Controversy: What are the True Biological Functions of Superfruit Antioxidants?

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Antioxidant Expertise of The Linus Pauling Institute

The Linus Pauling Institute was co-founded in 1973 by Linus Pauling, the only individual to win two, unshared Nobel Prizes (Chemistry, 1954; Peace, 1962). In 1996, the Institute moved to Oregon State University, Pauling's undergraduate alma mater. The work of the Institute builds on Pauling's concept of "orthomolecular medicine", which he defined as "the preservation of good health and the treatment of disease by varying the concentrations in the human body of substances that are normally present in the body and required for health." Therefore, the mission of the Linus Pauling Institute is to determine the function and role of vitamins and essential minerals (micronutrients) and chemicals from plants (phytochemicals, including flavonoids) in promoting optimum health and preventing or treating disease. An additional goal is to determine the role of oxidative stress and inflammation in human health and disease, and the protective effects of dietary antioxidant and anti-inflammatory compounds. Finally, through education and outreach, the Institute strives to help people everywhere achieve a healthy and productive life, full of vitality, with minimal suffering, and free of cancer and other debilitating diseases.

LPI researchers investigate the mechanisms by which dietary factors, oxidative stress, and inflammation affect disease initiation and progression at the molecular, cellular, organism, and human levels and how diet, antioxidants, and anti-inflammatories can be used in the prevention and treatment of diseases, thereby enhancing human health and well-being.

Major areas of research include cardiovascular and metabolic diseases, cancer, aging, immune function, and neurodegenerative diseases. Specific research projects in the Institute include: oxidative stress, inflammation, and transition metals in atherosclerosis and heart disease, and protective effects of alpha-lipoic acid and flavonoids; vitamin E metabolism and biological functions; oxidative and environmental stress in neurodegenerative diseases; stress response, alpha-lipoic acid, and mitochondrial dysfunction in aging; cancer chemoprevention by phytochemicals in tea and vegetables, including flavonoids, chlorophyll, indole-3-carbinol, and isothiocyanates; zinc and antioxidants in prostate cancer; novel biological functions of vitamin C; and the role of vitamin D and zinc in immune function.

In addition to conducting scientific research, the Institute convenes scientific conferences, sponsors scientific and public lectures, publishes a semi-annual research newsletter and responds to inquiries from the media and the public. A major effort is the Micronutrient Information Center (http://lpi.oregonstate.edu/infocenter), a free Web site containing up-to-date, peer-reviewed, scientifically accurate information on the functions and health benefits of vitamins, essential minerals, other nutrients, phytochemicals, and some foods and beverages. Detailed information on the biological activities and health benefits of flavonoids can be found at http://lpi.oregonstate.edu/infocenter/phytochemicals/flavonoids/.

Flavonoids

Flavonoids are a family of some 5,000 plant compounds having a common chemical structure called polyphenol. Flavonoids can be divided into chemically-related subclasses of polyphenols called isoflavones (found in soy products), flavanones (like naringenin from citrus fruits), flavanols (e.g., catechins from tea or cocoa), flavonols (e.g., quercetin from many fruits and vegetables), and anthocyanidins (from berries and grapes).

Following ingestion, flavonoids are likely to undergo a change in chemical structure during exposure to stomach acids and enzymes. Flavonoids are poorly absorbed into blood and rapidly eliminated from the body; thus, flavonoids have low eventual biological availability or 'bioavailability'—the fraction of ingested substance reaching target organs (1,2). Bioavailability is only about 10% of total intake for flavonoids like soy isoflavones and citrus flavonones, while it is even lower (about 2% of total intake) for most other flavonoids, including anthocyanidins, catechins, and quercetin. Unfortunately, many test tube experiments published in the scientific literature showing strong antioxidant activity of flavonoids have

used very high, unphysiological concentrations and parent chemical structures (rather than metabolites) of flavonoids. When these results are conveyed to the public, a misunderstanding may occur about the actual biological significance of flavonoids, leading consumers to believe incorrectly that flavonoids have important antioxidant value. Below, we summarize possible actions of dietary flavonoids in human physiology.

Minimal or No Direct Antioxidant Activity. Flavonoids have antioxidant activity in test tube experiments because they effectively scavenge free radicals. However, in the human body, flavonoids are not effective antioxidants because, even with high levels of dietary intake, cellular flavonoid concentrations are 100-1,000 times lower than concentrations of other important cellular antioxidants, including vitamin C, vitamin E, uric acid, and glutathione (3). Moreover, flavonoid metabolites often have even lower antioxidant activity than their parent flavonoids. For these reasons, the relative contribution of dietary flavonoids to antioxidant function in the body must be very small and physiologically negligible (1-3).

Potential Estrogenic and Anti-Estrogenic Activities. Soy isoflavones are called 'phytoestrogens'—plant-derived compounds that exert estrogen-like effects rather than antioxidant functions. Estrogen is a hormone that binds to estrogen receptors located in bone, liver, heart, brain, and reproductive tissue. Soy isoflavones can either mimic the effects of estrogen in some tissues or block its effects in others. Estrogenic effects in various tissues could help maintain bone density and improve cholesterol levels, while anti-estrogenic effects in reproductive tissue could potentially decrease the risk of hormone-associated cancers (e.g., breast, uterine, and prostate cancers).

Potential Effects on Cell-Signaling Pathways. Cells can respond to a variety of stresses or signals by increasing or decreasing activity of ‘cell-signaling pathways’ (also called ‘signal transduction pathways’). These pathways regulate many processes, including cell growth, cell proliferation, and removal of damaged cells (programmed cell death or ‘apoptosis’). Although it was originally assumed that flavonoids exert antioxidant effects in the body (see above), it has become increasingly clear that instead they modulate cell-signaling pathways (2).

Inside cells, the concentration of flavonoids needed to affect cell-signaling mechanisms is much lower than that needed to affect cellular antioxidant capacity, so this evidence is consistent with the low flavonoid concentrations kept in the body. The results of many laboratory experiments suggest that flavonoids may selectively inhibit a group of cell-signaling enzymes called kinases, which are important in maintaining normal cell function. Increased activity of these kinases appears to be needed at the start of various chronic diseases; flavonoids may selectively inhibit kinases, thereby lowering chronic disease risk (2).

In most of the following examples, flavonoids in their native chemical structure and in relatively high concentrations were applied directly into the experimental preparation (did not pass through the stomach). The results indicate that changes in cell signaling by flavonoids could help prevent cancer by:
• Increasing levels of detoxification enzymes: Detoxification enzymes carry out reactions that help excrete potentially toxic or carcinogenic (cancer-causing) compounds.
• Preserving normal cell cycle regulation: The ‘cell cycle’ is the sequence of events involving growth, replication, and division of a cell. If DNA damage occurs, the cell cycle can be transiently arrested in order for the DNA to be repaired, or if the damage is irreparable, for activation of pathways leading to removal of the damaged cell . Cancer may develop if DNA mutations are propagated, for instance, in the case of defective cell cycle regulation. Flavonoids appear to maintain normal cell cycle.
• Inhibiting proliferation and inducing programmed cell death (apoptosis): In contrast to normal cells, cancer cells proliferate rapidly and cannot respond to cell signals that initiate apoptosis. Flavonoids stimulate apoptosis in isolated cancer cells, so they may be important as dietary agents combating cancer.
• Inhibiting tumor invasion and angiogenesis: With the aid of enzymes called matrix-metalloproteinases, cancer cells invade normal tissue. Angiogenesis—the development of new blood vessels—is necessary for the growth of invasive, cancerous tumors. Flavonoids appear to act against both the invasion process and angiogenesis.
• Decreasing inflammation: Inflammation can result in increased production of free radicals by inflammatory enzymes, as well as the release of inflammatory mediators that promote cell proliferation and angiogenesis and inhibit apoptosis. In test tube studies, flavonoids act against inflammatory mechanisms.

Modulation of cell-signaling pathways by flavonoids could help prevent cardiovascular diseases (mainly heart attacks and strokes) by:
• Decreasing inflammation: Atherosclerosis is now recognized as an inflammatory disease of the arterial wall. Accordingly, several markers of inflammation like one called 'C-reactive protein' (CRP) have been

associated with increased risk of heart attacks and strokes. In test tube experiments and in preliminary studies with animals and humans, there is evidence that dietary flavonoids may lower CRP and inhibit atherosclerosis resulting from inflammation of the arterial wall.

• Decreasing vascular endothelial cell adhesion: Early in the development of atherosclerosis, inflammatory white blood cells are recruited from the blood to the arterial wall. This event is dependent on so-called adhesion molecules produced by vascular endothelial cells that line the inner walls of blood vessels (4). This process is inhibited by flavonoids.

• Increasing endothelial nitric oxide production: An enzyme called eNOS produces the chemical nitric oxide, which is needed to maintain normal blood vessel relaxation (vasodilation). Impaired nitric oxide-dependent vasodilation is linked to an increased risk of cardiovascular diseases. Nitric oxide also may reduce inflammation and inhibit smooth muscle cell proliferation, important factors in atherosclerosis. Dietary flavonoids (from tea or cocoa) may increase eNOS activity by binding to estrogen receptors (above) and stimulating cell-signaling pathways that activate eNOS (5).

• Decreasing platelet aggregation: Platelet aggregation is one of the first steps in the formation of a blood clot that can occlude a coronary or cerebral artery, leading to a heart attack or stroke, respectively. Thus, inhibiting platelet aggregation—an action that flavonoids appear to have—is important in the prevention of cardiovascular diseases.

In summary, dietary flavonoids cannot be significant antioxidants in humans, but they may affect a variety of cell-signaling pathways, possibly influencing the onset and progression of cancer or cardiovascular diseases.

References

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