Published by advancesin@www.advancersin.org

Chronic Diseases Prevention Review, 2025, Vol. 9, No.34

Online ISSN: 2158-0820
Advancersin Open Access Journals

RESEARCH ARTICLE

Title: Do Dietary Blueberries Delay Aging-Induced Cognitive Function?

Yang Zhang[1], Hongwei Si[1*]

ARTICLE HISTORY

Received: 05-Oct-2025
Revised: 09-Nov-2025
Accepted: 10-Dec-2025
DOI: 10.54762/cdpr2025-34.1-10

Abstract: Aging is accompanied by progressive declines in cognitive function and increased neurodegenerative diseases, mainly caused by oxidative stress, neuroinflammation, mitochondrial dysfunction, and impaired synaptic plasticity. Dietary interventions have been shown to be low-risk strategies to slow brain aging, with blueberries standing out for their high levels of phytochemicals, such as anthocyanins and other polyphenols, and their high antioxidant capacity. This mini review summarizes the anti-aging and anti-brain aging effects of blueberries across cellular, animal, and human studies, particularly emphasizing different types of blueberries, including wild (lowbush), northern highbush, southern highbush, rabbiteye, and half-high. The mechanisms of these anti-brain-aging effects of blueberries were summarized at the cellular level, reducing age-related oxidative stress and chronic inflammation, and at the molecular level, modulating multiple key signaling pathways, such as Nrf2, MAPK, and sirtuin-related pathways. Current issues and future studies on this topic are also outlined, such as the lack of comparative studies across blueberry types, various forms of blueberry supplements, insufficient dose-response investigations, and inconsistent intervention periods. All these limitations result in inconsistent, even controversial, conclusions on the blueberry's anti-brain-aging effects. Overall, current evidence supports the potential of dietary blueberries to promote healthy brain aging and to be a promising dietary strategy for cognitive resilience, although more comprehensive studies are needed.

Keywords: Blueberries; Brain aging; Cognitive function; Bioactive compounds; Phytochemicals; Oxidative stress; Neuroprotection; Dietary intervention

*Address correspondence to this author at the Department of Food and Animal Sciences, Tennessee State University, 3500 John A Merritt Blvd, Nashville, TN, 37209, USA hsi@tnstate.edu, 001-615-963-5443

1. Introduction

Aging is an essential factor in cognitive decline and the development of various neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. While the possible physiological and molecular mechanisms of brain aging are debated, a recent study reported that age-disproportionate atrophy (a faster rate of aging than chronological age) of the brain can be a diagnostic marker of neurodegenerative disorders [1]. Therefore, delaying brain aging may be a key approach to reducing the rates of neurodegenerative disorders, particularly as life expectancy worldwide continues to increase.

A healthy diet is one of the five interventions, including physical and cognitive activity, healthy diet, social engagement, and cardiovascular health monitoring that the structured, higher-intensity intervention had a statistically greater benefit on global cognition among older adults at risk of cognitive decline and dementia, the US POINTER randomized clinical trial [2]. Blueberries (*Vaccinium corymbosum*) are a key component of the study's healthy diet, suggesting that dietary intake of blueberries may help maintain brain health.

Indeed, increasing evidence supports the idea that blueberry intake improves brain function because of its unique nutrient and non-nutrient composition [3]. For instance, the high content of anthocyanins and flavonoids contributes to blueberry's high antioxidant activity and anti-inflammatory capacity, and the high levels of oxidants and inflammation are the major causes of brain aging [4]. However, the results of these anti-brain aging studies using blueberries are not consistent, particularly in animals and humans, which may be result from the different dosages, treatment periods, and

cateroies of blueberries, given that there is a big range of the contents of bioactive compounds in blueberry among different types such as wild, low bush, and high bush [5], different forms (fresh, powder and extracts). In this review, we focus on the anti-aging and anti-brain-aging effects and mechanisms of blueberries in cells, animals, and humans. In particular, we pay attention to the different categories of blueberries in all aspects.

2. Brain aging is a complicated process

Brain aging is caused by several interrelated mechanisms that cumulatively damage neuronal function. The primary mechanisms include oxidative stress and mitochondrial dysfunction; neuroinflammation and changes in the immune response; alterations in synaptic plasticity and neurotransmitter imbalance; and protein aggregation and neurodegeneration. As reactive oxygen species (ROS) accumulate in aging cells, neurons experience oxidative damage, leading to mitochondrial dysfunction, reduced energy production, and subsequent effects on neuronal viability and resilience, accelerating functional decline [6]. Aging increases the overactivation of microglial cells, the resident macrophages of the central nervous system, which generate chronic inflammation, disrupt healthy neuronal communication, weaken the blood-brain barrier, and lead to neurodegeneration [7]. Aging also affects synaptic plasticity, reducing brain's capacity to adapt to new information. Several neurotransmitters, such as dopamine, acetylcholine, and serotonin, are reduced, disrupting their corresponding functions related to memory, motivation, and focus [8]. Aggregation of misfolded proteins, such as beta-amyloid and tau, forms plaques and tangles, and can disrupt neural signaling pathways and damage cells, which are signs of Alzheimer's and other neurodegenerative diseases [9]. More research studies have found that gut microbiomes are associated with cognitive aging through communication with systemic inflammation [10].

3. Blueberries are an outstanding source of anti-aging bioactive compounds

There are five main types of blueberries grown in the United States: northern highbush, southern highbush, rabbit eye, lowbush, and half-high, according to the genetic background, growth environment, and features of the plant and fruits [11]. Northern highbush (*Vaccinium corymbosum)* is the most widely cultivated type, growing to 6-7 feet tall and producing high yields. It has good adaptability in colder environments and includes cultivars such as 'Duke', Bluecrop', and 'Liberty'. Southern highbush (*Vaccinium corymbosum hybrids*) is a hybrid of northern highbush and other species, growing in low-chill regions such as Florida and California, and is less cold-tolerant. Cultivars such as 'Emerald' and 'Misty' bloom early, making them susceptible to frost damage. Highbush blueberry cultivars are very different in bioactive compounds and antioxidant capacity, with certain cultivars showing consistently superior phenolic/anthocyanin levels—making them strong candidates for nutritional biofortification [12]. Lowbush blueberries *(Vaccinium angustifolium***)**, often referred to as "Wild blueberries," are much smaller in plant size (about 1 foot tall) and produce small, nutrient-dense berries. These are primarily managed wild stands in Maine and Canada and are often used in frozen blueberry products. Half-High blueberries, a cross between lowbush and northern highbush varieties, grow between 2 and 4 feet tall and are well-suited for extremely cold regions. Examples of these cultivars include 'Northblue' and 'Polaris.' In contrast, rabbiteye blueberries (*Vaccinium virgatum)*, native to the southeastern United States, are tall-growing plants up to 9 feet that require cross-pollination for optimal fruit production. Cultivars such as 'Powderblue' and 'Tifblue' are commonly grown in warmer climates.

Blueberries are called "Super fruit" because of the high levels of phytochemicals, bioactive compounds with health benefits, and nutrients. Blueberries contain five types of phytochemicals, including anthocyanins, phenolic acid, flavonoids, tannins, and stilbenes. Anthocyanins are the most abundant phytochemicals (typically 35%–74% of total content), responsible for the fruit's blue and purple pigments. Major types include malvidin, cyanidin, delphinidin, petunidin, and peonidin. The most common flavonoids include flavanols (such as quercetin, myricetin, and kaempferol) and flavan-3-ols (like catechin and epicatechin). responsible for the deep blue-purple coloration of blueberries, are present in varying amounts across different types. These phytochemicals may exert anti-aging effects via their high antioxidant and anti-inflammatory properties [13]. In addition, blueberries are rich in dietary fiber, vitamins and minerals [14], particularly vitamin C in fresh berries, which supports immune function and skin health. However, the content and list of phytochemicals in blueberry depend on the type, cultivar, growing environment, harvest, as well as the processed forms (fresh, powder, juice or extracts) of blueberry [15-18]. For instance, the total anthocyanin content is 250-

Table 1. Major bioactive compounds levels in five types of blueberries

Component (per 100g FW)	Wild/Low bush	Northern highbush	Southern highbush	Rabbiteye	Half-high	References
Total Phenolics (TPC)	400–600 mg	250–400 mg	200–350 mg	250–450 mg	300–450 mg	[15-17]
Total Anthocyanins (TAC)	250–400 mg	150–250 mg	100–200 mg	150–300 mg	200–300 mg	[15, 17-19]
Epicatechin	12.19 mg	1.26mg	0.62 mg	25.66mg	N/A	[20, 21]
Vitamin C	8-10 mg	10–15 mg	7-12 mg	7-15 mg	9-13 mg	[22-24]
ORAC (Antioxidant capacity)	6,000–9,000 µmol TE	3,500–6,000 µmol TE	3,000–5,000 µmol TE	3,500–6,000 µmol TE	4,000–6,500 µmol TE	[25, 26]

400 mg/100g fresh weight (FW), 150-250 mg/100g FW, 100-200 mg/100g FW, 150-300 mg/100g FW, and 200-300 mg/100g FW, in lowbush, northern highbush, southern highbush, rabbiteye, and half-high, respectively [16, 18-20] (See **Table 1** for the levels of other major phytochemicals, antioxidant capacity etc. of the five types of blueberries) [21-28]. Another example is that the epicatechin content range is wide across different rabbiteye cultivars: 0 mg/100g FW in Premier, 48 mg/100g FW in Woodard, and 129 mg/100g FW in Briteblue [15]. Therefore, the type, cultivar, processed forms, and growing environment should be noted in reporting blueberry health benefits and their phytochemical contents.

4. Dietary interventions: blueberries and aging

4.1 In vitro studies

Blueberry anthocyanin extracts (BAE) protected retinal pigment epithelial cells against the aging process; 0.1 ug/ml of BAE increased cell viability from 14.6% to 76.9% and reduced senescent cells from 92.5% to 58.2% [29]. Blueberry extract (0.1-0.5 mg/ml) can significantly increase the viability (33-53%) and proliferation rates (30%) of hippocampal human neural progenitor cells and was also able to reverse the decreases in viability and proliferation induced by a cellular stressor by 94-140% and 50-90%, respectively [30]. The serum from mice fed blueberries inhibits senescence pathways in osteoblastic cells [31].

4.2 Animal studies

Dietary intake of blueberry polyphenol extracts (67μg/mL, 200 μg/mL) increased the mean lifespan of *Caenorhabditis elegans* by 14% and 28%, as well as improved thermotolerance. These blueberry extracts also increased survival time during 16 hours of heat stress at 35 °C by 2.5-fold, but did not protect against oxidative stressors such as hydrogen peroxide or paraquat [32]. These effects may be mediated by regulating stress resistance and metabolic regulation through the CaMKII signaling pathway. Another study also found that blueberry polyphenol extracts extended yeast lifespan by 28% by activating sirtuin-dependent stress-resistance pathways, which play essential roles in regulating aging and cellular homeostasis [33]. In hypertensive rats, blueberry-enriched diet (2% w/w lyophilized, 371-399 mg/day, equivalent to 4.1 g of fresh blueberries) intakes for 6-12 weeks or 12 weeks reduced systolic and mean arterial pressures (20% compared to controls), decreased total ROS production (65%) and superoxide and peroxynitrite (70-80%) and increased catalase activity (30%) in kidney [34]. Another study found that rats fed with uncategorized blueberries (5% w/w of diet) experienced a 22% increase in median lifespan and improved mitochondrial respiratory chain activity, suggesting that blueberries help with age-related metabolic dysfunction and oxidative tissue damage [35].

4.3 Human studies

A randomized, controlled, double-blind, crossover intervention study reported that 12 weeks of anthocyanin (300 mg/day) supplementation improved endothelial function (12–15%) by increasing nitric oxide bioavailability and reducing arterial stiffness [36]. This improvement in endothelial function further enhanced cerebral blood flow and cognitive performance in adults with vascular risk factors [36]. Similarly, a single dose (222mg) of wild blueberry extract significantly reduced systolic and diastolic blood pressure by 5.6 mmHg and 3.2 mmHg, respectively, and attenuated natural cognitive decline compared to placebo in a healthy older adult population (aged 68-75) [37]. Interestingly, topical application of blueberry extract (100 μg/mL)-containing product on skin (twice daily, 12 weeks) increased in skin hydration (20-30%) and reduced oxidative and inflammatory marker levels, such as 4-hydroxynonenal, heme-oxygenase-1 (HO-1), and cyclooxygenase-2 (COX2) (40-50%) in ex vivo human skin explants [38, 39].

5. Brain interventions: blueberries and brain aging

5.1 In vitro studies

The neuroprotective properties of blueberries have been demonstrated in several approaches. First, blueberry extract (0.1-0.5 mg/ml) increased cell viability (33-53%) and proliferation rates (30%) and reversed the cellular stressor-induced decreases in viability (94-140%) and proliferation (50-90%) in human hippocampal neural progenitor cells [30]. Secondly, nonpolar blueberry extract (5 μg/mL) reduced tumor necrosis factor-α-induced (TNF-α) ROS production in human neuroblastoma cells, suggesting blueberries can reduce inflammation-driven oxidative stress in neural aging. [40]. The third study found that Aβ25-35-induced cytotoxicity, including decreased neuron viability and increased levels of lactate dehydrogenase and ROS, was effectively reversed by protocatechuic acid, the primary metabolite of blueberry extract [41]. Blueberry polyphenols may support brain aging by acting on several key pathways at once. By inhibiting enzymes involved in inflammation, neurotransmitter breakdown and amyloid formation, blueberry could also help preserve neuronal function and slow age-related cognitive decline [42].

5.2 Animal studies

Wild blueberries extract (30 or 60 mg/kg body weight) injection (intraperitoneally, i.p.) in male, 3-4-month-old Balb-c mice for 7 days significantly improved learning and memory (a step-through latency time of 228 ± 38 seconds compared to 101 ± 32 seconds in the control group) [43]. Additionally, both dosage groups reduced brain lipid peroxidation products (by 38% or 79%) and increased brain ascorbic acid levels (by 21% or 64%), indicating that blueberry extract increased brain antioxidant levels. The treatments also significantly decreased acetylcholinesterase (AChE) activity, an enzyme

that functions as a neurotransmitter and has lower levels associated with a healthy brain, suggesting that the cognitive improvements from blueberry extracts were mediated by increasing antioxidant activity and inhibiting AChE [43]. Aged rats fed with a blueberry-enriched diet (2% by weight for 8 weeks) had improved spatial memory retention for 30% in Morris water maze tests via reduced neuroinflammation, enhanced synaptic plasticity, and increased brain-derived neurotrophic factor signaling in hippocampal regions [44]. Contextual memory improved with both wild bluberry spectrum powder and extract, while untreated aged mice at 18 months declined [45]. Three weeks of 2% (w/w) blueberry supplementation improved spatial working memory in aged rats from 57% to 83% accuracy and was associated with increased hippocampal cAMP response element-binding protein (CREB) phosphorylation and brain-derived neurotrophic factor (BDNF), and providing cognitive benefits to neuroplasticity pathways [46]. A 2% blueberry-enriched diet, with a blend of two varieties decreased post-traumatic stress disorder (PTSD)-like neuroinflammation in rats by reducing hippocampal inflammatory cytokins and microglial activation, indicating anti-inflammatory neuroprotection [47]. Aged rats fed a 2% (w/w) blueberry-supplemented diet for 4 months showed restored object-recognition memory to young rats and had significantly lower nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) protein levels in 4 of 5 brain regions, correlating with better memory performance [48]. A 2% blueberry-supplemented diet resulted in the presence of anthocyanins within the brains of aged rats and was associated with improved memory performance, supporting a direct role of blueberry polyphenols in mechanisms relevant to brain aging [49]. Supplementation of a high-fat diet with 4% freeze-dried blueberry powder in middle-aged mice prevented diet-induced cognitive impairment, resulting in significant improvements in object recognition memory and spatial learning performance, bringing outcomes close to those observed in control diet–fed animals [50].

5.3 Human studies

A randomized, double-blinded, placebo-controlled study evaluated the effects of blueberry supplementation (1.0g/day, 12 weeks, n=23) on cognitive function in older patients with mild cognitive impairment. The results found that blueberry supplementation significantly improved several cognitive domains, including total cognitive aptitude test scores, spatial imagery efficiency, working memory, and recognition memory [51]. A similar study showed that older adults who consumed 1 cup (148 g fresh) of blueberries (50%:50% mixture of rabbiteye and northern highbush blueberry (*V. ashei Reade* 'Tifblue' and *V corymbosum* Rubel) per day for 12 weeks had a 16% improvement in memory accuracy and an increased activation in brain regions linked to executive function and memory consolidation, such as the prefrontal cortex and hippocampus [52]. A single dose (30g) of freeze-dried wild blueberry supplementation boosted executive function by 8-12% overall in 7-10-year-old children across several varieties of cognitive tasks compared to placebo [53]. A 6-month, double blinded RCT showed that 35g per day of freeze-dried wild blueberry powder significantly improved speed by decreased latency of 65ms on cognitive processing in adults with mild cognitive decline compared with placebo [54]. Healthy older adults consumed 30mL/day concentrated blueberry juice [55] or 444-621mL/day of wild blueberry juice [56] for 12 weeks showed increased resting brain perfusion and greater task-related brain activation and improved working memory compared to placebo. Supplementation with a phenolic-rich rabbiteye blueberry preparation in healthy older adults was associated with measurable improvements in cognitive performance, and these benefits were linked to circulating blueberry-derived phenolic metabolites, suggesting a direct contribution of blueberry bioactive to cognitive function during aging [57].

6. Mechanisms of anti-brain aging effects of blueberries

6.1 Cellular level

It is well known that aging results from cumulative damage to cellular components (DNA, proteins, lipids) by ROS, with mitochondria being both a primary source and a target of ROS. The brain is especially vulnerable due to its high oxygen consumption, lipid-rich content, and limited antioxidant defenses, which can damage neurons and promote inflammation [6, 58]. Blueberry phytochemicals, such as anthocyanins and phenolic acids, can directly scavenge ROS by donating hydrogen atoms or electrons and neutralize superoxide anion, hydroxyl radicals, and hydrogen peroxide. These chemicals also enhance endogenous antioxidant defenses, including superoxide dismutase, catalase, glutathione peroxidase, and heme oxygenase-1. For instance, anthocyanins decreased ROS levels, ROS-producing enzyme, malondialdehyde, and overall antioxidant enzyme expression and activity in HUVECs and HepG2 cells [59]. Polyphenols in wild blueberry (lowbush) extracts have anti-aging effects, partly by fighting ROS formation [60]. Blood biomarker studies show people with higher levels of specific antioxidants and fatty acids have "younger" brain structure and function [61]. On the other hand, increased resistance to oxidative stress contributes to extended lifespan in C. elegans [62].

Chronic inflammation is now recognized as a central driver of brain aging, accelerating cognitive decline and increasing the risk for neurodegenerative diseases. It is not just a consequence of aging but an active contributor to the pathological process [63]. There are four possible mechanisms: 1) Chronic activation of the brain's immune cells (microglia & astrocytes) leads to excessive release of toxic inflammatory chemicals; 2) Inflammation and oxidative stress form a vicious cycle; 3) Inflammatory chemicals can damage blood vessels and the brain's white matter; 4) Dysfunctional immune cells fail to properly clear toxic protein aggregates like amyloid-β and tau, hallmarks of Alzheimer's disease. The anti-inflammatory effects of blueberries worked through all four approaches [13]. For example, a 2% blueberry diet decreased microglial activation and astrogliosis in intraocular hippocampal grafts to middle-aged rats [64]. Blueberries exert antioxidant effects by directly scavenging ROS,

increasing SOD activity, and decreasing ROS production [59, 60, 65], as aforementioned. Blueberry extract neutralizes amyloid Aβ25-35-induced cytotoxicity [28] and reduces amyloid formation [42]. Wild blueberry extract significantly improved vascular function and attenuated natural cognitive decline compared to placebo in a healthy older adult population [37].

6.2 Molecular level

Nuclear factor erythroid 2-related factor 2 (Nrf2) plays a vital role in the balance of oxidants/antioxidants and in chronic inflammation, and its expression and activity are attenuated with aging. Blueberries can increase the mRNA levels of Nrf2 and the translocation to the nucleus of Nrf2, regulate its downstream molecules HO-1, NQO1, SOD, and finally mitigate oxidative stress and chronic inflammation in diabetic rats [66], human vascular endothelial cells [67], and aging rats [68]. The molecular antioxidant effects of rabbiteye blueberry anthocyanins are consistent with activation of the NRF2–ARE signaling pathway, leading to enhanced expression of endogenous antioxidant enzymes and reduced oxidative damage [69].

The mitogen-activated protein kinase (MAPK) pathway plays essential roles in regulating chronic inflammation, redox signaling, apoptosis, and stress responses. Under oxidative stress, aberrant activation of MAPKs, such as extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38, leads to cellular dysfunction and tissue injury [18, 52, 70, 71]. Blueberry extracts reversed amyloid-β (Aβ42, 25 μM) or lipopolysaccharide-induced ROS by downregulating MAPK phosphorylation in primary hippocampal neuronal cells [72]. Furthermore, blueberries strengthen cellular antioxidant capacity through MAPK-Nrf2 cross-talk in human aortic endothelial cells [25].

NF-kB pathway is a major driver of neuroinflammation and oxidative stress. The anti-inflammatory effects of blueberries may be mediated by inhibiting NF-κB activity [49], preventing IκB-α degradation and blocking NF-κB translocation to the nucleus [50], and inhibiting NF-κB expression [73]. The suppression of NF-κB reduces inflammatory markers (TNF-α, IL-6), exerts neuroprotective effects, and contributes to healthier brain aging.

Heat shock proteins (HSPs), such as HSP-12, HSP-16, and HSP-70, typically increase in expression as C. elegans ages [74]. It is widely used to dissect conserved mechanisms of aging because its stress-response and proteostasis pathways are evolutionarily preserved. Wild blueberries extract blocked the age-related increase in HSP mRNA levels and extended lifespan in *C. elegans* [32]. In rats, a 10-week blueberry diet completely restored the brain's HSP-70 response to stress in old rats, matching levels seen in young rats and enhancing learning and memory [35].

Telomere biology is a central mechanism in aging, linking telomere length to age-related diseases and mortality. Telomeres are protective DNA-protein complexes at chromosome ends composed of repetitive DNA sequences and sheltering proteins. After incomplete replication, the resulting DNA progressively shortens with each cell division due to lagging-strand DNA synthesis. Telomeric DNA can accelerate attrition after ROS damage due to its high susceptibility. Short telomeres trigger DNA damage responses such as p53/p16 activation, leading to irreversible cell-cycle arrest [21]. Polyphenols from blueberries delay telomere shortening and upregulate telomerase activity via sirtuin 1(SIRT1) activation and the mechanistic target of rapamycin (mTOR) pathway, thereby elongating telomeres and delaying cellular senescence [75].

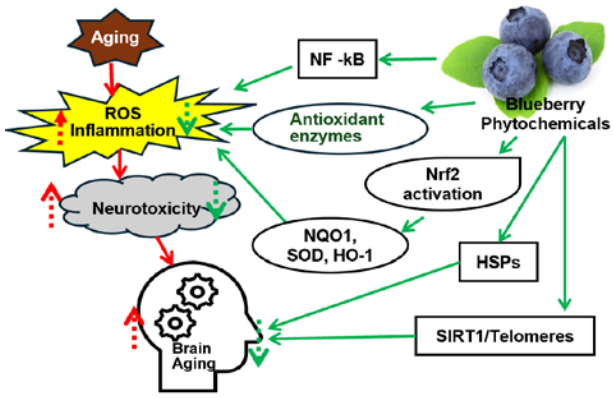

Fig (1). Possible mechanisms of blueberries delay brain aging

7. Current issues and future studies

While increasing studies have demonstrated the anti-brain-aging effects of blueberries via the aforementioned mechanisms, the results of these studies are inconsistent, even controversial, which results from these limitations/issues: **1)** only one type of blueberries was applied. Given that there are five major types of blueberries (northern highbush, southern highbush, rabbiteye, low/wild bush, and half-high) in North America, each type has different levels of phytochemicals, antioxidant capacity, etc. (**Table 1**), which are the primary molecules exerting an anti-brain aging effect. As shown in **Table 2**, wild bush is most applied type (7 out of 20), followed by rabbiteye (4 out of 20); 6 articles did not specify which type of blueberry; and 2 articles used a blend of highbush and rabbiteye. Therefore, it is worth comparing the anti-brain effects among these types of blueberries. **2**) Different forms and dosages of blueberries were used: fresh, freeze-dried powder, whole phenolic extracts, and pure anthocyanins and phenolic acids. For instance, 1 cup (148 g fresh) of blueberries (50%:50% mixture of blueberry cultivars *V. ashei Reade* 'Tifblue' and *V corymbosum* Rubel) per day was consumed by older adults for 12 weeks and resulted in a 16% improvement in memory accuracy [52]. For freeze-dried powder, 15g/day wild blueberry powder in children [53], but 24 g/day rabbiteye blueberries in older adults [53] were used in cognition studies. Wild blueberry extract (30-69mg/kg) has significantly improved cognitive performance [43]. It is hard to know whether these blueberries contain the same or similar

Table 2. Overview of blueberry types in anti-brain aging studies

Blueberry Type	Number of articles	Study Focus	Form Used	Key Findings/Limitations	References
Northern highbush	1 of 20	Single dose on older adults, 2-5 hours	Powder	Improve cognitive function	[71]
Southern highbush	n/a	n/a	n/a	n/a	n/a
Wild (Lowbush)	7 of 20	Cells, mice, rats, children, older adults, hours to 6 months	Powder, extract, or juice	Positive cognitive effects and faster executive functioning time in kids and older adults. Reduced ROS production	[37, 40, 43, 45 53, 54, 56]
Rabbiteye	4 of 20	Neural cells, aged mice, older adults, 3-5 months	Powder and extract	Improvement in cognitive function and memory in mice and older adults. Neuroprotective effects in human cells.	[26, 30, 50, 57
Blended	2 of 20	Rabbiteye and highbush in rats, older adults, 3-5 months	Powder, fresh berries	Decreased PTSD-like neuroinflammation in rats, improvement in memory accuracy, and an increased activation in brain	[47, 52]
Unspecified	6 of 20	Neural cells, rats, healthy older adults, older patients, hours to 16 weeks	Extracts, powder, juice	Improved cognitive, neural function, and memory, increased resting brain perfusion, and task-related brain	[35, 42, 46, 48 49, 51, 55]

amounts of phytochemicals as in these studies. Therefore, a similar number of primary phytochemicals should be used in future studies, regardless of the form of blueberries. **3**) Only a single dose was tested in most studies, especially in animal and human studies For example, only 1g/day of blueberry extracts in elder patient [51], 2% blueberry extract powder diet weight in rats [35] 15g/day wild blueberry freeze-dried powder in children [36], but 24 g/day rabbiteye blueberries freeze-dried powder in older adults [53], there is no comparison with lower or higher dosages on the protective effects, even these studies reported anti-brain aging effects. **4**) There is a big range of intervention periods in different studies. For instance, Wild blueberry extract (30-69mg/kg) on cognitive performance was only for 7 days, even though the results were significant [43]. 1 cup (148 g) of fresh blueberries per day was consumed by older adults for 12 weeks, resulting in a 16% improvement in memory accuracy [52]. Aged rats fed with a blueberry-enriched diet (2% by weight for 8 weeks) had improved spatial memory retention for 30% in Morris water maze tests [44]. In summary, all these factors, such as type, form, dosage, and intervention period, should be considered in future anti-brain-aging studies, given that neurodegenerative processes and aging occur gradually over time and that phytochemical levels vary among different types of blueberries.

LIST OF ABBREVIATIONS

AChE, acetylcholinesterase; BAE, Blueberry anthocyanin extracts; BDNF, phosphorylation and brain-derived neurotrophic factor; COX2, cyclooxygenase-2; CREB, cAMP response element-binding protein; ERK, extracellular signal-regulated kinase; FW, fresh weight; HO-1, heme-oxygenase-1; HSPs, heat shock proteins; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B; Nrf-2, Nuclear factor erythroid 2-related factor 2; PTSD, post-traumatic stress disorder; ROS, reactive oxygen species; SIRT1, sirtuin 1; mTOR, mechanistic target of rapamycin; TNF-α, tumor necrosis factor-α.

FUNDING

This work was funded by the National Science Foundation (grant number 2200536) to Hongwei Si.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

Hongwei Si: Conceptualization, writing, review & editing, funding acquisition, and project administration; **Yang Zhang**: writing—original draft preparation and data collection. All authors have read and agreed to the published version of the manuscript.

ReferencesLiterature Cited

1. Yoshinaga K, Matsushima T, Abe M, Takamura T, Togo H, Wakasugi N, Sawamoto N, Murai T, Mizuno T, Matsuoka T *et al*: **Age-disproportionate atrophy in Alzheimer's disease and Parkinson's disease spectra**. *Alzheimers Dement (Amst)* 2025, **17**(1):e70048.
2. Baker LD, Espeland MA, Whitmer RA, Snyder HM, Leng X, Lovato L, Papp KV, Yu M, Kivipelto M, Alexander AS *et al*: **Structured vs Self-Guided Multidomain Lifestyle Interventions for Global Cognitive Function: The US POINTER Randomized Clinical Trial**. *JAMA* 2025, **334**(8):681-691.
3. Giacalone M, Di Sacco F, Traupe I, Topini R, Forfori F, Giunta F: **Antioxidant and neuroprotective properties of blueberry polyphenols: a critical review**. *Nutr Neurosci* 2011, **14**(3):119-125.
4. Melzer TM, Manosso LM, Yau S-y, Gil-Mohapel J, Brocardo PS: **In pursuit of healthy aging: effects of nutrition on brain function**. *International journal of molecular sciences* 2021, **22**(9):5026.

5. Hislop LM, Luby CH, Loarca J, Humann J, Hummer KE, Bassil N, Zhao D, Sheehan MJ, Casa AM, Billings GT: **A Blueberry (Vaccinium L.) Crop Ontology to Enable Standardized Phenotyping for Blueberry Breeding and Research**. *HortScience* 2024, **59**(10):1433-1442.
6. Turrens JF: **Mitochondrial formation of reactive oxygen species**. *The Journal of physiology* 2003, **552**(2):335-344.
7. Muzio L, Viotti A, Martino G: **Microglia in neuroinflammation and neurodegeneration: from understanding to therapy**. *Frontiers in neuroscience* 2021, **15**:742065.
8. Dai H, Niu L, Peng L, Li Q, Zhang J, Chen K, Wang X, Huang R, Lee TMC, Zhang R: **Accelerated brain aging in patients with major depressive disorder and its neurogenetic basis: evidence from neurotransmitters and gene expression profiles**. *Psychol Med* 2025, **55**:e71.
9. Rajmohan R, Reddy PH: **Amyloid-beta and phosphorylated tau accumulations cause abnormalities at synapses of Alzheimer's disease neurons**. *Journal of Alzheimer's Disease* 2017, **57**(4):975-999.
10. Hoffman JD, Parikh I, Green SJ, Chlipala G, Mohney RP, Keaton M, Bauer B, Hartz AM, Lin A-L: **Age drives distortion of brain metabolic, vascular and cognitive functions, and the gut microbiome**. *Frontiers in aging neuroscience* 2017, **9**:298.
11. Strik BC: **Growing blueberries in your home garden**: Oregon State University, Extension Service; 2008.
12. Akbari A, Xu Y, Wei X, Liu Z, Ergün D, Akgöl C, Dong F, Ercişli S, Kafkas S, Liu C: **Bioactive and antioxidant properties in highbush blueberry cultivars: identifying superior cultivars for nutritional biofortification**. *Frontiers in Plant Science* 2025, **16**:1750179.
13. Felgus-Lavefve L, Howard L, Adams SH, Baum JI: **The Effects of Blueberry Phytochemicals on Cell Models of Inflammation and Oxidative Stress**. *Adv Nutr* 2022, **13**(4):1279-1309.
14. Kalt W, Forney CF, Martin A, Prior RL: **Antioxidant capacity, vitamin C, phenolics, and anthocyanins after fresh storage of small fruits**. *Journal of agricultural and food chemistry* 1999, **47**(11):4638-4644.
15. Sellappan S, Akoh CC, Krewer G: **Phenolic compounds and antioxidant capacity of Georgia-grown blueberries and blackberries**. *J Agric Food Chem* 2002, **50**(8):2432-2438.
16. Rossi G, Woods FM, Leisner CP: **Quantification of total phenolic, anthocyanin, and flavonoid content in a diverse panel of blueberry cultivars and ecotypes**. *HortScience* 2022, **57**(8):901-909.
17. Wang C, Zhang M, Wu L, Wang F, Li L, Zhang S, Sun B: **Qualitative and quantitative analysis of phenolic compounds in blueberries and protective effects on hydrogen peroxide-induced cell injury**. *Journal of separation science* 2021, **44**(14):2837-2855.
18. Li D, Li B, Ma Y, Sun X, Lin Y, Meng X: **Polyphenols, anthocyanins, and flavonoids contents and the antioxidant capacity of various cultivars of highbush and half-high blueberries**. *Journal of Food Composition and Analysis* 2017, **62**:84-93.
19. Sellappan S, Akoh CC, Krewer G: **Phenolic compounds and antioxidant capacity of Georgia-grown blueberries and blackberries**. *Journal of agricultural and food chemistry* 2002, **50**(8):2432-2438.
20. Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL: **Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption**. *Journal of agricultural and food chemistry* 2006, **54**(11):4069-4075.
21. Blackburn EH, Epel ES, Lin J: **Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection**. *Science* 2015, **350**(6265):1193-1198.
22. Li M-J, Deng Y-Y, Pan L-H, Luo S-Z, Zheng Z: **Comparisons in phytochemical components and in vitro digestion properties of corresponding peels, flesh and seeds separated from two blueberry cultivars**. *Food Science and Biotechnology* 2024, **33**(1):73-83.
23. Liu K, Chen B: **Bioactive components in blueberries and their roles in metabolic syndrome**. *The Journal of Nutrition* 2025.
24. Gonçalves AC, Nunes AR, Flores-Félix JD, Alves G, Silva LR: **Cherries and blueberries-based beverages: Functional foods with antidiabetic and immune booster properties**. *Molecules* 2022, **27**(10):3294.
25. Najjar RS, Mu S, Feresin RG: **Blueberry polyphenols increase nitric oxide and attenuate angiotensin II-induced oxidative stress and inflammatory signaling in human aortic endothelial cells**. *Antioxidants* 2022, **11**(4):616.
26. Miller MG, Hamilton DA, Joseph JA, Shukitt-Hale B: **Dietary blueberry improves cognition among older adults in a randomized, double-blind, placebo-controlled trial**. *European journal of nutrition* 2018, **57**(3):1169-1180.
27. Wang SY, Chen H, Ehlenfeldt MK: **Antioxidant capacities vary substantially among cultivars of**

rabbiteye blueberry (Vaccinium ashei Reade). *International Journal of Food Science and Technology* 2011, **46**(12):2482-2490.
28. Kalt W, Cassidy A, Howard LR, Krikorian R, Stull AJ, Tremblay F, Zamora-Ros R: **Recent research on the health benefits of blueberries and their anthocyanins**. *Advances in nutrition* 2020, **11**(2):224-236.
29. Liu Y, Song X, Zhang D, Zhou F, Wang D, Wei Y, Gao F, Xie L, Jia G, Wu W: **Blueberry anthocyanins: protection against ageing and light-induced damage in retinal pigment epithelial cells**. *British journal of nutrition* 2012, **108**(1):16-27.
30. Zheng T, Bielinski DF, Fisher DR, Zhang J, Shukitt-Hale B: **Protective Effects of a Polyphenol-Rich Blueberry Extract on Adult Human Neural Progenitor Cells**. *Molecules* 2022, **27**(19).
31. Zhang J, Lazarenko OP, Blackburn ML, Badger TM, Ronis MJ, Chen JR: **Blueberry consumption prevents loss of collagen in bone matrix and inhibits senescence pathways in osteoblastic cells**. *Age (Dordr)* 2013, **35**(3):807-820.
32. Wilson MA, Shukitt-Hale B, Kalt W, Ingram DK, Joseph JA, Wolkow CA: **Blueberry polyphenols increase lifespan and thermotolerance in Caenorhabditis elegans**. *Aging cell* 2006, **5**(1):59-68.
33. Lutchman V, Dakik P, McAuley M, Cortes B, Ferraye G, Gontmacher L, Graziano D, Moukhariq F-Z, Simard É, Titorenko VI: **Six plant extracts delay yeast chronological aging through different signaling pathways**. *Oncotarget* 2016, **7**(32):50845.
34. Elks CM, Reed SD, Mariappan N, Shukitt-Hale B, Joseph JA, Ingram DK, Francis J: **A blueberry-enriched diet attenuates nephropathy in a rat model of hypertension via reduction in oxidative stress**. *PloS one* 2011, **6**(9):e24028.
35. Galli RL, Bielinski DF, Szprengiel A, Shukitt-Hale B, Joseph JA: **Blueberry supplemented diet reverses age-related decline in hippocampal HSP70 neuroprotection**. *Neurobiology of aging* 2006, **27**(2):344-350.
36. Rodriguez-Mateos A, Rendeiro C, Bergillos-Meca T, Tabatabaee S, George TW, Heiss C, Spencer JP: **Intake and time dependence of blueberry flavonoid–induced improvements in vascular function: a randomized, controlled, double-blind, crossover intervention study with mechanistic insights into biological activity**. *The American journal of clinical nutrition* 2013, **98**(5):1179-1191.
37. Cheng N, Barfoot KL, Le Cozannet R, Fança-Berthon P, Lamport DJ, Williams CM: **Wild blueberry extract intervention in healthy older adults: a multi-study, randomised, controlled investigation of acute cognitive and cardiovascular effects**. *Nutrients* 2024, **16**(8):1180.
38. Ivarsson Jr J, Pecorelli A, Lila MA, Valacchi G: **Blueberry supplementation and skin health**. *Antioxidants* 2023, **12**(6):1261.
39. Pambianchi E, Hagenberg Z, Pecorelli A, Grace M, Therrien J-P, Lila MA, Valacchi G: **Alaskan Bog Blueberry (Vaccinium uliginosum) Extract as an Innovative Topical Approach to Prevent UV-Induced Skin Damage**. *Cosmetics* 2021, **8**(4):112.
40. Gustafson SJ, Dunlap KL, McGill CM, Kuhn TB: **A Nonpolar Blueberry Fraction Blunts NADPH Oxidase Activation in Neuronal Cells Exposed to Tumor Necrosis Factor-α**. *Oxidative Medicine and Cellular Longevity* 2012, **2012**(1):768101.
41. Li H, Zheng T, Lian F, Xu T, Yin W, Jiang Y: **Anthocyanin-rich blueberry extracts and anthocyanin metabolite protocatechuic acid promote autophagy-lysosomal pathway and alleviate neurons damage in in vivo and in vitro models of Alzheimer's disease**. *Nutrition* 2022, **93**:111473.
42. Samani P, Costa S, Cai S: **Neuroprotective Effects of Blueberries through Inhibition on Cholinesterase, Tyrosinase, Cyclooxygenase-2, and Amyloidogenesis**. *Nutraceuticals* 2023, **3**(1).
43. Papandreou MA, Dimakopoulou A, Linardaki ZI, Cordopatis P, Klimis-Zacas D, Margarity M, Lamari FN: **Effect of a polyphenol-rich wild blueberry extract on cognitive performance of mice, brain antioxidant markers and acetylcholinesterase activity**. *Behavioural brain research* 2009, **198**(2):352-358.
44. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, Bickford PC: **Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation**. *Journal of Neuroscience* 1999, **19**(18):8114-8121.
45. Beracochea D, Krazem A, Henkouss N, Haccard G, Roller M, Fromentin E: **Intake of wild blueberry powder improves episodic-like and working memory during normal aging in mice**. *Planta Medica* 2016, **82**(13):1163-1168.
46. Williams CM, Abd El Mohsen M, Vauzour D, Rendeiro C, Butler LT, Ellis JA, Whiteman M, Spencer JP: **Blueberry-induced changes in spatial working memory correlate with changes in hippocampal CREB phosphorylation and brain-derived neurotrophic factor (BDNF) levels**. *Free Radical Biology and Medicine* 2008, **45**(3):295-305.
47. Ebenezer PJ, Wilson CB, Wilson LD, Nair AR: **The anti-inflammatory effects of blueberries in an**

animal model of post-traumatic stress disorder (PTSD). *PloS one* 2016, **11**(9):e0160923.

48. Goyarzu P, Malin DH, Lau FC, Taglialatela G, Moon WD, Jennings R, Moy E, Moy D, Lippold S, Shukitt-Hale B: **Blueberry supplemented diet: effects on object recognition memory and nuclear factor-kappa B levels in aged rats**. *Nutritional neuroscience* 2004, **7**(2):75-83.
49. Andres-Lacueva C, Shukitt-Hale B, Galli RL, Jauregui O, Lamuela-Raventos RM, Joseph JA: **Anthocyanins in aged blueberry-fed rats are found centrally and may enhance memory**. *Nutritional neuroscience* 2005, **8**(2):111-120.
50. Carey AN, Gomes SM, Shukitt-Hale B: **Blueberry supplementation improves memory in middle-aged mice fed a high-fat diet**. *Journal of agricultural and food chemistry* 2014, **62**(18):3972-3978.
51. Jiang Y, Sun S: **Blueberry Extracts Supplementation Improves Cognitive Function in Elderly Patients with Mild Cognitive Impairment (P14-013-19)**. *Current Developments in Nutrition* 2019, **3**:nzz052. P014-013-019.
52. Boespflug EL, Eliassen JC, Dudley JA, Shidler MD, Kalt W, Summer SS, Stein AL, Stover AN, Krikorian R: **Enhanced neural activation with blueberry supplementation in mild cognitive impairment**. *Nutritional neuroscience* 2018, **21**(4):297-305.
53. Whyte AR, Schafer G, Williams CM: **Cognitive effects following acute wild blueberry supplementation in 7-to 10-year-old children**. *European journal of nutrition* 2016, **55**:2151-2162.
54. Cheatham CL, Canipe III LG, Millsap G, Stegall JM, Chai SC, Sheppard KW, Lila MA: **Six-month intervention with wild blueberries improved speed of processing in mild cognitive decline: a double-blind, placebo-controlled, randomized clinical trial**. *Nutritional Neuroscience* 2023, **26**(10):1019-1033.
55. Bowtell JL, Aboo-Bakkar Z, Conway ME, Adlam A-LR, Fulford J: **Enhanced task-related brain activation and resting perfusion in healthy older adults after chronic blueberry supplementation**. *Applied Physiology, Nutrition, and Metabolism* 2017, **42**(7):773-779.
56. Krikorian R, Shidler MD, Nash TA, Kalt W, Vinqvist-Tymchuk MR, Shukitt-Hale B, Joseph JA: **Blueberry supplementation improves memory in older adults**. *J Agric Food Chem* 2010, **58**(7):3996-4000.
57. Rutledge GA, Sandhu AK, Miller MG, Edirisinghe I, Burton-Freeman BB, Shukitt-Hale B: **Blueberry phenolics are associated with cognitive enhancement in supplemented healthy older adults**. *Food & function* 2021, **12**(1):107-118.
58. Gemma C, Vila J, Bachstetter A, Bickford PC: **Oxidative Stress and the Aging Brain: From Theory to Prevention**. In: *Brain Aging: Models, Methods, and Mechanisms.* edn. Edited by Riddle DR. Boca Raton (FL); 2007.
59. Yang W, Guo Y, Liu M, Chen X, Xiao X, Wang S, Gong P, Ma Y, Chen F: **Structure and function of blueberry anthocyanins: A review of recent advances**. *Journal of Functional Foods* 2022, **88**:104864.
60. Youdim KA, Shukitt-Hale B, MacKinnon S, Kalt W, Joseph J: **Polyphenolics enhance red blood cell resistance to oxidative stress: in vitro and in vivo**. *Biochimica et Biophysica Acta (BBA)-General Subjects* 2000, **1523**(1):117-122.
61. Terracina S, Petrella C, Francati S, Lucarelli M, Barbato C, Minni A, Ralli M, Greco A, Tarani L, Fiore M *et al*: **Antioxidant Intervention to Improve Cognition in the Aging Brain: The Example of Hydroxytyrosol and Resveratrol**. *Int J Mol Sci* 2022, **23**(24).
62. Larsen PL: **Aging and resistance to oxidative damage in Caenorhabditis elegans**. *Proceedings of the National Academy of Sciences* 1993, **90**(19):8905-8909.
63. Jin R, Chan AKY, Wu J, Lee TMC: **Relationships between Inflammation and Age-Related Neurocognitive Changes**. *Int J Mol Sci* 2022, **23**(20):12573.
64. Willis LM, Freeman L, Bickford PC, Quintero EM, Umphlet CD, Moore AB, Goetzl L, Granholm AC: **Blueberry supplementation attenuates microglial activation in hippocampal intraocular grafts to aged hosts**. *Glia* 2010, **58**(6):679-690.
65. Yu H-R, Chen B-H: **Analysis of phenolic acids and flavonoids in rabbiteye blueberry leaves by UPLC-MS/MS and preparation of nanoemulsions and extracts for improving antiaging effects in mice**. *Foods* 2023, **12**(10):1942.
66. Song Y, Huang L, Yu J: **Effects of blueberry anthocyanins on retinal oxidative stress and inflammation in diabetes through Nrf2/HO-1 signaling**. *Journal of Neuroimmunology* 2016, **301**:1-6.
67. Tang JS, Vissers MC, Anderson RF, Sreebhavan S, Bozonet SM, Scheepens A, Melton LD: **Bioavailable blueberry-derived phenolic acids at physiological concentrations enhance Nrf2-regulated antioxidant responses in human vascular endothelial cells**. *Molecular nutrition & food research* 2018, **62**(5):1700647.

68. Albrahim T: **Effect of Blueberry Supplement on Alleviating Aged-Associated Kidney Dysfunction in Rats**. *Nutr Food Sci* 2025, **13**(1).
69. Wang J, Zhao X, Zheng J, Herrera-Balandrano DD, Zhang X, Huang W, Sui Z: **In vivo antioxidant activity of rabbiteye blueberry (Vaccinium ashei cv.'Brightwell') anthocyanin extracts**. *Journal of Zhejiang University-SCIENCE B* 2023, **24**(7):602-616.
70. Travica N, D'cunha NM, Naumovski N, Kent K, Mellor DD, Firth J, Georgousopoulou EN, Dean OM, Loughman A, Jacka F: **The effect of blueberry interventions on cognitive performance and mood: A systematic review of randomized controlled trials**. *Brain, behavior, and immunity* 2020, **85**:96-105.
71. Dodd GF, Williams CM, Butler LT, Spencer JP: **Acute effects of flavonoid-rich blueberry on cognitive and vascular function in healthy older adults**. *Nutrition and Healthy Aging* 2019, **5**(2):119-132.
72. Joseph JA, Shukitt-Hale B, Brewer GJ, Weikel KA, Kalt W, Fisher DR: **Differential protection among fractionated blueberry polyphenolic families against DA-, Aβ42 and LPS-induced decrements in Ca2+ buffering in primary hippocampal cells**. *J Agric Food Chem* 2010, **58**(14):8196-8204.
73. Shukitt-Hale B, Lau FC, Carey AN, Galli RL, Spangler EL, Ingram DK, Joseph JA: **Blueberry polyphenols attenuate kainic acid-induced decrements in cognition and alter inflammatory gene expression in rat hippocampus**. *Nutr Neurosci* 2008, **11**(4):172-182.
74. Lund J, Tedesco P, Duke K, Wang J, Kim SK, Johnson TE: **Transcriptional profile of aging in *C. elegans***. *Current Biology* 2002, **12**(18):1566-1573.
75. Pereira QC, Dos Santos TW, Fortunato IM, Ribeiro ML: **The molecular mechanism of polyphenols in the regulation of ageing hallmarks**. *International Journal of Molecular Sciences* 2023, **24**(6):5508.