



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Blueberries

Evidence Summary

Blueberries are a good addition to a healthy diet with some benefits, but they are probably not going to provide a noticeable cognitive change on their own.

Neuroprotective Benefit: Blueberries are a good addition to an otherwise healthy diet but are unlikely to have a large cognitive benefit on their own.

Aging and related health concerns: Similar to its neuroprotective effects, blueberries are a very good addition to a healthy diet, but blueberry supplementation itself is unlikely to provide a great benefit.

Safety: Blueberries are safe for consumption. There are some concerns of pesticides with high consumption of non-organic blueberries.



What is it?

Blueberries contain many substances that may promote health including vitamin C, procyanidins, flavonols, phenolic acids, and derivatives of stilbenes. However, most benefits are ascribed to their anthocyanin content, which can range from 25-495mg/100g. Anthocyanins give blueberries their dark color and are reported to be antioxidant, anti-inflammatory, antihypertensive, anti-atherosclerotic, antimicrobial, anticancer, and neuroprotective. However, these benefits may primarily come from anthocyanin metabolites as anthocyanin is extensively metabolized and only 2% of the parent compound reaches circulation. Much of it, in fact, is not even absorbed, with a reported 85% reaching the colon. One hypothesis is that blueberries increase beneficial gut microbes *Bifidobacterium* and *Lactobacillus* which may themselves provide health benefits.

Neuroprotective Benefit: Blueberries are a good addition to an otherwise healthy diet but are unlikely to have a large cognitive benefit on their own.

Types of evidence:

- One observational study of blueberry consumption
- One small RCT for cognition in patients with subjective memory impairment
- One small open label study for cognition in patients with subjective memory impairment
- One small RCT for cognition in cognitively healthy elderly
- One RCT for uric acid and lipid levels in patients with MCI
- Many preclinical studies

Human research to suggest prevention of dementia, prevention of cognitive decline, or improved cognitive function?

In 16,000 women over the age of 70, the cognition of those who ate at least one serving of blueberries/week declined less over four years than those who ate less than one serving/month. These results were also seen with other sources of anthocyanins, such as strawberries, but not with other sources of flavonoids, such as tea, apples, onions, and oranges. The blueberry consumers in the highest quintile were about 1.5-2.5 years cognitively younger than the lowest quintile ([Devore et al, 2012](#)). Despite these results, other confounders, such as fish intake (which was greater in the blueberry group) cannot be discounted.

An RCT in 37 cognitively healthy elderly reported that consumption of 12g of blueberry powder twice per day over 3 months slightly improved a couple of aspects cognition but largely did not provide any benefit ([Miller et al, 2017](#)). An RCT in 16 patients with subjective memory impairment reported that 16



weeks of 148g blueberry powder/day (vs. a blueberry-flavored placebo powder) had no significant effects on cognition (though there was a trend for benefits in some measures) but increased BOLD activation (indicative of brain usage) in a many brain regions ([Boespflug et al, 2017](#)). In an open label study in 9 patients with subjective memory impairment, 6-gml/kg per day of wild blueberry juice slightly improved cognition from baseline ([Krikorian et al, 2010](#)). In a final study in patients with MCI, 35g of blueberry powder (equivalent to 2 cups of fresh blueberries) each day over 6 months did not change uric acid levels after 6-12 months, but in women decreased triglycerides, total cholesterol and HDL-c ([Cheatham et al, 2016](#)).

Human research to suggest benefits to patients with dementia:

None.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

In aged rats, 8 weeks of blueberry supplementation was reported to improve cognition and motor performance, increase neurogenesis, increase IGF-1 and IGF-1R, increase ERK1/2, increase dopamine release from brain slices, and increase levels of HSP90 (a chaperone protein). Blueberry supplementation increased levels of anthocyanins throughout the brain ([Joseph et al, 1999](#); [Andreas-Lacueva et al, 2005](#); [Shukitt-Hale et al, 2015](#); [Casadesus et al, 2004](#); [Shukitt-Hale et al, 2005](#)).

In an Alzheimer's mouse model, 8 weeks of blueberry supplementation improved cognition and increased ERK signaling in the hippocampus but did not change levels of amyloid beta ([Joseph et al, 2003](#)). Other studies in aged mice or in mouse models of accelerated aging suggest that blueberry supplementation may improve cognition, reduce lipid peroxidation, increase glutathione levels, increase SOD levels (another antioxidant protein), and decrease acetylcholinesterase activity ([Papandreou et al, 2009](#); [Tan et al, 2014](#); [Beracochea et al, 2016](#)). *In vitro* studies suggest that blueberry may be anti-inflammatory and neuroprotective ([Zhu et al, 2008](#); [Brewer et al, 2010](#)).

APOE4 interactions:

None reported

Aging and related health concerns: Similar to its neuroprotective effects, blueberries are a very good addition to a healthy diet, but blueberry supplementation itself is unlikely to provide a great benefit.

Types of evidence:

- One C. elegans, fly, rat, and mouse study on longevity
- An observational study on myocardial infarction
- Multiple small RCTs and cross-over trials on cardiovascular disease (CVD), metabolic, and inflammatory biomarkers

Longevity

Blueberry polyphenols increased mean and max lifespan of worms at standard (but not lower) temperatures by 28% and 14%, respectively. It also improved measures of healthspan (pharynx contraction) and reduced cellular damage ([Wilson et al, 2006](#)). Blueberry extract decreased lipid peroxidation and cataract morbidity in a rat model of accelerated aging ([Kolossova et al, 2004](#)). It extended mean lifespan (10%), but not max, in flies and increased anti-oxidant proteins ([Peng et al, 2012](#)). It had no effect on lifespan in male mice when started at 12 months ([Spindler et al, 2013](#)).

Other studies

In an observational study of 93,600 women over 18 years, those in the highest quintile of anthocyanin intake had a reduced risk for myocardial infarction than those in the lowest (HR 0.68; 95%CI 0.49-0.96) ([Cassidy et al, 2013](#)). Other studies looking at blueberry consumption and CVD or metabolic biomarkers are small (<50) and have mixed results. In post-menopausal women with stage 1 hypertension, 22g of blueberry powder/day over 8 weeks reduced blood pressure, pulse wave velocity, and nitric oxide levels but not markers of oxidative DNA damage ([Johnson et al, 2017](#); [Johnson et al, 2015](#)). In contrast, 6 weeks blueberry consumption in adults with metabolic syndrome reported no change in blood pressure or insulin sensitivity but improved endothelial function ([Stull et al, 2015](#)). This contrasts another study by the same researchers in obese, insulin resistant patients that reported an improvement in insulin sensitivity with no improvement in inflammatory biomarkers ([Stull et al, 2010](#)).

Other studies have reported modest improvements in blood pressure from baseline (~3mm/Hg) from baseline and a measure of arterial stiffness in sedentary individuals ([McAnulty et al, 2014](#)), blood pressure (~5% change) in patients with metabolic syndrome ([Basu et al, 2010](#)), improved anti-oxidant capacity of plasma serum in patients with metabolic syndrome or CVD risk factors ([Basu et al, 2010](#); [Riso et al, 2013](#)), and improved gait speed in older adults ([Schrager et al, 2015](#)). In healthy subjects, blueberry polyphenols was reported to provide an acute improvement of flow-mediated dilation (a measure of endothelial function) ([Rodriguez-Mateos et al, 2013](#)).

Safety: Blueberries are safe for consumption. There are some concerns of pesticides with high consumption of non-organic blueberries.

Blueberry consumption is safe. There are some concerns that blueberries may contain a higher level of residual pesticide than many other fruits ([here](#), [here](#)); however, all fruits and vegetables tested by USDA [were below](#) tolerated levels established by the EPA.

Sources and dosing:

Most of the previous studies used 1-2 cups of blueberry/day (or the powdered equivalent 20-40g/day). One study reported benefits in plasma antioxidant capacity with only 35g of blueberry/day. 1 cup of blueberries is roughly 150g.

Research underway:

Nine blueberry clinical trials are currently recruiting ([here](#)), most for metabolic diseases. One study is testing cognition in middle aged overweight individuals with subjective memory complaints ([NCT02751866](#)).

Search terms:

Pubmed:

- blueberry + alzheimer, cognition, aging, lifespan, apoe, cardiovascular, neuropathy, hypotension, observational, safety, pesticide

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit [Cognitive Vitality's Rating page](#).