





Your Brain on **Blueberries**

Chemical compounds common to berries, tofu, tea and other foods can shore up memory and boost brainpower

By Mary Franz

What is blue, sweet and juicy and may help ward off those nagging memory lapses? If you guessed blueberries, you would be right. Americans apparently cannot get enough of the delicious fruit. In 2008, the latest year that data are available, per capita blueberry consumption in the U.S. reached an all-time high of 12.3 ounces, roughly the size of one standard supermarket carton—an increase from 9.2 ounces in 2007. Whether we are eating more blueberries because they are good for us or just taste good is anyone's guess, but now there is even more reason to load up the shopping cart with plump *Vaccinium cyanococcus*: they may protect our brain.

Emerging research suggests that compounds in blueberries known as flavonoids may improve memory, learning and general cognitive function, including reasoning skills, decision making, verbal comprehension and numerical ability. In addition, studies comparing dietary habits with cognitive function in adults hint that consuming flavonoids may help slow the decline in mental facility that is often seen with aging and might even provide protection against

disorders such as Alzheimer's and Parkinson's.

Researchers once assumed that flavonoids worked in the brain as they do in the body—as antioxidants that protect cells from damage caused by ubiquitous unstable molecules known as free radicals. Now, however, new research demonstrates that the power of flavonoids to bolster cognition results mainly from interactions between flavonoids and proteins integral to brain-cell structure and function.

To date, scientists have identified more than 6,000 different flavonoids, which come in a variety of types [see table on page 57]. These compounds are widely distributed in fruits and vegetables, cereal grains, cocoa, soy foods, tea and wine. Thus, overdosing on blueberries alone is not necessary to keep your mind in good shape.

Memorable Diets

As powerful antioxidants, flavonoids protect us from the cellular damage caused by free radicals, which are formed by our bodies during metabolism, and are also spawned by pollution, cigarette smoke and radiation. As a result, researchers have for decades investigated the potential of these compounds

for boosting immunity, staving off cancer and reducing excess inflammation; flavonoids also appear to help regulate blood flow and blood pressure.

About 15 years ago chemist Ronald Prior and the late neuroscientist James Joseph of the Department of Agriculture's Agricultural Research Service were measuring the antioxidant, disease-fighting potential of various foods when Joseph heard about preliminary data hinting that people who ate modest amounts of fruits and vegetables performed better on cognitive tests than those who consumed little or none of these foods. The researchers were intrigued and wanted to test the idea that an antioxidant-rich diet might improve brain function.

Prior and Joseph fed chow enriched with extracts

meals was responsible for the animals' superior performance. Noting that all the test foods were rich in flavonoids, Prior and Joseph speculated that these compounds might be behind the cerebral tune-up.

Meanwhile studies of humans were also indicating that eating meals full of flavonoids might have cognitive benefits. In a study published in 2007 epidemiologist Luc Letenneur and his colleagues at INSERM in France asked 1,640 cognitively healthy older adults to fill out a questionnaire about their dietary habits and take a test of their cognitive function. They followed the subjects for 10 years, repeating the questionnaire and test four times during that decade. At each testing period, the investigators quantified the subjects' consumption of five

Those who regularly consumed wine, tea and chocolate lowered their risk of a poor cognitive score by 70 percent.

of strawberry, spinach or blueberries to 19-month-old, middle-aged rats for eight weeks, equivalent to about a decade in the human life span. At the end of the eight weeks the now aging rats fed regular food did significantly worse on learning and motor skills such as walking elevated planks, climbing poles, balancing on rotating rods and swimming through mazes, reflecting normal mental decline. In contrast, rats eating the supplemented diet performed *better* at these tasks than they had at the start of the study. (The rats fed the blueberry helpings got an extra boost in motor function; for reasons that remain unclear, they were much more adept than even the rats eating strawberries and spinach at maintaining their balance in the plank and rod tests.)

This was an "aha!" moment for the scientists: something in the fruit- and vegetable-enriched

different flavonoids and correlated those amounts with their cognitive test scores, controlling for other health habits known to affect cognition such as exercise, smoking and obesity.

Subjects with the highest levels of flavonoid intake at the start of the study also performed best on thinking skills such as the ability to do simple arithmetic, recall items in different categories, repeat words and phrases, and identify time and place. In addition, their performance on such tests tended to be more stable over time than that of individuals whose diets included very low levels of flavonoids, whose thinking skills tended to decline over time. Those with the best scores in this study were eating between 18 and 37 milligrams of flavonoids a day, which translates to about 15 blueberries, a quarter of a cup of orange juice and half a cup of tofu.

Other studies correlating flavonoid intake with cognition have hinted at benefits from particular flavonoid-rich foods. In an investigation published in 2009 a research team led by nutritionist Eha Nurk at the University of Oslo in Norway asked 2,000 adults in their early 70s to fill out food-frequency questionnaires and then tested them on measures of mental agility such as their memory of events in their lives, speed at naming objects, and ability to quickly come up with words beginning with a particular letter of the alphabet. Individuals who reported that they regularly consumed wine, tea and chocolate—which are especially rich in flavonoids—performed significantly better on these cognitive dimensions than those who consumed these items only rarely. The adults who did not con-

FAST FACTS

Fruit for Thought

- 1>> Compounds in blueberries known as flavonoids may improve memory, learning and general cognitive function—and could slow age-related decline in mental function.
- 2>> Scientists have identified more than 6,000 different flavonoids. These chemicals are widely distributed in fruits and vegetables, cereal grains, cocoa, soy foods, tea and wine.
- 3>> Researchers now believe flavonoids affect cognition by interacting with proteins that are integral to brain-cell structure and function.

Flavors of Flavonoids

Scientists have discovered thousands of different flavonoids, chemical compounds that may lead to improved memory, thinking and coordination. These compounds are known as polyphenols because they contain multiple “rings,” each of which is attached to an alcohol (OH) group. Flavonoids come in several flavors, or subgroups, the most widely studied of which, along with their most common food sources, appear in the table.

Flavonoid Group	Example Compounds	Food Sources
Flavonols	Quercetin, kaempferol	Spinach, peppers and onions
Flavones	Luteolin, apigenin	Parsley and celery
Flavanones	Eriodictyol, hesperetin	Citrus fruits
Flavanols	Catechin, epicatechin	Tea, cocoa and wine
Anthocyanidins	Cyanidin, peonidin	Berries, grapes and wine
Isoflavones	Genistein, daidzein	Soy foods such as tofu



Tea contains compounds called flavonoids that studies suggest are active in the brain. Flavonoids, which are also present in many fruits and vegetables, can improve our memory and thinking skills.

sume any wine, tea or chocolate scored worst of all. Individuals who reported drinking wine regularly (but in moderation) had about a 45 percent lower risk of poor cognitive performance, defined as a score in the lowest 10th percentile on the test. The corresponding benefit for tea or chocolate was a 10 to 20 percent diminished risk. Those who regularly consumed all three items decreased their chances of a poor score by 70 percent.

Soy, Pine Bark and Cocoa

In addition to associating flavonoid consumption with improved cognition, researchers in recent years have tested the effects of adding flavonoids to people’s diets, the rough human equivalent of the work with rats. Although it is hard to control people’s base diets—humans are not all eating the same chow—adding flavonoids to your diet might preserve or improve memory, thought processing and other cognitive capacities. In 2009 nutrition re-

searcher Anna Macready and her colleagues at the University of Reading in England published a review of 15 small dietary intervention trials in which researchers tested this thesis by asking people to add flavonoid-containing foods to their meals. The flavonoids came from either soy products, supplements (*Ginkgo biloba* or pine bark extract) or, in one case, a beverage containing cocoa.

Although interpretation of the findings was complicated by inconsistencies in the types of cognitive testing, the authors concluded that flavonoid consumption from any of the sources examined improved aspects of cognition such as verbal comprehension, simple reasoning and decision making, object recall, and recognition of numerical patterns. Flavonoids also seemed to hone fine motor skills such as finger tapping. Consuming the equivalent of about one and a half cups of tofu or two and a half cups of soy milk a day was enough to produce the improvement, as was taking 120 mg (one to two capsules) of ginkgo, 150 mg (about three capsules) a day of pine bark extract or 172 mg of flavonoids from the cocoa drink. The latter is equivalent to about seven 1.5-ounce squares of dark chocolate.

Among flavonoid-containing foods, our beloved blueberries may provide particularly strong protection for the human brain. In a study published in 2010 psychiatry researcher Robert Krikorian of the University of Cincinnati and his colleagues gave memory tests to nine adults older than 75 who had mild memory loss. The participants then drank two cups of wild blueberry juice (simi-

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Parsley, Sage, Rosemary and Thyme

We can spice up our minds not only by choosing which foods we eat but also by seasoning our savory dishes in specific ways. Spices and herbs, including sage, oregano and thyme, are chock-full of brain-boosting compounds called flavonoids, and recent research suggests that these compounds may have powers over our mood as well as our mental faculties.

After ingesting the oil of common sage and Spanish sage, people immediately perform better on tests of word recall as compared with those who took a placebo, several studies have shown. Individuals who swallowed a capsule containing sage oil also report increases in their alertness, calmness and contentedness. Now psychologists at Northumbria University in Newcastle, England, have found that simply smelling the extract of sage can reproduce some of these effects. In July 2010 the researchers reported that people who took a computerized battery of tests in a room infused with the aroma of common sage demonstrated, on average, a more accurate memory than people who took the same tests in an unscented room. They also reported feeling more alert.

These and other studies of sage have employed the essential oil, a concentrated extract from the plant used for aromatherapy, rather than the familiar dried or fresh sage leaves used in cooking. Yet researchers believe that eating sage regularly in its leaf form may produce similar, albeit milder, memory-enhancing effects.

These studies did not attempt to pin down which component of the plant was responsible for the memory effects, but flavonoids very likely play a role. Sage is high in hispidulin, a flavonoid that has been shown in cell culture studies to interact with brain cell receptors for gamma-aminobutyric acid (GABA), a neurotransmitter that affects cognition and mood.

Flavonoids from spices other than sage can also produce observable changes in mood, at least in rodents. In June 2010 pharmacologists at Federal University of Ceará in Fortaleza, Brazil, reported that the flavonoid carvacrol, which makes up the bulk of oregano and thyme oils, has an antidepressant effect in mice. After drinking a solution of dissolved carvacrol, the rodents tried harder to escape from a swimming tub—an experimental setup used to assess depression in the animals.



By blocking different chemical pathways in the brains of the mice, the researchers showed that carvacrol's effects depend on its interaction with dopamine, a neurotransmitter known best for governing feelings of reward. It is unclear whether eating small amounts of oregano and thyme would boost mood, but the scientists hope that isolating and studying carvacrol could lead to new antidepressant drugs.

Beyond herbs familiar in the kitchen, many traditional medicinal herbs contain flavonoids that seem to have a protective effect on the brain. One such herb is *Epimedium brevicornum Maxim*, better known in the U.S. by its unfortunate nickname: "horny goat weed." In November 2010 microbiologists at the Korea Institute of Science and Technology and at Peking University in Beijing showed that rats with the rodent equivalent of Alzheimer's disease, marked by protein clumps in the brain, learn and remember better if their chow is supplemented with the most prominent flavonoid in horny goat weed: icariin. This compound apparently prevents the clumps from causing brain cells to commit suicide—suggesting that icariin might one day be useful as a treatment for Alzheimer's. —Karen Schrock

lar to about five cups of blueberries) every day for 12 weeks, after which they received a repeat test on their ability to recall words and pairs of objects. The blueberry drinkers performed about 30 percent better on average than did a comparison group of seven elderly adults who drank a flavonoid-free, sweetened beverage resembling blueberry juice. Despite the small sample size, the trial strongly suggested that adding blueberries to your diet can

boost your memory, at least if you are older, Krikorian says. He also speculates that regular blueberry consumption may stave off the cognitive decline that often comes with aging.

Brain-Cell Snacks

How might flavonoids influence cognition? By examining brain tissue from rats that ingested flavonoid-containing foods, researchers have shown

within the past decade that some classes of flavonoids cross into the brain from the blood. Once in the brain, the compounds could influence cognition by acting as antioxidants, but recently scientists have questioned this theory. Data suggest that flavonoids are present in the brain in much smaller quantities than other antioxidants, such as vitamin C. Thus, compounds other than flavonoids are likely to be doing the bulk of free-radical scavenging there. Instead scientists have found that flavonoids change the chemistry of neurons in other ways.

Joseph and his colleagues discovered early on that four-month-old juvenile mice fed blueberry-enriched chow for eight months displayed higher levels of enzymes called kinases in their brain cells than did those who ate the standard chow. Although scientists do not know how flavonoids might spur kinase production, many types of kinases are essential to learning and memory; thus the additional enzyme could help boost cognition.

More recently, Jeremy Spenser, a nutritional biochemist at Reading, has outlined ways in which flavonoids may influence the actions of proteins critical to thought. Flavonoids may, for example, help to regulate the activity of kinases as well as that of enzymes called phosphatases; the correct balance of these is critical for maintaining the integrity of the synapses, or junctions, between neurons and thereby sustaining normal patterns of brain-cell activity.

Soy isoflavones may improve memory by acting like weak estrogens, binding to and stimulating estrogen receptors on neurons. Exciting these receptors is known to trigger changes in both neuronal shape and chemistry in the hippocampus, a structure involved in memory and whose function most likely diminishes with age. These changes may facilitate communication between neurons and thereby improve memory. Some flavonoids may even spur the growth of new nerve cells in the hippocampus.

Flavonoids may even defend neurons from damage and death and so combat neurodegenerative diseases such as Alzheimer's and Parkinson's. Animal and cell culture data suggest that flavonoids may ameliorate the effects of neurotoxins such as glutamate—a neurotransmitter that at high concentrations damages neurons—by preventing these toxins from binding to their receptors on neurons. Flavonoids also may oppose the action of enzymes called secretases that are involved in the destruction of nerve cells and that may be elevated in neurodegenerative disorders.

In the future, imaging technologies such as functional magnetic resonance may enable researchers



to see how consuming flavonoids alters brain activity in real time. For example, in a study published in 2006 researchers used fMRI to detect increased cerebral blood flow during a letter-digit matching test in subjects consuming a flavonoid-rich cocoa drink. Such findings may guide the development of dietary interventions for reversing or preventing cognitive decline.

The science does not yet reveal which flavonoid-containing foods have the greatest potential for enhancing learning and memory. But eating flavonoid-rich foods is probably better than taking supplements. Processing may destroy or reduce the actual flavonoid content of supplements, and intact fruits and vegetables are likely to contain the amounts and combinations of these compounds that are most beneficial to the brain. Following the current USDA dietary guidelines—which call for eating two cups of fruit and two and a half cups of vegetables every day—will ensure that you get a generous variety of these health-bestowing compounds. Indeed, taking such advice just might help you remember where you put your car keys. **M**

Mind-boosting flavonoids, which are found in wine and blueberries, among other foods, are thought to stave off the decline in cognition that often accompanies aging.

(Further Reading)

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