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Foundation for the
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Science, Inc.

VitalLongevity™

Logo: Life's blood flows through the hourglass; the stopcock represents the alteration of aging and disease as biomedical research progresses.

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Why Blueberries?

The media bombard us with advice, often contradictory, about what we should (or should not) eat to promote health, but it is difficult to find a nutritionist anywhere who does not endorse a diet rich in plants. But why? And which ones? Because of the inherent difficulty in studying a population (human) that lives outside a laboratory, carefully controlled intervention studies—studies where a population is divided into two groups and one of them changes its diet—are few in number. Further, many large population-based studies lump the consumption of all fruits and vegetables together. Take, for example, the US Department of Agriculture's food pyramid recommendation of 6 servings of fruits/vegetables per day. Apples, oranges, and iceberg lettuce, theoretically all equal. This issue of *VitaLongevity* looks at potential benefits researchers are finding in diets rich in highly colored fruits, especially blueberries, a fruit particularly rich in polyphenols. Polyphenols are a group of naturally occurring compounds found in plants where they perform a variety of functions from sopping up reactive oxygen (free radicals) produced during photosynthesis to attracting pollinators. There are three main groups of polyphenols (see Table 1), the most diverse of which are the flavonoids.

Flavonoids may be broken down into subclasses, the most colorful of which are the anthocyanins. Anthocyanins (from Greek: *ανθος* (anthos) = flower + *κυανος* (kyanos) = blue) are water-soluble pigments that may appear red, purple, or blue according to pH. It is anthocyanins that give blueberries their distinctive hue. Anthocyanins are found mostly in flowers and fruits and predominately in the outer cell layers. Because of their small size, blueberries and cranberries have more pigment-filled skin relative to flesh.

When examining the health effects of whole fruit consumption, it is very challenging to pinpoint the health-active component(s)—fiber, trace minerals, vitamins, or non-nutritive compounds such as polyphenols. Indeed, new findings suggest that the three main groups of polyphenols possess unique properties that go beyond their test tube abilities as antioxidants. In addition, polyphenol content can vary by cultivar. For example, not all blueberries are equal: the smaller berries of wild varieties

(lowbush) generally contain more polyphenols than the larger berries from highbush varieties usually found in the supermarket. Polyphenol content can also vary by geographic and climactic variables. For example, anthocyanin concentration in fruit increases with ripeness and sun exposure. Organically grown fruits and vegetables contain 10-50% more secondary compounds such as polyphenols than conventionally grown crops, hypothetically because plants grown without pesticides are forced to defend themselves from pests and disease by producing higher levels of protective compounds.

Whole Food or Supplements?

Diets rich in antioxidant-filled fruits and vegetables provide undeniable health benefits, yet taking the same

antioxidants as supplements (e.g., vitamin E capsules or vitamin tablets) has consistently failed to produce the same beneficial results in studies on their use. This is likely because other food components deserve some credit, with unique combinations of compounds in foods acting synergistically, or that supplements have less bioavailability than whole foods. For example, in counteracting the oxidative stress to the mucosal lining of the GI tract, antioxidant polyphenols in

fibrous foods remain in the intestine longer than do supplements. This gives the antioxidants in foods longer to neutralize reactive oxygen species (ROS).

Further, scientists now question the widely held premise that antioxidants in foods (or supplements) neutralize ROS outside the GI tract. Most ROS are produced in mitochondria, which are locked in their own membrane inside the cell, an area particularly inaccessible to antioxidants. Ironically, an antioxidant can be a pro-oxidant in certain environments within the body. In such instances, the antioxidants in food might themselves generate low levels of ROS. This may create a tolerable level of stress that then induces cells to produce more of the beneficial enzymes catalase and superoxide dismutase, which are themselves powerful antioxidants. Supplements, especially in high doses, might not work (or be harmful) if they produce too many ROS.

There are, however, many studies indicating that polyphenols may provide benefits outside their role as

Common Classes and Sources of Polyphenols

Polyphenols	Examples	Foods
Hydroxybenzoic acids	Gallic acid	Black tea, blackberries
Hydroxycinnamic acids	Chlorogenic acid Caffeic acid	Blueberries Kiwi
Stilbenes	Resveratrol Pterostilbene	Red grapes Blueberries
Lignans	Secoisolariciresinol	Linseed
Phenolic alcohols	Tyrosol	Extra virgin olive oil
Flavonoids		
• Flavonols	Quercetin	Blueberries
• Flavones	Apigenin	Parsley, celery
• Flavanones	Hesperetin	Citrus fruit
• Isoflavones	Daidzein	Soy products
• Anthocyanins	Cyanidin	Blueberries
• Flavan-3-ols	Catechins Proanthocyanidins	Green tea Apples

Table 1

antioxidants. Below is an overview of just some of the research investigating the effect of anthocyanins on cancer, cognition, and cardiovascular disease. It is important to note that these experiments generally use animals or cell cultures that are fed (or exposed to) high doses of purified extracts, and it is still unclear whether (or how) these results might apply to humans.

Polyphenols & Cancer

Studies show specific anti-cancer activities of polyphenols: arresting cell growth, regulating enzymes that convert carcinogens or toxic byproducts into harmless materials, interfering with energy production needed by quickly-growing cancer cells, and inhibiting DNA damage from various agents. GI cancers are natural targets for polyphenol intervention because their cells are so accessible to ingested polyphenols. Those rats fed anthocyanin-rich juices (blueberry and pomegranate) developed significantly fewer cancerous lesions than rats fed a juice-free diet. Quercetin and resveratrol, two other polyphenols found in dark-hued fruits, are being investigated for anti-cancer activity. In another study, rats fed freeze-dried blackberries showed inhibition of chemically-induced cancer of the esophagus by 30-60% and cancer of the colon by 80%. While the majority of anthocyanins in food are broken down in the GI tract, we do not know how the polyphenols provide protection against cancer in these studies, but the results were striking enough to encourage further research.

Polyphenols & Cognition

The cells of the brain are protected by the blood-brain barrier, a highly selective membrane that determines which blood-borne substances may enter the brain. Anthocyanins and other polyphenols, however, are small molecules that can cross the blood-brain barrier in small quantities. Once there, some studies have found that they localize in areas important to learning and memory. This might partially explain why age-related deficits, such as a decrease in balance, coordination, spatial learning, and short-term memory, were reversed in rats fed a diet containing a high dosage of blueberry extract.

Age-related hearing loss (diminished speech discrimination caused by processing speed in the auditory cortex) might

be alleviated by components found in blueberries. After eight weeks of a diet rich in blueberry extract, aged rats not only reversed the decline in the speed of auditory processing but also had enhanced processing capability.

Because oxidative stress is a significant element in the damage caused by ischemic strokes, the antioxidant properties of anthocyanins would seem the logical mechanism by which neurons are protected from stroke-induced damage. Surprisingly, however, while rats fed a diet rich (14.3%) in lowbush blueberries did suffer significantly less neuronal damage following an induced ischemic stroke, when compared to rats fed a blueberry-free diet there was no detectable antioxidant effect in the plasma or urine of these rats. Something in the anthocyanin-rich blueberry diet appears to be protecting the neurons; it remains to uncover the mechanism(s).

Polyphenols & Cardiovascular Disease

In another study, pigs and hamsters fed a diet high in cholesterol and supplemented with a large quantity of blueberries or freeze-dried blueberry skins showed a significant drop in total cholesterol compared to control groups fed only a high cholesterol diet. Other putative heart-protective effects of polyphenols in laboratory experiments include: beneficial alterations in structural features of the aorta, protection of the lining of blood vessels against a variety of injuries, anti-clotting/anti-thrombotic activity, and blood pressure reduction by altering molecules found in vascular cells that help to control blood pressure.

Potential Health Actions of Polyphenols

- Anti-oxidation
- Anti-inflammation
- Anti-carcinogenic
- Anti-angiogenic
- Prevention of urinary tract infections
- Cytotoxic to *H. pylori*
- Reduced cardiovascular disease risk (reduced cholesterol, LDL-oxidation prevention)
- Nervous system protection and improved brain function
- Improved eyesight and night vision
- Improved hearing
- Decreased disease activity in colitis
- Anti-microbial properties

Table 2

Tidbits

- Flavonoid content of selected foods is online at <www.ars.usda.gov/nutrientdata/flav>.
- 95% of resveratrol in red wine is destroyed by the digestive system before it can enter the blood.
- Buy orange juice with pulp: the pulp contains high levels of the flavanone hesperetin.
- Eat fruits preferably fresh or frozen; heat can lower the anthocyanin content.
- Refrigerated apples maintain their flavonoid concentration long-term.
- Colorful skin/peel usually has more healthy pigments.

Information for Donors

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