

Phytonutrient Research Review

Executive Summary

- Increased consumption of fruits and vegetables is associated with reduced risk of many chronic diseases, but fewer than 10% of U.S. adults meet recommendations.
- Living plants produce numerous types of phytonutrients that exhibit important health benefits for humans via the concept of xenohormesis.
- The Mediterranean food plan has shown impressive health benefits due to its richness in plant foods and diverse phytonutrient content.
- Phytonutrients confer beneficial health effects through numerous mechanisms, including modulation of signal transduction pathways, antioxidant properties, and hormonal effects.
- Whole plant extracts have shown synergy and benefits compared to purified compound(s).
- Oxygen radical absorbance capacity assay (particularly Total ORAC_{FN}) and the comet assay are important and useful tools to assess the potential antioxidant capacity of phytonutrients.

The Phytonutrient Paradigm

Exploring the Healing Properties of Plant Foods, Spices, and Herbs

INTRODUCTION

Throughout history in traditional Chinese medicine, Ayurvedic medicine, and other cultures, botanicals have been used to improve health or treat illnesses (Table 1). Today, consumption of fruits, vegetables, herbs, and spices is associated with reduced risk of many chronic diseases. The USDA Dietary Guidelines for Americans 2010 recommend increased consumption of a variety of vegetables, especially dark-green, red, and orange vegetables, as well as beans and peas. We now have learned that these living plants produce a wide variety of phytochemicals—commonly referred to as phytonutrients—that play very important roles in human health.

This research review will briefly describe plant-based diets (particularly the Mediterranean diet) and human health, followed by detailed discussion on the health benefits of various phytonutrients and their proposed biological mechanisms. Two scientific methods that evaluate the antioxidant capacity of phytonutrients are also described.

Plant	Traditional Recommendations
Aloe vera	Peptic ulcers, topically for burns
Cinnamon	Flatulent dyspepsia, anorexia, intestinal colic, nausea, vomiting, common cold
Echinacea	Fevers, influenza, poisonous conditions, wounds, antiseptic, tonsillitis, syphilis
Ginger	Nausea, anorexia, to improve circulation
Globe artichoke	Liver tonic and antitoxic, rheumatism, gout, clearing the complexion
Hops	Insomnia, neuralgia, headache, hysteria, indigestion, mucous colitis, inflammation
Marigold	Gastric or duodenal ulcer, inflammatory skin lesions, amenorrhea
Olive leaf	Hypertension, cough, fever, diuretic, liver stimulant, emmenagogue, stomachache
Rosemary	Stimulate the mind and memory, chronic circulatory weakness, poor digestion
Saw palmetto	Prostatic hypertrophy, cystitis, asthma, sex hormone disorders, cough
Turmeric	Liver disorders, fevers, leprosy, jaundice, ulcer, common cold, pain, dizziness
Valerian	Insomnia, hysterical states, cramps, intestinal colic, rheumatic pains, epilepsy

Table 1. Examples of plants and their traditional use.¹

PLANT ADAPTATION AND BENEFITS TO HUMANS

To fully appreciate the healing properties of phytonutrients in plants, spices, and herbs, it is important to understand their evolution. Unlike animals, plants are physically attached to the ground and are sustainable throughout their life cycles. As such, they are unable to move away from constant environmental stressors and harmful conditions, such as ultraviolet (UV) light, pathogens, climate variations, and water and nutrient availability. After millions of years of evolution, plants have developed a complex adaptation strategy to enhance their well-being and survival in a harsh environment through synthesis of compounds—including various phytonutrients—that stimulate their cellular stress response. This phenomenon is termed *hormesis*.²

As plants and animals coexist (and because animals generally depend on plants as food supply), animals have evolved to detect the chemical cues produced by stressed plants and respond in a way that increases their own well-being and chance of survival. This mutualistic, interspecies hormesis is termed *xenohormesis*—a phenomenon in which environmentally stressed plants produce bioactive compounds that confer stress resistance and survival benefits to animals and humans that consume them.³

While the term xenohormesis may not be familiar, the concept is likely to be. For example, wine grapes—when exposed to harsh sun, ozone, water deficit, bacteria, or fungi—synthesize a protective polyphenolic compound called resveratrol.^{4,5} This compound can reduce UV damage via its antioxidant property and increase resistance against diseases via its antimicrobial property.^{6,7} Today, resveratrol is one of the most studied phytonutrients due to its wide array of health benefits.

PLANT-BASED DIETS AND HEALTH

Previous epidemiologic studies have found that high consumption of plant-based foods is associated with reduced risk of various chronic diseases.⁸⁻¹⁰ Several large-scale prospective cohort studies that examined this association have confirmed protective effects of increased fruit and vegetable consumption. For example, reduced incidence of ischemic stroke among men in the Framingham Heart Study, reduced risk of coronary artery disease in the Physicians' Health Study, and reduced risk of cardiovascular disease (CVD) in the Women's Health Study.¹¹⁻¹³

Because of the significant impact fruits and vegetables can have on public health, national organizations, such as the American Heart Association and the Centers for Disease Control and Prevention, actively promote and educate the general public to increase their fruit and vegetable intake.

Mediterranean diet. One of the most extensively studied dietary patterns is that of the Mediterranean region, known for a traditional diet rich in minimally processed fruits, vegetables, legumes, nuts, olive oil, whole grains, fish, and moderate amounts of red wine. This diet has been suggested to provide not only essential nutrients—protein, fat, carbohydrates/fiber, vitamins, and minerals—but also other plant food substances believed to support health.¹⁴

The health benefits associated with Mediterranean dietary plans are impressive:

- Meta-analysis studies found that the Mediterranean diet was associated with reduced risk of metabolic syndrome, had a protective role in improving waist circumference, HDL, triglycerides, systolic/diastolic blood pressure, and glucose,¹⁵ and might be a useful tool to reduce body weight and body mass index (BMI).¹⁶
- A systematic review reported that the Mediterranean diet might help prevent type 2 diabetes by improving HbA1c and glucose, indices of glycemic control.¹⁷
- A review article concluded that people who adhered to Mediterranean diet principles had a longer lifespan; were less likely to die of CVD, cancer, or other causes; and had a reduced risk for peripheral arterial disease.¹⁸
- A cumulative analysis of 8 cohort studies found the Mediterranean diet was associated with a significant reduction in mortality from CVD and cancer, and incidence of Alzheimer's disease and Parkinson's disease.¹⁹

Some applications of the Mediterranean diet result in high intakes of refined carbohydrates (e.g. starchy foods) which are high in glycemic load, and may not be ideal for those with diabetes or insulin resistance.²⁰ Research has shown that reducing the glycemic load of the Mediterranean diet (such as increasing plant foods and reducing refined carbohydrates) would improve postprandial glucose response, reduce craving and overeating, and enhance various health benefits that are associated with the Mediterranean diet.^{20,21}

Because of these study findings—as well as the long history of using botanicals in traditional medicine—scientists have wanted to know what plant constituents contribute to the health benefits seen in those who consume diets that include a larger amount and variety of plant-based foods, herbs, and spices.

TYPES OF PHYTONUTRIENTS

Phyto means “plant” in Greek, and scientists have learned that the bioactive compounds known as *phytochemicals* (or the more consumer-friendly *phytonutrients*) are important constituents of plants—many of which are synthesized to enhance defense and survival.

Numerous phytonutrients have been identified and extensively studied, and a majority can be grouped in (but not limited to) the following classes and subclasses, with well-known compounds in parentheses:²²

- Carotenoids
 - Carotenes (α -carotene, β -carotene)
 - Xanthophylls (lutein, zeaxanthin)
- Phenolic compounds
 - Flavonoids
 - Flavones (apigenin, luteolin)
 - Flavonols (quercetin, myricetin, kaempferol)
 - Flavanones (hesperidin, naringenin)
 - Flavanols or catechins [epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin (EC)]
 - Anthocyanidins
 - Isoflavones (daidzein, genistein)
 - Phenolic acids (caffeic acid, chlorogenic acid, gallic acid, ferulic acid)
 - Stilbenes (resveratrol)
 - Curcuminoids (curcumin)
- Phytoestrogens
 - Isoflavonoids
 - Stilbenes
 - Lignans (matairesinol, secoisolariciresinol)
 - Coumestans (coumesterol)
- Cyclic monoterpenes (limonene)
- Organosulfur compounds (allicin, diallyl disulfide)
- Glucosinolates (glucoraphanin, glucobrassicin)
- Capsacinoids (capsaicin)
- Alpha acids (humulone, lupulone)

PHYTONUTRIENT PROPERTIES

Phytonutrients are responsible for the color in plants (Table 2), as well as other organoleptic properties—including smell and taste (e.g., bitter, acrid, astringent).²³ Again, these are the evolutionary products of the hormetic response, making plants unpalatable to predators as a measure of self-preservation.²⁴

Although bitter phytochemicals are toxins to microorganisms, insects, and pests, the amount is considered very low for large animals and humans—and the plants are of great benefit to these populations. The old Chinese proverb “Better medicine is bitter to the taste” is considered to describe the concept of xenohormesis.

Unfortunately, the food industry routinely engages in the removal of the valuable bitter polyphenols from plant foods (such as olives, grapefruit juice, and red wine) through selective breeding and other debittering processes due to consumer demand for better taste.²⁵⁻²⁸

PHYTONUTRIENT MECHANISMS OF ACTION

Numerous mechanisms of action of how phytonutrients confer beneficial health effects have been proposed, and extensive review articles have been published.²⁹⁻³⁴ Table 3 provides a list of representative phytonutrients and their proposed mechanism(s), 3 of which are briefly discussed in more detail.

Modulation of signal transduction pathways. Cells are very sensitive and responsive to outside stimuli. Through signal transduction pathways (cascades), our cells receive, process, and respond according to this outside information. When ingested, phytonutrients can initiate adaptive cellular stress responses (i.e., xenohormesis) that lead to the modulation of multiple signal transduction pathways and signal transduction molecules, such as Nrf2, AMPK, SIRT-1, FOXO, AP-1, STAT, and NF-κB.^{30,31,34}

One of the most important stress response signal transduction pathways involves the release and translocation of transcription factor Nrf2 into the nucleus. Inside the nucleus, Nrf2 binds to the antioxidant response elements (ARE) or electrophile response elements (EpRE) of genes encoding phase-2 detoxification enzymes and various antioxidant enzymes. The cell becomes more resistant to oxidative stress and inflammation, and more capable of eliminating toxicants.³⁴ Oxidative stress, inflammation, and toxin buildup have been linked to the pathogenesis of many chronic diseases.

Color	Phytonutrients	Major Dietary Sources
GREEN	EGCG, isothiocyanate, lutein/zeaxanthin, Isoflavones	Green tea, cruciferous vegetables (broccoli, kale, cabbage), green leafy vegetables, soybean/soy products
RED	Lycopene, ellagic acid	Tomato, pomegranate, strawberry, walnut
WHITE	Allicin, quercetin	Garlic, onion, shallot, leek, apple
PURPLE - BLUE	Anthocyanidins, resveratrol	Blueberry, elderberry, grape
YELLOW - ORANGE	α-carotene, β-carotene, hesperitin, β-cryptoxanthin	Pumpkin, carrot, orange, cantaloupe, sweet potato, lemon, squash, pepper, tangerine

Table 2. For the general public interested in learning the basics of phytonutrients and how to increase consumption for health benefits, this simplified chart "groups" phytonutrients by color. (Adapted from America's Phytonutrient Report, prepared by Exponent for Nutralite in 2009.)

Another pathway that phytonutrients mediate involves the

stimulation of transcription factor SIRT-1, leading to:^{30,31}

- Decreased apoptosis, inflammation, and carcinogenesis
- Increased stress resistance and insulin sensitivity (hence better energy utilization)
- Many other health benefits

Phytonutrients have also been shown to modulate transcription factors NF-κB and STAT3 that regulate the expression of at least 400 gene products and have significant implication in chronic disease and cancer prevention and treatment.^{35,36}

Antioxidant properties. Cells are constantly exposed to free radicals, reactive oxygen species, and other oxidizing agents, from external sources (e.g., cigarette smoking, electromagnetic radiation, dietary carcinogens) and internal sources (e.g., energy production, metabolism). Oxidants are essential for many physiological functions, but overproduction can cause oxidative stress and damage to proteins, lipids, and especially DNA in the cell. Long-term oxidative stress is involved in the etiology of many diseases, including CVD, rheumatoid arthritis, eye disease, and even cancer.³⁷⁻³⁹

Due to their chemical structures, such as the phenolic ring in flavonoids, many phytonutrients possess antioxidant properties.⁴⁰ By donating electrons and neutralizing free radicals, phytonutrients help prevent attack on cell components. In fact, research has suggested that the family of flavonoids alone exerts antioxidant activity beyond scavenging free radicals—the expanding list includes downregulation of radical production, elimination of radical precursors, metal chelation, inhibition of xanthin oxidase, elevation of endogenous antioxidants, inhibition of oxidative DNA adduct formation, DNA repair enhancement, and inhibition of LDL oxidation.⁴¹⁻⁴³

Hormonal effects. Phytoestrogens are phytochemicals that structurally mimic and modulate the action of estrogens (mainly 17β-estradiol). Phytoestrogens are able to bind to estrogen receptor β (ERβ), whereas estradiol has a much higher binding affinity for ERα.⁴⁴

ERs are distributed widely throughout the body. ERα is expressed in classic estrogen target tissues, such as endometrium and mammary tissue. ERβ is found in the cardiovascular system, brain, bone, kidney, lung, and intestinal mucosa.⁴⁴ Because of the wide distribution of ERs, the effects of phytoestrogens are highly complex. Depending on multiple factors, phytoestrogens have been reported to exert estrogenic, antiestrogenic, anticarcinogenic, antioxidant, and cardioprotective activities.^{22,45,46}

IMPORTANT ISSUES RELATED TO PHYTONUTRIENTS

Although a diet rich in fruits and vegetables can reduce the risk for many chronic diseases, few American adults consume enough. And, as supplements containing phytonutrients grow in popularity, questions of quality and potential effectiveness also increase.

Fruit and vegetable intake. The USDA generally recommends the following (ChooseMyPlate.gov):

- Adult women: ~9 daily servings of fruits and vegetables
 - 2.0 to 2.5 cups of vegetables (4 to 5 servings)
 - 1.5 to 2.0 cups of fruit (3 to 4 servings)
- Adult men: ~10 daily servings of fruits and vegetables
 - 2.5 to 3.0 cups of vegetables (5 to 6 servings)
 - 2.0 cups of fruit (4 servings)

A recent study of food consumption data from the National Health and Nutrition Examination Surveys (NHANES) 2003-2006 showed that only 7% of women and 5% of men in the United States met the (age-specific) recommendations. This suggests that the majority of Americans are unlikely to fully receive the health benefits provided by fruits and vegetables—including those associated with phytonutrients. Furthermore, phytonutrient intake in this population reflects consumption of a limited number of plant foods, indicating a lack of diversity in fruit and vegetable selections.⁴⁷

Purified compounds versus whole plant extracts.

Approximately 1 in 5 adults in the US use botanical supplements.⁴⁷ Consumers are facing a wide variety of botanical supplements, and it can be a daunting task to determine individual needs—let alone identify inaccurate labels, exaggerated claims, or product quality. And one of the most fundamental issues in formulating supplements is the choice between purified compound(s) or whole plant extracts.

The existence of high dose, purified compounds on the market is understandable. An old paradigm in biomedical research is the quest for “magic bullets” for therapeutic use. This single-target-based approach has been successful in pharmaceutical industries for decades. Scientists, including researchers in the nutrition field, have become familiar with studying a single bioactive compound acting on very selective ligands. But the past 2 decades have witnessed a significant increase in late-stage attrition in drug candidates that are highly selective.

As systems biology becomes available and convincing, researchers have (sometimes reluctantly) realized the arrival of the next, emerging paradigm: network pharmacology.⁴⁸ Instead of a single pathway, a network of pathways involving multiple signaling molecules drives the biological response.

Phytonutrient	Proposed Mechanisms
Catechins	Antioxidant Inhibits multiple stages of carcinogenesis Reduces LDL oxidation
Cynarin	Antioxidant Hepatoprotective
Chlorogenic acid	Antioxidant Hepatoprotective Cardioprotective Antihypertensive
Anthocyanins	Antioxidant Chemopreventive Neuroprotective Improves insulin sensitivity Anti-inflammatory Phase II detoxification
Caffeic acid	Antioxidant Hepatoprotective
Hesperidin	Antioxidant Anti-inflammatory
Lycopene	Antioxidant Chemopreventive
Lutein/ zeaxanthin	Antioxidant
Resveratrol	Antioxidant Anti-aging Chemopreventive Cardioprotective
Ellagic acid	Phase II detoxification Anti-atherogenic Anti-inflammatory
Carnosic acid	Antioxidant Antibacterial Chemoprotective
Carnosol	Antioxidant Antibacterial Chemoprotective Phase II detoxification
Glucosinolates	Chemopreventive Carcinogen detoxification
Isoflavones	Hormonal activities Anti-carcinogenic Antioxidant Anti-inflammatory Cholesterol lowering
Humulone	Antibacterial Antioxidant Anti-inflammatory
Berberine	Anti-diabetic Lipid lowering
Phytosterols	Cholesterol lowering

Table 3. Representative dietary phytonutrients and their proposed mechanisms of action based on in vitro and in vivo studies.⁴⁹⁻⁸⁹

Diverse phytonutrients, synergistic effect. Nature, as it turns out, has known the importance of a network approach all

along. As Drs. Mary Ann Lila and Ilya Raskin elegantly stated, "...the evolutionary significance of a large number of phytochemicals present in each plant lies in their intricate mutually potentiating effects that provide protection against diverse pathogenic microbes and herbivores..." And "...by relying on combination of pleiotropic, multitargeted molecules, plants may have perfected interacting phytochemical complexes, which may be exploited by modern medicine during its gradual transition from single-ingredient drugs to multicomponent therapeutics."⁹⁰

Supporting this paradigm are emerging data demonstrating that a plant mixture provided more potent antioxidant or enzyme-upregulating activities than single isolated active ingredient(s).^{90,91} Synergy has also been found in herbal combinations compared to the constituent herb used alone.⁹²

The benefit of consuming diverse phytonutrients is demonstrated in a recent study in which volunteers were randomized to 2 special diets for 2 weeks:⁹³

- Both diets provided 8 to 10 daily servings of fruits and vegetables and the same macronutrient content.
- One diet was designed with a high diversity of 18 botanical families; the low diversity diet represented only 5 botanical families.
- Researchers found that only the high botanical diversity diet reduced DNA oxidation.
- They suggested that smaller amounts of many phytonutrients had greater beneficial effects than larger amounts of fewer phytonutrients.

Evaluations of phytonutrients in the natural product industry. The interest for natural products continues to increase as consumers have become more aware of the scientific research on phytonutrients and their potential health benefits. Consumers also have higher demand for quality control, efficacy assessment, and even product-specific scientific validation from supplement marketers.

Quality control measures in botanical supplements should optimally include verifying plant species, phytonutrient profiles, and presence of other key bioactive compounds via high performance chromatography tests (e.g., hpTLC, HPLC). Another important task is to provide accurate assessment of the potential total antioxidant capacity of a product, which provides a starting point for a comprehensive antioxidant analysis that may include evaluation of the potential to protect DNA stability.

Total ORAC_{FN} Assay

One of the most commonly used chemical assays is the Oxygen Radical Absorbance Capacity (ORAC) assay. However, the traditional ORAC assay does not truly measure the "total" antioxidant capacity of the tested substance or mixture; it only measures the antioxidant activity against the peroxy radical, the most common free radical in human biology.⁹⁴

A newly developed ORAC measures antioxidant capacity against 5 primary reactive oxygen species found in humans, including hydroxyl, peroxy, peroxy nitrite, singlet oxygen, and superoxide anion. This more comprehensive measure of total antioxidant capacity is termed Total ORAC for Food and Nutrition (Total ORAC_{FN}), and should allow companies to design/refine their product formulations and help companies differentiate themselves from competitors.

Comet Assay

An in vitro test, which is more biologically relevant than chemical assays, allows a more advanced testing for the antioxidant properties of phytonutrients. Single-cell gel electrophoresis, or the comet assay, is a rapid, sensitive method for detecting most kinds of DNA damage (e.g., strand breaks, alkali-labile sites, and cross-linking) at the level of individual cells.⁹⁵ The comet assay has been widely utilized in biomonitoring, genotoxicological, and ecotoxicological research.⁹⁶

Among nutrition researchers, the comet assay has been mostly used to investigate whether the test nutrient(s) protect cells from strand breaks caused by an oxidative damage-inducing agent.⁹⁷ The assay can be conducted in both in vitro and in vivo conditions.^{98,99} Some nutrition research utilizing the comet assay:

- Cigarette smoke contains carcinogens, such as benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide, which can induce DNA damage in upper aerodigestive tract cells. When cells from fresh oropharyngeal mucosa biopsies were pre-incubated with EGCG, the carcinogen-induced damage was significantly reduced.¹⁰⁰
- A study comparing the genoprotective effects of different plant extracts found that bearberry extracts, grapeseed polyphenols, and olive leaf extract significantly reduced DNA damage caused by hydrogen peroxide or tert-butylhydroperoxide in U937 lymphoma cells.¹⁰¹
- In a human dietary study, a significant anti-genotoxic effect against H₂O₂-induced DNA damage was observed in peripheral blood lymphocytes of volunteers who were fed cruciferous and legume sprouts for 14 days when compared with the control diet for 14 days.¹⁰²

CONCLUSIONS

Fast food lifestyles may contribute to a lower intake of health-promoting nutrients, while contributing to “overnourishment” of fats, sugars, and energy intake that can negatively influence health. Despite the growing awareness of healthier lifestyle choices, adult consumption of phytonutrient-rich fruits and vegetables in the US remained relatively flat over the past decade. And the economic cost attributed to this inadequate consumption grew from \$29.3 billion to \$56.2 billion. Yet still less than 15% of physician offices currently provide or order diet or nutrition services for their patients.¹⁰³

We now know that phytonutrients help humans adapt to internal and external stressors similar to how they benefit plants. And it may very well be in our nature to seek them out. Dietary phytonutrients may also offer greater benefit when consumed in a more diverse combination.

As the benefits of phytonutrients continue to be revealed and grow in awareness, so do advancements in testing the potential effectiveness of phytonutrients to support cellular health to defend wellness throughout the body. The quality of dietary supplements containing botanicals and phytonutrients remains an important consideration.

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