

# Fruit Polyphenols and Their Effects on Neuronal Signaling and Behavior in Senescence

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**ABSTRACT:** The onset of age-related neurodegenerative diseases superimposed on a declining nervous system could exacerbate the motor and cognitive behavioral deficits that normally occur in senescence. It is likely that, in cases of severe deficits in memory or motor function, hospitalization and/or custodial care would be a likely outcome. This means that unless some way is found to reduce these age-related decrements in neuronal function, healthcare costs will continue to rise exponentially. Thus, it is extremely important to explore methods to retard or reverse the age-related neuronal deficits as well as their subsequent, behavioral manifestations. Applying molecular biological approaches to slow aging in the human condition may be years away. So it is important to determine what methods can be used today to increase healthy aging, forestall the onset of these diseases, and create conditions favorable to obtaining a “longevity dividend” in both financial and human terms. In this regard, epidemiological studies indicate that consumption of diets rich in antioxidants and anti-inflammatory compounds, such as those found in fruits and vegetables, may lower the risk of developing age-related neurodegenerative diseases, such as Alzheimer’s or Parkinson’s diseases (AD and PD). Research suggests that the polyphenolic compounds found in fruits, such as blueberries, may exert their beneficial effects by altering stress signaling and neuronal communication, suggesting that interventions may exert protection against age-related deficits in cognitive and motor function. The purpose of this article is to discuss the benefits of these interventions in rodent models and to describe the putative molecular mechanisms involved in their benefits.

**KEYWORDS:** oxidants; antioxidants; Alzheimer’s; Parkinson’s; life span

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## INTRODUCTION

There is a great deal of research indicating that, even in the absence of neurodegenerative disease, there are numerous motor<sup>1,2</sup> and cognitive<sup>3</sup> behavioral deficits that occur during aging. The alterations in motor function may include decreases in balance, muscle strength, and coordination<sup>1</sup> while memory deficits are seen on cognitive tasks that require the use of spatial learning and memory.<sup>4,5</sup> These decrements have been reported in numerous studies in animals<sup>3-5</sup> and humans.<sup>6,7</sup> Age-related deficits in motor performance are thought to be the result of alterations in the striatal dopamine system<sup>8</sup> or in the cerebellum,<sup>9,10</sup> with both structures showing significant changes with age. Alterations in cognition appear to occur primarily in secondary memory systems that reflect the storage of newly acquired information.<sup>8,11</sup> It is thought that the hippocampus mediates “place” learning, and that the prefrontal cortex is critical to acquiring the rules that govern performance in procedural knowledge. The dorsomedial striatum appears to mediate response and cue learning.<sup>12-15</sup> While the mechanisms involved in both motor and cognitive deficits during aging remain to be discerned, it is clear that oxidative stress (OS)<sup>16</sup> and inflammation<sup>17,18</sup> are involved.

One purpose of this article is to review the putative oxidant and inflammatory mechanism(s) involved in these behavioral decrements, and to attempt to specify possible nutritional interventions that could prevent or reverse these age-related declines. It appears that one intervention that might prevent or reverse these decrements involves the use of dietary supplementation with fruits or vegetables. All plants, including fruit- or vegetable-bearing plants, synthesize a vast array of chemical compounds that are not necessarily involved in the plant's metabolism. These “secondary compounds” instead serve a variety of functions that enhance the plant's survivability, not the least of which are their antioxidant/anti-inflammatory activities. Thus, a second purpose of this article is to describe the beneficial effects of fruits and vegetable supplementation in brain/behavioral aging.

## OXIDATIVE STRESS AND AGING

OS results from the shift toward reactive oxygen species (ROS) production in the equilibrium between ROS generation and the antioxidant defense system.<sup>19</sup> In the brain, this is particularly important, since studies have found indications of increased OS in brain aging, including reductions in redox active iron,<sup>20,21</sup> as well as increases in Bcl-2<sup>22</sup> and membrane lipid peroxidation.<sup>23</sup> Studies have also shown that there are significant increases in cellular hydrogen peroxide.<sup>24</sup> Additionally, there is significant lipofuscin accumulation<sup>20</sup> along with alterations in membrane lipids.<sup>25</sup> Recent studies

have also suggested the involvement of lipid rafts with OS sensitivity.<sup>26</sup> Importantly, the consequences of these increases in OS at several levels may result in disruption of calcium homeostasis, alterations in cellular signaling cascades, and changes in gene expression,<sup>27–32</sup> which combine to contribute to the increased vulnerability to OS seen in the aging population<sup>33,34</sup> and which is elevated in neurodegenerative diseases, such as Alzheimer's disease (AD)<sup>35–37</sup> and Parkinson's disease (PD).<sup>38,39</sup>

OS vulnerability in aging also may be the result of microvasculature changes and increases in oxidized proteins and lipids,<sup>40</sup> as well as alterations in: (a) membrane microenvironment and structure;<sup>41,42</sup> (b) calcium buffering ability; and (c) the vulnerability of neurotransmitter receptors to OS (see below). Additional "vulnerability factors" include critical declines in endogenous antioxidant protection, involving alterations in the ratio of oxidized-to-total glutathione,<sup>43</sup> and reduced glutamine synthetase.<sup>44</sup> Taken together, these findings indicate that there are increases in OS in aging, that the central nervous system (CNS) may be particularly vulnerable to these increases (see Refs. 41,45 for review), and the efficacy of antioxidants may be reduced in aging. However, it is important to note here that OS may only be a partial contributor to neuronal and behavioral changes in senescence. A very closely associated factor involves inflammatory processes. For example, OS may contribute to these age-related diseases by inducing the expression of proinflammatory cytokines through activation of the OS-sensitive nuclear factor kappa B (NF- $\kappa$ B).<sup>46,47</sup> NF- $\kappa$ B in turn upregulates the inflammatory response leading to a further increase in ROS,<sup>48</sup> which results in a continuous increase in OS and inflammation, and thus, vulnerability to further stressors.

### **INFLAMMATORY/OXIDATIVE STRESS INTERACTIONS AND BEHAVIORAL DEFICITS**

As mentioned above, evidence also suggests that in addition to OS, CNS inflammatory events may have an important role in affecting neuronal and behavioral deficits in aging.<sup>49</sup> It has been shown that activated glial cells increase in the normal aging brain, which exhibits greater immunoreactivity in markers for both microglia and astrocytes.<sup>50–53</sup> Additionally, increased glial fibrillary acid protein expression is observed by middle age,<sup>50</sup> and in the elderly this increase even occurs in the absence of a defined stimulus.<sup>54</sup> Glial cells mediate the endogenous immune system within the microenvironment in the CNS,<sup>55</sup> and their activation is the hallmark of inflammation in the brain.<sup>56</sup> Activated microglia produce inflammatory molecules, such as cytokines, growth factors, and complement proteins.<sup>54,57,58</sup> These proinflammatory mediators in turn activate other cells to produce additional signaling molecules that further activate microglia in a positive feedback loop to perpetuate and amplify the inflammatory signaling cascade.<sup>59</sup> Activated microglia produce proinflamma-

tory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>60,61</sup>

Increases in TNF- $\alpha$  have also been reported as a function of age,<sup>62</sup> as well as associated inhibition of glia.<sup>63</sup> Similarly, research in both aged mice and humans has found increases in TNF- $\alpha$ , IL-6,<sup>62,64,65</sup> and C-reactive protein.<sup>66</sup> All of these changes appear to be accompanied by upregulations in downstream indicators of inflammation (e.g., complement C1q) in microarray studies.<sup>67</sup>

Additionally, studies indicate that the expression of one form of cyclooxygenases (COX), 2, appears to be associated with amyloid beta deposition in the hippocampus,<sup>68,69</sup> and inflammatory prostaglandins (PG), such as PGE show increases in the hippocampus, as well as other areas in aging.<sup>70</sup> Since the PG synthesis pathway appears to be a major source of ROS in brain,<sup>71</sup> and in other organ systems, these findings indicate that inflammation may be accompanied by and even generate its “evil twin,” OS in producing the deleterious effects of aging. Thus, such factors as cytokines, COX, PGs, etc. may act as extracellular signals in generating additional ROS that are associated with decrements in neuronal function or glial neuronal interactions<sup>72–76</sup> and ultimately the deficits in behavior that have been observed in aging.

If this is the case, it should be possible to induce behavioral (cognitive and motor) deficits similar to those seen in aging using procedures that induce oxidative and/or inflammatory stressors. Indeed, these changes have been induced in several experiments.

Rodent studies have suggested that young animals exposed to OS show similar neuronal and behavioral changes to those seen in aged animals. The results have shown that young animals irradiated with particles of high energy and charge (HZE) produce behavioral deficits paralleling those observed in aging.<sup>77–79</sup> HZE particles (specifically 600 MeV or 1 GeV <sup>56</sup>Fe) also disrupt the functioning of the dopamine-mediated behaviors, such as motor behavior,<sup>80</sup> spatial learning and memory behavior,<sup>81</sup> and amphetamine-induced conditioned taste aversion.<sup>82</sup>

Inflammatory mediators have been shown to produce similar deficits in behavior.<sup>17</sup> For example, administration of lipopolysaccharide (LPS, intrahippocampally) was found to upregulate inflammatory mediators, induce degeneration of hippocampal pyramidal neurons, and produce decrements in working memory.<sup>83–85</sup> Similarly, chronic ventricular infusion of LPS into young rats produces many of the same alterations in behavior that has been reported in AD, which are accompanied by inflammatory, neurochemical, and neuropathological alterations.<sup>17,18,83–85</sup>

Thus, these studies and those reviewed above suggest that one method to forestall or perhaps even reverse the behavioral/declines that have been observed in aging might be to increase endogenous antioxidant/anti-inflammatory protection. Research described below suggests that this may be provided through nutritional intervention.

## BENEFICIAL EFFECTS OF FRUIT SUPPLEMENTATION ON BEHAVIORAL AND NEURONAL DEFICITS IN AGING

While there are numerous studies suggesting that various antioxidant supplements can be effective in antagonizing the behavioral deficits seen in aging (see Ref. 86 for review), research from several laboratories suggests that the combinations of antioxidant/anti-inflammatory polyphenolics found in fruits and vegetables may show efficacy in aging. All plants, including fruit- or vegetable-bearing plants, synthesize a vast array of chemical compounds that are not necessarily involved in the plant's metabolism. These "secondary compounds" instead serve a variety of functions that enhance the plant's survivability. These compounds may be responsible for the putative multitude of beneficial effects of fruits and vegetables on health-related issues, two of the most important of which may be their antioxidant and anti-inflammatory properties.

There has been an increasing interest in the beneficial effects of polyphenolic nutritional antioxidants on combating the deleterious effects of OS and inflammation in aging and age-related neurodegenerative diseases,<sup>87-93</sup> while epidemiological studies have shown that nutritional antioxidants may forestall the onset of dementia<sup>94-96</sup> and may provide protection against stroke (reviewed in Refs. 95,96). The question arises, however, as to which of the nutritional antioxidants may be the most effective. It appears that some of the most beneficial can be derived from the large class of polyphenols known as flavonoids. A subset of the flavonoids known as anthocyanins are particularly abundant in brightly colored fruit, such as berryfruits and concord grapes and grape seeds. Anthocyanins are responsible for the colors in the fruits and they have been shown to have potent antioxidant/anti-inflammatory activities,<sup>97-99</sup> as well as to inhibit lipid peroxidation and the inflammatory mediators COX-1 and 2.<sup>100,101</sup>

### *Motor and Cognitive Behavioral Improvements*

Given their potent, antioxidant/anti-inflammatory properties and the increased vulnerability to OS and inflammation in aging and the findings mentioned above concerning protection against stroke and dementing diseases, it might be postulated that fruits abundant in flavonoids would be effective in altering behavioral deficits in aging. Thus, we have shown that long-term (from 6 to 15 months of age; F344 rats) feeding with a supplemented AIN-93 diet (strawberry extract or spinach extract [1-2% of the diet]) retarded age-related decrements in cognitive or neuronal function. Results indicated that the supplemented diets could prevent the onset of age-related deficits in several indices (e.g., Morris water maze performance).<sup>102</sup>

In a subsequent experiment,<sup>103</sup> spinach, strawberry, or blueberry (BB) extract supplementation reversed age-related deficits in neuronal and behavioral

(cognitive, Morris water maze performance) function in aged (19 months) F344 rats. A more recent study has suggested that, in addition to Morris water maze performance, BB supplementation was also effective in reversing cognitive declines in object recognition.<sup>104</sup>

In the case of motor performance, research has suggested that BB supplementation improved performance on tests of motor function that assessed balance and coordination, (e.g., rod walking and the accelerating rotarod), while none of the other supplemented groups (e.g., spinach) differed from control on these tasks.<sup>103</sup> However, in subsequent experiments, we have shown that the cognitive/neuronal variables are sensitive to a greater number of fruits than those seen with respect to motor behavior. Thus far, only BB, cranberry,<sup>105</sup> strawberry,<sup>106</sup> and concord grape juice,<sup>107</sup> have been effective in reversing the motor behavioral deficits. This may be the result of brain region selectivity of the polyphenolic compounds from the various fruits and vegetables. This is more clearly seen in a recent study in which young rats (3 months of age) were given a control diet or one supplemented with either BB or strawberry extracts (2% for 8 weeks) and then exposed to <sup>56</sup>Fe irradiation (1.5 Gy @ 1 GeV).<sup>108</sup> We had previously shown that these irradiations produce deficits in cognitive and motor behavior similar to those seen with respect to aging. The results indicated that either strawberry or BB supplementations provided protection against the deleterious effects of radiation on these behaviors. However, the results also suggested that: (a) BB supplementation prevented irradiation-induced deficits in memory tasks that depend on intact striatal functioning, such as reversal learning (i.e., when the platform was moved from one quadrant to another in the Morris water maze), and (b) strawberry supplemented animals showed fewer deficits on the probe trial measures (when the platform was removed from maze), suggesting retained place information, which is a hippocampus-dependent behavior. We are examining these differences with respect to motor performance but with cognitive performance it appears the polyphenolic compounds in BBs may be working mainly in the striatum, while those in strawberries may primarily affect the hippocampus.

Regional polyphenol specificity notwithstanding, it also appears that the beneficial effects of these supplementations may involve more than opportunistic free radical scavenging, since assessments of free radicals using 2',7'-dichlorofluorescein diacetate (DCF-DA) in an early study<sup>103</sup> suggested that this activity was limited in the brains of the animals examined. Subsequent findings from our group and others have suggested that these mechanisms involved alterations in cell signaling.

### ***Learning/Memory and BB Alterations in Cell Signaling***

In general, the antioxidant effects of flavonoids also appear to involve transcriptional upregulation of antioxidant enzymes related to glutathione synthesis

and/or glutathione. The enzymes for glutathione (reviewed in Refs. 109,110) or heme-oxygenase<sup>111</sup> synthesis are dependent on extracellular signal-regulated kinases (ERK) 1 and 2, and through ERK-1 and -2, iNOS activity. There is also a great deal of evidence to suggest that a possible direct link exists between the antioxidant activity of flavonoids and their putative mitogen-activated protein (MAP) kinase altering activity. Such direct effects would greatly expand the potential antioxidant/anti-inflammatory properties of the flavonoids to include direct mediation of cell signaling in a variety of functions. As examples, delphinidin inhibits endothelial cell proliferation and cell cycle progression by ERK-1 and -2 activation.<sup>112</sup> Additional research indicates that phytochemicals can regulate MAP kinase and other signaling pathways at the level of transcription.<sup>113</sup> Given the numerous studies showing the involvement of ERK in diverse forms of memory, such as: contextual fear conditioning;<sup>114</sup> long-term potentiation;<sup>115</sup> striatum-dependent learning and memory;<sup>116</sup> hippocampus-dependent spatial memory;<sup>117</sup> and inhibitory avoidance,<sup>118</sup> these findings suggest that the putative signaling modifying properties of flavonoids may prove to be invaluable in altering the neuronal and behavioral effects of aging.

Indeed, in an earlier study,<sup>119</sup> APP/PS1 transgenic mice, given BB supplementation (as in Ref. 103) beginning at 4 months of age and continued until they were 12 months of age, exhibited Y-maze performance that was similar to those seen in nontransgenic mice and significantly greater than that seen in the nonsupplemented transgenic animals. Interestingly, no differences between the supplemented and nonsupplemented APP/PS1 mice in the number of plaques were observed, even though behavioral declines were prevented in the BB-supplemented animals.<sup>119</sup> Further analyses of the data indicated that the BB-supplemented APP/PS1 mice exhibited greater levels of hippocampal ERK, as well as striatal and hippocampal protein kinase C $\alpha$  (PKC) than that seen in the transgenic mice maintained on the control diet.<sup>119</sup> Two of the most important functions of PKC may be the regulation of synaptic plasticity and modulation of short- to long-term memory. Studies have shown that PKC activity is important in memory formation, particularly spatial memory (see Ref. 120 for review) and that treatment with PKC inhibitors impairs memory formation.<sup>121</sup> A later study confirmed the findings seen with respect to ERK in aged animals and also showed that the increases in ERK were correlated with increased neurogenesis.<sup>122</sup>

Since we had also shown in a previous study that striatal slices from rats on a BB-supplemented diet showed increases in carbachol-stimulated GTPase activity (improved G-protein-muscarinic receptor coupling/uncoupling),<sup>103</sup> we examined this parameter as well. The results indicated that carbachol-stimulated GTPase (an indicator of muscarinic receptor function and subsequent cognitive performance) was significantly enhanced in the BB-supplemented APP/PS1 mice compared to the nonsupplemented transgenic mice.

Therefore, it appears from these studies and others that at least part of the beneficial effects of the berryfruit supplementation on behavior in the aged animals may involve enhancements of cell signaling associated with learning and memory.

### *Stress Signaling*

The findings discussed above showing the relationships among cell signaling, learning, and memory still beg the question, however, on the putative role of the fruit polyphenols on OS/inflammatory signaling. In other words, it may be that BB and possibly other berryfruits (e.g., concord grapes) may produce their beneficial effects by reducing stress signaling. One of the important stress signals is NF- $\kappa$ B, and it has been shown that aged male Fischer 344 rats fed a BB-supplemented diet showed reductions of age-induced increases in NF- $\kappa$ B expression compared to those of aged nonsupplemented controls in the frontal cortex, hippocampus, and the striatum.<sup>104</sup> Similar decreases in NF- $\kappa$ B by BB supplementation were produced in animals (4-month-old rats) given intrahippocampal injections of kainic acid (KA). KA is an excitotoxin, which produces neuronal lesions and induces an inflammatory response in the brain.<sup>123,124</sup> Gene expression analysis revealed that BB supplementation normalized NF- $\kappa$ B to control levels and reduced the expression of the cytokines, IL-1 $\beta$ , and TNF- $\alpha$  in the hippocampus. BB supplementation also increased the expression of the neuroprotective trophic factor insulin growth factor-1 (IGF-1) in KA-injected animals, suggesting that BB exerts its effect through different cascades with respect to inflammation and neurotrophic events.<sup>124</sup> These alterations in stress signaling were associated with enhanced behavioral performance (Morris water maze) and reduced microglial activation.<sup>126</sup>

Similar changes in microglial activation were also seen in *in vitro* mouse microglial (BV2) cells treated with BB extract and exposed to LPS. The study found that incubation with BB significantly and dose-dependently inhibited the production of nitrite (a stable metabolite of nitric oxide) in LPS-conditioned media. This reduction was accompanied by a decline in the mRNA and protein expression of inducible nitric oxide synthase.<sup>125</sup> Furthermore, the proinflammatory cytokines IL- $\beta$  and TNF- $\alpha$  from LPS-conditioned media were found to be reduced in a dose-responsive manner. Intracellular ROS levels were also found to be attenuated by BB treatment.<sup>125</sup> These findings provided further evidence that the antioxidant and anti-inflammatory properties of BBs may involve alterations in stress signaling.

## CONCLUSIONS

There is now an abundance of data emerging from several labs, which suggest that: (a) OS and inflammation are major sources contributing to the deleterious

effects of aging and the development of age-related neurodegenerative diseases,<sup>126–132</sup> and (b) the plethora of natural antioxidants found in plant food matrices, such as fruits and vegetables, possess neuroprotective, as well as cardioprotective, and chemoprotective properties.<sup>128–134</sup> Moreover, it appears that the effects of berryfruit, such as BBs, and possibly, concord grapes may also exert their antioxidant/anti-inflammatory effects by directly altering the oxidative/inflammatory stress signaling pathways.

Additionally, BBs have been shown to increase the expression of protective MAP kinases,<sup>119</sup> as well as neuronal signaling associated with learning and memory, which result in increases in neurogenesis, accompanied by increases in the levels of ERK and IGF-1 expression.<sup>122</sup> These alterations, and others that are being studied, may be mediating the enhancements in cognitive and motor behavioral performance in berryfruit-supplemented senescent animals. Thus, nutritional interventions with high antioxidant fruits, such as berryfruits, may prove to be a valuable asset in strengthening the brain against the ravages of time and retard or prevent the development of age-related neurodegenerative diseases.

Thus, nutrition may prove to be a valuable asset in “quenching the fires” of inflammation and OS in aging and perhaps AD. Since OS is an early change in aging that is superimposed upon a stress vulnerable aging brain, early nutritional intervention may prevent or delay the onset of this disease.

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