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Review

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Berry Fruit Enhances Beneficial Signaling in the Brain

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ABSTRACT: Increased lifespans have led to population aging and brought attention to healthcare concerns associated with old age. A growing body of preclinical and clinical research has identified neurological benefits associated with the consumption of berry fruits. In addition to their now well-known antioxidant effects, dietary supplementation with berry fruits also has direct effects on the brain. Intake of these fruits may help to prevent age-related neurodegeneration and resulting changes in cognitive and motor function. In cell and animal models, berry fruits mediate signaling pathways involved in inflammation and cell survival in addition to enhancing neuroplasticity, neurotransmission, and calcium buffering, all of which lead to attenuation of age- and pathology-related deficits in behavior. Recent clinical trials have extended these antioxidant, anti-inflammatory, and cognition-sparing effects to humans. This paper reviews recent evidence for the beneficial signaling effects of berry fruits on the brain and behavior.

KEYWORDS: *berries, brain, aging, signaling, antioxidants, anti-inflammatory, behavior*

INTRODUCTION

Over the past century, lifespans in the developed world have increased dramatically as a result of improved nutrition, sanitation, and healthcare. As more people live past the age of 65, population aging is bringing about societal changes in employment, habitation, and family structures and increasing the burden of healthcare on society. With "baby boomers" nearing retirement, this demographic shift has highlighted the effects of age-related pathology. Despite more likely causes of death, such as heart disease (leading cause of death),[1] many older adults are more fearful of neurodegenerative diseases, such as Alzheimer's disease (AD) (currently the sixth leading cause of death), due to the resulting loss of dignity, identity, and independence associated with dementia, potential stigma surrounding dementia, and a lack of knowledge about dementia.[2,3]

Even in the absence of neurodegenerative disease, aging has a profound effect on cognition. Whereas some psychological domains are spared or even enhanced with increased age (e.g., knowledge), declining mental ability is observed across many domains, including attention, executive function, memory, reasoning, spatial orientation, and processing speed.[4−7] Subclinical but measurable cognitive decline begins in early adulthood and often increases in magnitude throughout adulthood and old age.[6,8] Additionally, changes in the central nervous system contribute to declines in mobility during aging.[9] Importantly, even mild impairments in cognition and mobility can necessitate the additional provision of care.[10]

Underlying these cognitive changes are age-related alterations to the brain. Notably, both atrophy and decreased neurotransmitter levels are observed in the prefrontal and parietal cortices, caudate nucleus, hippocampus, and cerebellum, brain regions known to be critical to the cognitive domains most affected by aging (for a review, see ref 9). An early contributing factor to both normal and pathological changes in brain functioning is the accumulation of oxidative damage coupled with decreased endogenous antioxidant defenses.[11−14] The brain is particularly prone to oxidative damage due to its high level of oxygen consumption.[15] Oxidative stress often results in chronic inflammatory responses that can also contribute to accumulating neural damage.[16] It has therefore been proposed that strategies that enhance antioxidant defenses and dampen pro-inflammatory signaling cascades may forestall some of the effects of aging.[12,16,17]

Plant foods, including fruits, vegetables, and their juices, are our primary source of exogenous antioxidant and anti-inflammatory compounds. Phenolic compounds are a class of secondary metabolites found throughout the plant kingdom having structures that contain a benzene ring and one or more hydroxyl substituents, including functional derivatives.[18] The thousands of unique polyphenolic compounds can be categorized into a variety of families,[19] for example, phenolic acids, flavonoids, stilbenes, coumarins, and tannins. In plants, phenols are essential to plant pigment, growth, reproduction, resistance to pathogens, and mediation of solar radiation and photosynthesis byproducts (e.g., reactive oxygen species). Additionally, when phenolic compounds are introduced to biological systems, they show antiallergic, antianxiety, anti-carcinogenic, anti-inflammatory, antioxidant, antiproliferative, antitumorigenic, and antiviral properties.[20−22]

Although the composition and content of polyphenolic compounds in individual dietary sources vary depending upon agricultural, processing, and storage variables, berry fruits are a rich source of phenolic compounds, particularly anthocyanins. Anthocyanins are a class of flavonoids that produce the bright red, purple, and blue pigments seen in many berries[23] and are among the most consumed flavonoids in the American diet.[24]

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Anthocyanins are potent antioxidant and anti-inflammatory agents.[25,26] Once consumed, anthocyanins from berry fruits are bioavailable and increase serum antioxidant capacity.[27,28] Importantly, animal models have shown that anthocyanins are neuroavailable, as well, with anthocyanins residing in tissue longer than in plasma.[29−32] Although much research has focused on anthocyanins, berry fruits contain a wide array of other polyphenolic compounds for which neuroavailability is still unknown. Additionally, the relative contribution of polyphenolics to neuroprotection, compared to their metabolites, is still poorly understood.

A growing body of literature supports a role for dietary berry fruits in maintaining brain health during aging. The present paper reviews recent evidence for the beneficial effects of berry fruits on cellular signaling in the brain; an earlier review focused on the ability of berry fruits to modulate behavior during aging.[17]

IN VITRO STUDIES

Berry fruits and their chemical constituents can alter cellular signaling and provide protection at the cellular level. Dreiseitel and colleagues[33] explored the effects of anthocyanins and related compounds (anthocyanidins, proanthocyanidins, etc.) on human brain monoamine oxidases (MAO) A and B, expressed in baculovirus-infected insect cells. Monoamine oxidases are tissue specific and, in the brain, MAOs are expressed in catecholaminergic (MAO A[34]) and serotonergic (MAO B[35]) neurons, as well as in glia,[36] where they catalyze the oxidization of norepinephrine and serotonin. Increased MAO activity is associated with AD.[37−39] Anthocyanins were found to inhibit both MAO subtypes in vitro. Therefore, increased consumption of certain berry fruits containing anthocyanins, in addition to other phenolic compounds known to inhibit MAOs,[40−42] may be useful in combating neurological disorders stemming from reduced levels of amines in the brain by blocking the enzymes that break them down.

Acetylcholine is a neurotransmitter involved in learning and memory. During aging, muscarinic acetylcholine receptors (mAChR) in the brain show reduced sensitivity, with the greatest reductions in sensitivity seen in patients with AD (for a review, see ref 43). Fluorescence imaging experiments from our laboratory have shown impaired calcium buffering among mAChR (M1 subtype) transfected COS-7 cells when challenged with either amyloid-β_{42} (Aβ), the protein that accumulates in the brain during AD, or dopamine, a neurotransmitter that induces oxidative stress in high doses, prior to depolarization. However, pretreatment of cells with a variety of berry extracts protected cells from Aβ_{42}- and dopamine-induced calcium dysregulation and showed similar results in terms of cell viability.[44] Berry protection appears to be partially mediated by the mAChR i3 domain in both M1 and M3 subtypes.[44,45] The addition of blueberry extract to dopamine-treated, transfected cells altered activation of signaling critical to learning and memory, decreasing activation of phosphorylated cyclic AMP response element binding protein (CREB) and protein kinase C gamma (PKCγ) while increasing activation of extracellular signal-regulated kinase 1/2 (ERK1/2). Similar results were obtained with primary hippocampal neuronal cells.[46] Therefore, consumption of berry fruits may normalize calcium buffering and promote optimal regulation of neurotransmission during aging.

Given the protective effects of berry fruits on neuronal calcium homeostasis, a variety of blueberry fractions were examined, including fractions with or without sugars and organic acids, an anthocyanin fraction, both high and low molecular weight proanthocyanidin fractions, and chlorogenic acid.[47] Whole blueberry extract improved Ca^{2+} recovery and cell viability while reducing free radical levels and stress signals in response to lipopolysaccharide, dopamine, and Aβ_{42} to a greater extent than any of the fractions. These findings showed that phytochemicals present in berry fruits may prevent age-related disruption in calcium homeostasis in the brain through their effect on stress signaling and that their protective effects may rely on the synergistic effects of the various constituent polyphenolic families.

Levels of ceramide, a sphingolipid involved in the regulation of cellular proliferation and survival, increase in both AD patients and mouse models of AD,[48,49] potentially as a result of oxidative stress.[50,51] Additionally, levels of ceramide are positively associated with amyloid precursor protein-mediated levels of Aβ_{42}.[52,53] Experiments in our laboratory showed that ceramide pretreatment significantly reduced the percentage of cells that depolarized in response to oxotremorine, but pre- or posttreatment with blueberry extract prevented ceramide-induced Ca^{2+} response decrements.[54] Notably, the percentage of cells that depolarized was higher when blueberry extract was administered prior to ceramide than when it was administered later.

Ceramide, dopamine, and Aβ_{42} induce increases in stress signaling, such as PKCγ and p38 MAPK, and increase phosphorylation of transcription factors that control cellular stress response, such as nuclear factor-κB (NF-κB) and protein 53.[55] Blueberry, however, attenuated these increases in activation of stress signals and downstream transcription factors, suggesting that blueberry suppresses stress pathways and preserves calcium homeostasis, even in the presence of stressors.

Wolfberry, *Lycium barbarum* (also known as gogi berry), also shows neuroprotective effects in cell models of AD. In Aβ_{25-35}- and Aβ_{1-42}-challenged primary cortical neurons, pretreatment with wolfberry reduced the number of apoptotic cells and attenuated cell survival and inflammatory markers such as lactate dehydrogenase release, caspase-3-like activity, and levels of phosphorylated c-jun N-terminal kinase (JNK), which were increased by exposure to Aβ.[56] Glutamate dysregulation leading to neuronal excitotoxicity is also observed in AD, and similar effects were observed when neurons were challenged with glutamate or high levels of *N*-methyl-D-aspartic acid.[57] Using this same model, wolfberry also attenuated the effects of homocysteine,[58] a known risk factor for AD.[59] However, wolfberry was unable to protect neurons against cytotoxicity induced by H_2O_2 and failed to reduce intracellular free radicals.[57] These findings suggest that wolfberry may have direct neuroprotective effects on the brain, independent of antioxidant effects.

Mulberry, *Morus alba*, has shown protective effects against oxidative stress in cell models of Parkinson's disease. Widely used as a model of Parkinson's disease, 6-hydroxydopamine (6-OHDA) is a neurotoxin, which selectively damages dopaminergic and noradrenergic neurons. In SH-SY5Y human neuroblastoma cells, challenged with 6-OHDA, mulberry pretreatment prevented decreases in cell viability, inhibited the generation of intracellular free radicals and extracellular nitric oxide, inhibited caspase-3-like activity, and prevented alteration of apoptotic signaling by restoring anti-apoptotic B-cell lymphoma 2 expression and preventing increases in pro-

apoptotic B-cell lymphoma 2-associated X protein expression.[60] Primary dopaminergic neurons, pretreated with mulberry, also showed improved survival rates when challenged with 6-OHDA.[60] Whereas berries activate a variety of cellular mechanisms, linked to neuroprotection, in vitro, animal and human studies are required to elucidate the specific mechanisms linking berry consumption and conservation of central nervous system function during aging.

IN VIVO EVIDENCE

There is now a substantial body of literature supporting the protective effects of berry fruits on behavior in animal models of aging and neurodegeneration. Early experiments in our laboratory showed that aged rats, maintained for 2 months on a 2% blueberry or 2% strawberry diet, displayed improved spatial working memory, relative to age-matched controls in the Morris water maze (MWM[61]), a cognitive test in which rats repeatedly located submerged platforms in a pool of opaque water.[62−64] Later research demonstrated that aged rats consuming blackberry and purple grape juice[65] performed better on the MWM than controls not consuming fruit products.[66]

Recent studies have confirmed research demonstrating positive effects of dietary berry supplementation on behavior and stress signaling. Consumption of a 2% blueberry diet for 4 months enhanced novel object recognition in aged rats.[67] Moreover, this enhancement in memory was positively associated with attenuation of age-related increases in NF-κB levels among blueberry-fed rats. In mice, blueberry intake improved memory retention in a step-down passive avoidance task and had an anxiolytic effect in the elevated plus maze, with blueberry-fed mice spending more time in open arms of the maze than mice not consuming blueberries.[68] Acetylcholinesterase activity was reduced in salt-soluble and detergent-soluble brain fractions of mice treated intraperitoneally with blueberry extract, and a step-through passive avoidance test also revealed enhanced memory.[69] Additionally, blueberry treatment increased brain levels of the antioxidants ascorbate and glutathione while decreasing levels of malondialdehyde, a marker of lipid peroxidation.[69] Oxotremorine-enhanced dopamine release was increased and free radical production was decreased in the striatum of rats fed either a blueberry or strawberry diet, whereas striatal carbachol-stimulated GTPase activity, a response previously been shown to decline with age[70] that is critical for g-protein-dependent signal transduction, was increased only in blueberry-fed animals.[61]

Recently, the anti-inflammatory effects of berry fruits, observed in cell models, have been replicated in vivo. Intracranial administration of kainic acid (KA) is a useful model of age-related glutamate excitotoxicity, oxidative stress, and inflammation,[71,72] which is sensitive to dietary manipulation.[73] Young rats that consumed a diet containing 2% blueberry for 8 weeks were protected from performance decrements induced by bilateral KA microinfusion into the CA3 region of the hippocampus when locating a hidden platform in the water maze.[74] Relative to controls, berry-fed animals showed attenuated levels of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and NF-κB, which were increased in control animals following systemic KA administration. Berry-fed animals also showed lower levels of OX-6, indicating decreased microglial activation and increased levels of insulin-like growth factor 1 (IGF-1), which stimulates cell survival and proliferation pathways in response to KA administration. A separate study[75] showed that young rats that consumed a blueberry diet for 8 weeks and later received bilateral intracranial injection of KA were protected from KA-induced performance decrements in a 14-unit T-maze, relative to controls. Berry-fed rats were partially protected from KA-induced neuronal losses in the CA1 region of the hippocampus, a brain structure important for learning and memory.

In addition to beneficial effects on cognition, intake of berry fruits improves motor control in aged animals. Relative to rats given a standard laboratory diet, aged rats fed a diet containing 2% blueberry display better balance and coordination[61] than age-matched controls, an effect also achieved by dietary supplementation with cranberries,[76] grape juice,[65] and blackberries.[66] In contrast, evidence for strawberry's enhancement of motor behavior in aged rats and mice is less clear.[61,77−79] Recently, the effect of dietary mulberry supplementation on motor behavior was investigated in a mouse model of Parkinson's disease, an age-related neurodegenerative disorder in which loss of dopaminergic neurons in the substantia nigra leads to progressive loss of motor control. Mice, injected with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that selectively destroys dopaminergic neurons, showed increased latency to turn and subsequently escape when positioned at the top of a vertical pole,[60] indicating impairment in motor control. However, a 15 day treatment with mulberry extract prevented these MPTP-induced coordination decrements. Berry enhancement of motor control may allow for higher activity levels throughout aging and enable exercise-based neuroprotection mechanisms.

Berry fruits can also up-regulate neurogenesis in aged rats. Aged rats maintained on a blueberry diet showed greater proliferation of precursor cells in the dentate gyrus than rats fed a control diet.[80] Blueberry also increased levels of IGF-1, IGF-1 receptors, and ERK1/2, with increases in signaling associated with decreased reference memory errors in the radial-arm water maze. Similarly, aged blueberry-fed rats showed improved spatial working memory in a cross maze[81] in which rats had to avoid a previously visited maze arm to receive a food reward. These performance improvements were associated with attenuated levels of a variety of signaling molecules involved in stress, survival, and neural plasticity in the hippocampus, including increased levels of phosphorylated CREB, ERK1/2, protein kinase B, and MAPK-activated protein kinase 1b as well as increased levels of brain-derived neurotrophic factor (BDNF), proBDNF, and activity-regulated cytoskeleton-associated protein relative to age-matched controls that showed decreased signaling.

In cortical neurons, dendritic arborization and spine density decrease as a function of age.[82,83] Blueberry consumption in aged rats increased dendritic arborization in layer II−III cortical neurons[82] as well as spine density.[83] Neurons in the striatum of aged rats appear to increase in arborization and spine density, relative to young animals, and blueberry, paradoxically, reduced dendritic arborization and spine density, thus returning striatal neurons to a morphology associated with younger rats.[84] Increased adult neurogenesis and normalizing neuronal structure may therefore counteract age-related changes in neural morphology and cerebral atrophy.

Berry fruits are protective against neurodegeneration in rodent models. Senescence-accelerated mice (SAM) are strains bred to display various age-related disorders (prone; SAMP) or act as controls (resistant; SAMR[85]). In SAMP8 mice, which develop Aβ depositions and display behavioral deficits, a diet

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containing mulberry attenuated declines in learning and memory in active and passive avoidance tasks, bringing performance in line with SAMR1 mice, which do not develop aging-like pathology.[86] SAMP8 mice consuming a diet containing 0.9% mulberry extract also showed attenuated Aβ expression in the brain, and Aβ expression was negatively associated with performance in both the active and passive avoidance tasks. Additionally, mulberry consumption altered MAPK signal transduction by preventing increases in JNK and p38 MAPK, observed in SAMP8 on the standard diet but not in SAMR1 controls, and by preventing decreased expression of ERK1/2, which was reduced in the brains of SAMP8 mice, relative to levels observed in SAMR1 mice. Mulberry extract also prevented a reduction, observed in SAMP8 mice, in nuclear translocation of the nuclear factor-E2-related factor 2, a key regulator of antioxidant defenses, relative to SAMR1 controls.

Whereas Alzheimer's disease does not spontaneously develop in rodents,[87] transgenic mouse models have been created to model specific aspects of AD pathology. In double-transgenic mice expressing amyloid precursor protein and presenilin-1 mutations, dietary supplementation with blueberry rescued performance in a Y-maze alternation task. Moreover, a trend existed for a correlation between Y-maze performance and increases in hippocampal phosphoprotein kinase Cα.[88] Transgenic mice also showed decreased levels of striatal low-K_m GTPase activity and increased levels of neutral sphingomyelin-specific PLC activity, both of which were normalized in blueberry-fed transgenic mice. Blueberry-fed transgenic mice also displayed increased levels of ERK1/2 activity in the hippocampus. A trend indicating a reduction of total Aβ in the brains of blueberry-fed mice was observed. Taken together, these preclinical findings suggest that dietary supplementation with berry fruits has the potential for a multiplicity of effects, in addition to their antioxidant properties, including the activation of a variety of signaling pathways that result in neuroprotection, neurogenesis, and ultimately spared cognitive and motor behavior.

CLINICAL EVIDENCE

The effects of berry fruits on human health have only recently been investigated. In one study, cranberry, but not blueberry, consumption increased serum antioxidant capacity in healthy women.[89] However, in another study, consumption of blueberry in conjunction with a high-fat meal increased postprandial serum antioxidant status, relative to participants fed only the high-fat meal.[90] Similarly, both acute and prolonged (16 day) consumption of strawberries increased serum antioxidant capacity.[27] Chronic consumption of strawberry (6 weeks) was also able to moderately reduce fasting levels of serum c-reactive protein, IL-1β, and TNF-α among overweight men and women, relative to placebo controls.[91] Following a high-carbohydrate/high-fat meal, chronic strawberry consumption also resulted in attenuated meal-induced increases in postprandial levels of serum IL-1β. Berry consumption may, therefore, counteract peripheral pro-inflammatory signaling induced by the consumption of a Western diet and mitigate risk factors for neurodegeneration.

Importantly, new evidence shows that berry fruits can reduce cognitive deficits among older adults. Mild cognitive impairment (MCI) is a clinical designation that describes a degree of mental decline having severity between that of normal aging and dementia.[92] A diagnosis of MCI is a strong risk factor for dementia.[93] Older adults with MCI who consumed grape juice (6−9 mL/kg/day) for 12 weeks showed increased learning and a trend toward increased delayed recall and spatial memory for word lists in the California Verbal Learning Test (CVLT[94]), relative to adults given a placebo.[95] In a similar study, older adults with MCI consuming blueberry juice (6−9 mL/kg/day) for 12 weeks[96] showed increased delayed recall for word lists in the CVLT, relative to baseline, and a trend toward better performance, relative to placebo controls. Additionally, blueberry-fed participants showed improved performance in the Verbal Paired Associates Learning Test,[97] relative to both baseline and placebo controls. However, more research is needed to determine the most efficacious intake levels in humans and to explore the potential for overconsumption of berry fruits.

Recent clinical research has linked changes in walking speed and gait variability to declines in cognitive ability and even life expectancy among older adults during "normal" aging.[98−102] On the basis of these findings and existing evidence for the protective effects of berry fruits on motor ability in rodent models, future clinical research should incorporate measures of cognition paired with measures of motor control, balance, and mobility to determine whether berry supplementation can enhance motor control in older, nonpathological, adults.

DISCUSSION

In conclusion, berry fruits possess neuroavailable, neuroactive phytochemicals that offer antioxidant, anti-inflammatory, and direct effects on the brain. A growing body of preclinical research has shown that berry fruits are capable of enhancing both cognition and motor control in animal models. Additionally, dietary supplementation with berry fruits reduces serum oxidative and inflammatory markers in humans and, in the case of grapes and blueberries, improves cognition among older adults with MCI.

Although the past decade has revealed the potential for dietary berry fruit to affect brain aging, many research questions remain to be answered. Each type of berry fruit is composed of a unique combination of phytochemicals. Currently, researchers possess an incomplete picture of the neuroavailability and mechanisms of action for the wide variety of phytochemicals present in berry fruit and their respective metabolites. More research is required to demonstrate each constituents' availability and mechanism of action specific to individual brain subregions. Furthermore, although it is tempting to assume that a single bioactive constituent may be responsible for the observed benefits of berry consumption, it is equally likely that the effects result from the synergism of multiple phytochemicals and their metabolites. In the context of the Western diet, it is not yet clear whether the consumption of a variety of high-polyphenol foods, such as mixed berries, would provide additive benefits that exceed those of supplementation with a single berry fruit.

Given that neurodegeneration and cognitive decline are chronic processes, throughout adulthood, future research should also identify critical periods during which increased consumption of berry fruits is most effective and the extent to which berry fruits prevent or even reverse the deleterious effects of aging. Furthermore, the optimal dietary intake, necessary duration of supplementation, and longevity of the effects following the cessation of supplementation should also be explored. In addition to the preclinical research currently

underway, further research will be needed to transition these preclinical findings to human populations.

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ABBREVIATIONS USED

MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6-OHDA, 6-hydroxydopamine; AD, Alzheimer's disease; Aβ, amyloid-β; BDNF, brain-derived neurotrophic factor; MAO, brain monoamine oxidases; CVLT, California Verbal Learning Test; JNK, c-jun N-terminal kinase; ERK1/2, extracellular signal-regulated kinases 1/2; IGF-1, insulin-like growth factor 1; IL-1β, interleukin-1β; MCI, mild cognitive impairment; MAPK, mitogen-activated protein kinase; MWM, Morris water maze; mAChR, muscarinic acetylcholine receptors; NF-κB, nuclear factor-kappa B; CREB, cyclic AMP response element binding protein; PKCγ, protein kinase C gamma; SAMP, senescence-accelerated mice, prone; SAMR, senescence-accelerated mice, resistant; TNF-α, tumor necrosis factor-alpha.

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