly enhanced brachial artery dilation after exercise. Enhanced blood flow to exercising muscles increases oxygen and nutrient delivery to the muscle, prolonging the ability of the muscle to perform at a high level for longer periods of time. Studies have shown that ATP has long-term benefits on cardiovascular health in nonathletic populations. In 11 hypertensive women\*, ATP supplementation induced faster recovery of heart rate variability and reduced systolic blood pressure after 30 minutes of aerobic exercise.<sup>25</sup> In 53 older women and men\* with overweight and obesity, 90 days of supplementation with 400 mg ATP significantly increased flow-mediated dilation by 2.8%.<sup>11</sup>

### ***Recovery From Surgery***

Scientists have speculated that ATP could enhance recovery after surgery because of its beneficial effects as an analgesic and on vasodilation. In a clinical study of 244 patients who had undergone a total knee replacement, 120 mg ATP supplementation for 4 weeks significantly increased strength after surgery. In addition, ATP supplementation decreased perceived pain, reduced the need for rescue pain medication by 5%, and shortened the average length of hospital stay by 12%.<sup>26</sup>

### ***Nutritional Management of Lower Back Pain***

The potential benefit of oral ATP supplementation on subacute low back pain relief was evaluated in 161 men and women\*\* with category 1 or 2 subacute lower back pain.<sup>27</sup> Daily supplementation with 90 mg ATP for 1 month significantly reduced participants' self-assessment of their disability levels and reduced their use of rescue analgesics. In another study from the same research group, 157 participants supplemented with 90 mg ATP for approximately 90 days were three times less likely to report a condition that had worsened or remained unimproved and also took fewer rescue medications.<sup>28</sup>

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\* Study participants were described as women. Gender was not further specified.

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