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REPORT

Maintaining Youthful Cognitive Function with Blueberries

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Published scientific studies show that blueberries are packed with nutrients that not only improve cognitive function and delay neurological decline but also protect delicate brain structures against oxidative damage.

Rich in powerful polyphenol compounds, blueberries have been shown to uniquely protect the brain against noxious influences such as free radicals, radiation, inflammation, and excitotoxicity. Furthermore, blueberries may even reverse age-related deficits in cognitive and motor function. Scientists have noted that blueberry compounds are readily absorbed into the

bloodstream, then cross into the brain where they influence regions involved in memory and motor function—suggesting therapeutic roles against Parkinson’s and Alzheimer’s.

In this report, we speak with some of the scientists at the forefront of this exciting area of research.

BLUEBERRIES: A NUTRITIONAL POWERHOUSE

Modern science has made much progress in discovering the benefits of specific compounds found in fruits and vegetables, such as vitamin C and resveratrol. Nutrient-dense “superplants” go a step further and are packed with complex blends of phytonutrients that work together to promote optimal health.



One such “superfruit” is the blueberry, which contains a powerhouse of nutrients that may defend the body against the ravages of aging and disease. Blueberries are rich in polyphenols, of which some of the most beneficial are a class of flavonoids called anthocyanins, which give the berry its intense blue color.¹ These remarkable compounds as well as proanthocyanidins, flavonols, and tannins, which are also found in blueberries, act not only as antioxidants,² but have been shown in the laboratory to fight inflammation as well.

This dual effect gives anthocyanins the potential to fight cancer,³⁻⁶ cardiovascular disease,⁵ inflammation,⁷ and aging and degeneration of nerve cells.^{8,9}

Oxidative stress and inflammation are thought to be common culprits not only in aging itself, but also in cardiovascular disease, Alzheimer’s disease, and other neurodegenerative diseases plaguing our graying population. Population studies suggest that consuming a diet high in antioxidants, such as those found in fruits and vegetables, may forestall the onset of Alzheimer’s disease and other dementias.^{10,11} Polyphenolic compounds found in blueberries can decrease the age-enhanced vulnerability to oxidative stress and inflammation. Compared with other fruits and vegetables, blueberries are among the highest in antioxidant capacity, or in their ability to scavenge harmful free radicals, as measured by the oxygen radical absorbance capacity (ORAC) test.¹² Similarly, wild blueberries outpace other fruits such as cranberry, apple, and grapes in the cellular antioxidant activity assay, a newly developed, next-generation technology that measures antioxidant effects within the cells themselves.¹³

Despite the undisputed advances made possible through a variety of drugs available to combat various diseases, drugs have powerful effects, some beneficial, some potentially harmful. The potential risks must be considered when prescribing or taking medications, especially for chronic diseases of aging in which treatment may be needed over the long term.

On the other hand, fruits and vegetables that are naturally found in our diet can be safely processed by the body without concern for possible side effects. Appropriate intervention with blueberries and their extracts may promote health and combat disease—without the risk of adverse complications common with powerful drugs.



A wealth of studies published in 2007 reveal that blueberries do just that. Animal studies have shown that pterostilbene, an active ingredient in blueberries, may specifically help to prevent colon cancer.¹⁴ Another constituent of blueberries—tannins—can kill disease-causing bacteria,¹⁵ while blueberry phenolics have a beneficial effect on bacteria in the colon, thereby reducing gastrointestinal inflammation.¹⁶ Further up-to-the-minute research shows that the antioxidant power of blueberries promotes eye health and protects against chromosomal damage,⁹ while anthocyanins found in berries may also improve the function of brain cells, with corresponding behavioral improvements.⁸

BLUEBERRY EXTRACT PROTECTS BRAIN CELLS FROM INJURY

In an exciting study published recently, the National Institute of Aging looked at the effect of a blueberry-enriched diet in protection from brain injury in rats. 17 Young rats received a diet containing 2% blueberry extract, or a control diet, for at least eight weeks. Some of the rats were then given injections of kainic acid, a noxious chemical producing oxidative stress and overexcitability of nerve cells, into the hippocampus, a brain region involved in memory and learning.

Rats that received kainic acid injections clearly had impaired learning performance compared with control rats. However, those rats that had received the blueberry-supplemented diet before kainic acid injection had much less impairment than those that received the control diet. Even more amazingly, microscopic examination of brain tissue confirmed that rats receiving the control diet and kainic acid injections had significantly greater loss of brain cells than rats pretreated with the blueberry-supplemented diet.

Donald K. Ingram, PhD, from the Nutritional Neuroscience and Aging Laboratory, Pennington Biomedical Research Center, Louisiana State University System in Baton Rouge, who collaborated with the National Institute of Aging on this study told Life Extension, “Beyond the demonstrated antioxidant activity, blueberries appear to stimulate stress responses that protect cells [from] a great variety of injuries.” He added, “Evidence that blueberries could be helpful to the aging brain is derived from a variety of carefully conducted rodent studies showing improved performance of aged animals in behavioral tasks, as well as increased protection against various forms of brain injury relevant to human neurodegenerative disease.”



Dr. Ingram’s group took their findings one step further. They found that serum from the blood of rats fed the blueberry-enriched diet actually protected cells grown in the laboratory from death induced by hydrogen peroxide, a potent oxidative stressor that generates many free radicals. The researchers concluded that blueberry supplementation may protect against neurodegeneration and cognitive impairment caused by excitotoxicity and oxidative stress.¹⁷

“Given the epidemiological evidence that diets high in fruit and vegetable content, particularly those of dark color [may help protect against oxidative stress], consumption of blueberries could be highly recommended as part of a healthy diet,” Dr. Ingram said. “There is a great need now for systematic clinical trials to confirm the beneficial effects of blueberry consumption on a number of important health measures, including behavioral function as well as risk factors for age-related disease, such as cardiovascular disease and diabetes.”

BLUEBERRY EXTRACT MAY PREVENT AGE-RELATED BRAIN IMPAIRMENT

The potential health benefits of eating blueberries and similar fruits, and the scientific evidence supporting this potential, were also highlighted recently at the 2nd International Symposium on Berry Health Benefits, held in June 2007 at Oregon State University in Corvallis.

One of the main presenters at this symposium was James A. Joseph, head of the Neuroscience Laboratory of the USDA-ARS Human Nutrition Research Center on Aging at Tufts University in Boston, MA.



His group sought to confirm whether blueberry supplementation promotes communication between nerve cells, and so theoretically reduces the risk of cognitive and motor impairments associated with aging. Using an animal model, Dr. Joseph’s group studied the effects of a blueberry-supplemented diet on movement and memory problems related to aging, as well as on the underlying chemical and physical changes in the brain.⁸

“We fed rats a diet containing blueberries, strawberries, or spinach (the equivalent of you eating a large spinach salad, or a cup of blueberries, or about a pint of strawberries) for eight months, beginning at about 19 months of age, at which time they’re starting to show signs of aging in cognitive and motor function,” Dr. Joseph told Life Extension. “We showed that these animals did better than the ones that were maintained on non-supplemented diets.”

Compared with the rats that received the control diet, the aging rats that received supplemented diets were much less likely to develop impairments in water maze performance and on other tests of memory, learning, and coordination, such as balancing on a narrow or spinning rod. What was even more exciting was that when aged rats that already had impairments on these tests were given blueberry extract, their performance improved or even returned to normal!⁸

“The blueberries were pretty good at blocking some of the effects of the oxidative stressors; in other words, they were fairly good scavengers of free radicals, [and] we also started looking at other mechanisms, and other potential benefits that they might have,” Dr. Joseph said. “We showed that neurogenesis—the growth of new neurons—is increased in these animals, which goes along with the behavioral improvements that we saw.”

Increased levels of a neuronal chemical known as extracellular signal-regulated kinase (ERK), which protects nerve cells, gave further proof of neurogenesis in the blueberry-supplemented animals. In fact, ERK has been shown to be crucial for a variety of memory tasks, making it uniquely poised to change the neuronal and behavioral effects of aging.

Not only is blueberry supplementation associated with growth of new nerve cells,¹⁸ but existing nerve cells are better able to communicate with one another through a process known as signal transduction. Levels of enzymes involved in signal transduction, such as GTPase and protective mitogen-activated protein (MAP) kinases, actually increased in the blueberry-supplemented animals.

This led the researchers to suggest that “nutritional interventions with high antioxidant fruits, such as berryfruits, may prove to be a valuable asset in strengthening the brain against the ravages of time and retard or prevent the development of age-related neurodegenerative diseases.”⁸

Not surprisingly, researchers in Dr. Joseph’s laboratory have confirmed that anthocyanins in blueberries are able to cross the blood-brain barrier of supplemented animals and localize in various brain regions important for learning and memory.¹⁹ Using mouse microglial cells (cells that nourish, protect, and enhance the function of brain cells) they also studied the mechanisms by which anthocyanins protect nerve cells and enhance their function.²⁰

“The anthocyanins were localized in the brain, and the more different ones that were localized in the brain, the better the cognitive behavior was,” Dr. Joseph said. “We know that they are very good antioxidants, and very good anti-inflammatories. What we know from our work in mouse microglial cells is that these polyphenols can inhibit the stress pathways at several points involved in the inflammatory pathways, with reductions in inflammatory cytokines.”

This research suggests that blueberries produce antioxidant and anti-inflammatory effects by directly changing oxidative and inflammatory stress-signaling pathways. In the laboratory, blueberry extract prevented harmful biochemical changes associated with exposing microglia to an inflammatory substance.²⁰



“In Alzheimer’s disease and in Parkinson’s disease, it’s postulated that these microglia become very overactivated and start to destroy the cells, functioning deleteriously instead of being beneficial to the brain,” Dr. Joseph explained. “When that happens, they can’t be activated and used for other purposes.”

Although injury and stress ordinarily activate the microglia to release substances that will protect nerve cells, pathological activation of microglia may aggravate the progressive damage associated not only with Alzheimer’s disease and Parkinson’s disease, but also with stroke, multiple sclerosis, and human immunodeficiency virus (HIV)- or AIDS-associated

dementia.^{20,21}

An interesting model system to study Alzheimer’s disease is the transgenic mouse that is genetically engineered to have variations in amyloid precursor protein (APP) and presenilin-1 (PS1), proteins that are important in producing the brain pathology characteristic of Alzheimer’s disease. Because of the APP mutation, transgenic mice have increased amounts of amyloid-beta, a protein fragment that makes up the “neuritic plaque,” which is the hallmark of this disorder. When transgenic mice were maintained on a blueberry-supplemented diet, the levels of two neuroprotective chemicals, extracellular signal-regulated kinase and protein kinase C, which are involved in learning and memory, were found to be increased.

Transgenic mice fed the blueberry-supplemented diet were also better able to navigate a maze than their counterparts fed a control diet, even though both groups of animals developed brain plaques. In transgenic mice, blueberry supplements appeared to enhance signaling at the level of the kinases, thereby increasing the sensitivity of brain receptors in the striatum that are involved in memory.^{8,22}

Blueberry extract also reduced stress signaling caused by exposing brain cells from the hippocampus to the neurochemical

BLUEBERRY EXTRACT PROTECTS SPECIFIC BRAIN REGION FROM INJURY

In collaboration with NASA at Brookhaven National Laboratory, Dr. Joseph's group is studying a model system to help understand the injurious effects of radiation on the brain. Young rats exposed to about 150 rads of heavy particle radiation, of the type that astronauts are exposed to on long-term space flights, develop impairments in motor and cognitive function similar to those seen with aging.^{8,24}

"If we pretreat these animals for eight weeks with a diet containing blueberries or strawberries, we find that we can block the effects of the radiation," Dr. Joseph said. "What's interesting is that on some behaviors, the strawberries work better, and, on other behaviors, the blueberries work better."

Specifically, the proanthocyanins in blueberries seem to be drawn to the striatum, a brain structure controlling movement as well as certain memory tasks. The striatum is also one of the brain regions most affected by Parkinson's disease.

In terms of whether there are actual brain regions where these polyphenols may have receptors, Dr. Joseph said, "If you think about it for a moment, why not—there are opioid receptors in the brain, caffeine receptors, and [marijuana] receptors. We haven't isolated them yet, but we're trying to tease out these mechanisms and see which may have the most effect as far as producing the beneficial properties of blueberries."

If the proanthocyanins in blueberries have specific benefits within the striatum, it seems reasonable to assume that blueberry extract might nurture the predominant population of nerve cells located in the striatum, namely, neurons containing the neurotransmitter known as dopamine. Depletion of dopamine from the striatum is the biochemical basis underlying the rigidity, stiffness, and tremor seen in Parkinson's disease.

In a rat model of Parkinson's disease and its treatment,²⁵ dopamine was depleted from the striatum, into which embryonic nerve cells containing dopamine were transplanted. Compared with control rats fed standard lab chow, those fed a diet containing 2% blueberry extract had significantly greater survival of transplanted nerve cells. These nerve cells also functioned well, as seen by better balance on a rotating rod test in the rats given blueberry extract than the controls.

"These findings provide support for the potential of dietary phytochemicals as an easily administered and well-tolerated therapy that can be used to improve the effectiveness of dopamine neuron replacement," the authors wrote.²⁵

WHAT YOU NEED TO KNOW: BLUEBERRIES

- Compounds in blueberries known as flavonoids, especially the anthocyanins, have antioxidant and anti-inflammatory properties, giving them great potential to fight aging, Alzheimer's disease, and other chronic ailments.
- Blueberries appear to protect cells from a wide range of injuries by exerting potent antioxidant and anti-inflammatory effects to directly change oxidative and inflammatory stress-signaling pathways.
- In animal studies, a blueberry-enriched diet has been shown to protect against loss of brain cells seen with different types of brain injury and aging, as well as against associated impairments in memory, learning, and coordination.
- Blueberry supplementation is also associated with growth of new nerve cells, and with better communication between existing nerve cells through the process known as signal transduction.
- Anthocyanins in blueberries enter the brains of supplemented animals, where they lodge in the striatum, a specific area controlling certain types of memory and motor function. The striatum is also predominantly involved in Parkinson's disease.
- Population studies in humans suggest that diets high in fruit and vegetables—particularly those of dark color, such as blueberries—may protect against oxidative stress, Alzheimer's disease, and other chronic conditions.
- Experts interviewed by Life Extension highly recommend consumption of blueberries as part of a healthy lifestyle program.

HUMAN STUDIES WITH BLUEBERRIES

In human volunteers, studies have shown that polyphenols and antioxidants in blueberry juice are easily absorbed and result in increased blood levels.²⁶

Testing blood samples of these volunteers showed that drinking a blueberry-apple juice cocktail for four weeks resulted in 20% protection against chemical damage to the DNA in white blood cells. Individuals with certain genetic variations were more likely than others to show this protective effect.

In other research, it is known that antioxidant capacity in the blood normally decreases after a heavy meal because metabolizing the food increases free radicals. However, studies in healthy volunteers have shown that eating blueberries increases the level of antioxidant capacity in the blood. Eating high-antioxidant foods, such as blueberries, with each meal as part of a healthy diet is therefore a tasty antidote to prevent periods of oxidative stress that ordinarily follow eating.¹²

BLUEBERRIES FOR LIFE

“If I told you to take a certain drug, or to have a certain procedure, without knowing whether or not it’s been tested fully in people and found not to be harmful, I’d be very remiss in doing that, but I have no trouble recommending that someone eat berries or add foods with a lot of antioxidants to their diet,” Dr. Joseph concluded. “There is a lot of data out there which suggests that people who eat a diet high in fruits and vegetables are less likely to develop some of the diseases that occur in aging. It’s like your mother said: eat your fruits and veggies—they’re good for you.” •

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

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