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## Flavanols, Mild Cognitive Impairment, and Alzheimer's Dementia

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### Abstract

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Alzheimer's disease (AD) is a dementing neurological disorder that results in progressive memory loss and cognitive decline thought to be associated with buildup of amyloid plaques and neurofibrillary tangles in the brain. Vascular Dementia (VaD) is another common dementing disorder characterized by decreased brain perfusion. Together, AD and VaD constitute mixed dementia, an extremely common type of dementia associated with aging. Neuroimaging research suggests that brain vascular atrophy results in mild cognitive impairment (MCI), a possible precursor for AD. Additionally, literature suggests that attention to cardiovascular risk factors such as hypertension could reduce or delay the incidence of mixed dementia. Furthermore, foods and beverages rich in natural antioxidant flavanoids (i.e. epicatechin and catechin) are currently being advocated as possible preventative agents for a number of pathological conditions ranging from coronary heart disease to dementia. Experimental evidence is mounting that oxidative stress is involved in the pathophysiology of AD, and numerous studies are indicating that polyphenolic antioxidants found in fruits and vegetables can be useful in countering this and blocking neuronal death. More specifically, several cocoa studies suggest that daily intake of cocoa flavanols leads to cardiovascular benefits including vasodilatation via a nitric oxide mechanism and increased brain perfusion. The following text will consider an important question that thus arises regarding the potential of flavanols as effective agents for the prevention and delay of the onset of brain vascular atrophy and subsequently MCI and AD. It will also review the molecular mechanisms through which flavanols operate to accomplish their protective effects.

**Keywords:** Brain vascular atrophy, mild cognitive impairment, Alzheimer's disease, flavanols, oxidative stress, antioxidants

### Introduction

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Over the past few decades, the number of people suffering from dementia has risen significantly. One estimate has the number of people with the condition doubling between the years of 1990 and 2020. These numbers are alarmingly high and, if not addressed in the near future, will constitute a grave epidemic [1]. AD is the most common form of senile dementia and affects at least 4.5 million Americans [2-3]. More than \$100 billion is spent exclusively on direct care of those suffering from AD each year [3]. The etiology and pathogenesis of AD is

largely unknown but a number of hypotheses have been proposed and research in this field is very active and ongoing. A few of the hypotheses that have been proposed over the years include abnormal phosphorylation of the protein tau, unconventional infectious agents, trace element neurotoxicity, growth factor deficiency, excitatory amino acid insult, altered calcium homeostasis, free radical toxicity, deficits in energy metabolism, and altered protein processing resulting in abnormal  $\beta$ -amyloid peptide ( $A\beta$ ) accumulation [4].

The amyloid hypothesis established largely by John Hardy and his colleagues particularly has received a great deal of attention. It essentially states that “deposition of amyloid  $\beta$  protein ( $A\beta$ P), the main component of the plaques, is the causative agent of Alzheimer's pathology...” [5]. Hardy is now awaiting results from the first clinical trials of agents designed to break down the  $A\beta$  plaques that build up in AD afflicted brains. If two or three of these agents fail, evaluation and modification of the amyloid hypothesis will be necessary [6].

Another popular theory, the vicious cycle hypothesis, proposes that the form of dementia known as AD is characterized by a vicious metabolic cycle in which fibrillar aggregates of amyloid beta ( $A\beta$ ) peptides build up in affected regions of the brain [7-8]. This aggregation is thought to be caused by a number of factors including (i) up-regulation of  $\beta$ -secretase and  $\gamma$ -secretase proteolytic activity that generate  $A\beta$  from amyloid precursor protein (APP), (ii) down-regulation of  $\alpha$ -secretase activity which hinders the production of  $A\beta$ , (iii) increased synthesis or stability of APP which is a precursor of  $A\beta$ , and (iv) reduced efficiency of protease mechanisms such as the activity of insulin-degrading protease (IDE) which catabolizes  $A\beta$  [9]. Other proteases that have been proven to degrade  $A\beta$  include cathepsin D [10], serine protease-2-macroglobulin complex [11], and neprilysin [12]. Neprilysin is thought to be the most potent  $A\beta$  degrading enzyme *in vivo* among endopeptidases whose activities are sensitive to thiorphan and phosphoramidon [12].

It is thought that the formation of  $A\beta$  aggregates then triggers the activation of microglia and induces the formation of oxidants, cytokines, and prostanoids that work to increase the production of  $A\beta$  via neurons and astrocytes, making the vicious cycle come full circle.  $A\beta$  aggregation may initiate the killing of neurons either directly or indirectly by increasing their sensitivity to excitotoxicity [9]. In addition, research using AD mouse models suggests that deposition of neurotoxic forms of  $A\beta$  aggregates may induce neuronal apoptosis due to abnormal proteolytic processing of APP [13]. Low levels of telomerase, especially the catalytic subunit of telomerase TERT, and associated proteins that protect neurons from apoptosis [14-15] have been linked to increased levels of oxidative stress and mitochondrial dysfunction following exposure of the neuron to  $A\beta$  peptides [16]. Further, neurons showed decreased vulnerability to amyloid  $\beta$ -peptide-induced apoptosis as a result of overexpression of TERT in pheochromocytoma cells [16]. Other studies suggest that oxidative stress induces the transcription of  $\beta$ -amyloid precursor protein cleaving enzyme 1 (BACE1) perhaps via  $\gamma$ -secretase activity involving the c-jun N-terminal kinase (JNK)/c-jun pathway, thereby promoting pathological levels of  $A\beta$  in AD; increased levels of BACE1 have been found in vulnerable regions of AD brains as well [17].  $A\beta$  aggregates may also trigger the formation of neurofibrillary tangles and disrupt neuron structure and function by promoting excess phosphorylation of the tau protein [9]. In AD, the six adult tau isoforms are abnormally phosphorylated and form paired helical filaments. These helical filaments are the major fibrous component of the characteristic neurofibrillary lesions in AD [18]. Recent studies strongly suggest that conformational changes and truncation of tau occur after the phosphorylation of tau. Two pathways have been proposed for the pathological processing of tau protein during AD. These include either phosphorylation and cleavage of tau followed by the Alz-50 conformational change or phosphorylation followed by the conformational change and then cleavage [19]. In addition, there is evidence that  $A\beta$  aggregation disrupts the protective function of astrocytes as well, leading to the death of neurons [9].

Data suggests that a major key factor in controlling the prevalence of dementia is attention to vascular risk factors such as hypertension, coronary artery disease, hyperlipidemia, and smoking [2]. Many studies have confirmed that good control of hypertension prevents dementia as do administration of statins [20-21]. The control of cholesterol is another important factor because cholesterol-rich “lipid raft” regions promote  $\beta$ - and

$\gamma$ -secretase activities and thereby high cholesterol may promote A $\beta$  production from APP [22-24]. Further, it seems that there is a direct link between brain vascular atrophy and mild cognitive impairment (MCI), a precursor for AD. In the following text, the use of flavanols known to promote cardiovascular health, in part by inhibiting brain vascular atrophy, shall be investigated for potential use in preventing and delaying the onset of MCI and AD.

## Polyphenols and Neurodegenerative Diseases

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A number of studies have shown that polyphenols affect neurons in the brain. One such study determined that polyphenols found in fruits may help in lessening the motor and cognitive behavioral deficits in motor function and memory respectively by altering stress signaling and neuronal signaling using rodent models [25-27]. The AD pathophysiology has a direct relation to the oxidative stress on neurons. Oxidative stress may cause neuronal damage and modulate intracellular signaling, leading to cellular death by apoptosis or necrosis [27]. It appears that as aging continues, the central nervous system (CNS) becomes more susceptible to the negative effects of oxidative stress [26]. Early in the pathology of AD, the A $\beta$  amyloid peptide employs different mechanisms such as apoptosis, mitochondrial dysfunction, and the nuclear transcription factor NF- $\kappa$ B to destroy neurons. The toxicity of the plaques also involves transition metals, the formation of hydrogen peroxide, and the buildup of reactive oxygen species. This results in oxidative stress that leads to the development of AD [5, 28-30]. The CNS is especially susceptible to increases in the ratio of oxidized glutathione to total glutathione, the accumulation of lipofuscin along with bcl-2, increases in membrane lipid peroxidation, reductions in glutamine synthetase, reductions in redox-active iron, and alterations in membrane lipids [26]. In accordance with this, it has been found that most tissues from post-mortem AD brains contain elevated levels of lipid peroxidation products [31], as well as protein and DNA oxidation products.

A growing body of evidence suggests that the interaction of redox-active metals and A $\beta$  elevates oxidative stress. The dyshomeostasis of cerebral biometals such as Fe, Cu, Zn, and APP/A $\beta$ /metal redox interactions contribute to the neuropathology of AD [32-33]. It has also been determined that metals can interact directly with A $\beta$ , constituting one of the primary lesions in AD pathology. Metals bind and promote in vitro aggregation of A $\beta$  peptides into tinctorial A $\beta$  amyloid. Further, A $\beta$  amyloid plaques in post-mortem AD brains are abnormally enriched in copper, iron, and zinc. Metal chelators have been shown to dissolve these proteinaceous deposits from postmortem AD brains and thereby attenuate the cerebral A $\beta$  amyloid burden in APP transgenic mouse models. In addition, our experiments have shown that redox-active Cu(II) and Fe(III) are reduced in the presence of A $\beta$  concurrent with the production of reactive oxygen species: H<sub>2</sub>O<sub>2</sub> and hydroxyl (OH<sup>-</sup>) radicals. These A $\beta$ /metal redox reactions are silenced by redox-inert Zn(II) but are exacerbated by biological reducing agents and lead to oxidation damages in AD brains. In addition, H<sub>2</sub>O<sub>2</sub> mediates A $\beta$  cellular toxicity and increases the production of both A $\beta$  and APP. Moreover, the 5' untranslated region (5'UTR) of APP mRNA has a functional iron-response element (IRE) consistent with biochemical evidence that APP is a redox-responsive metalloprotein. Therefore, the redox interactions between A $\beta$ , APP, and metals may be at the heart of a pathological feedback system in which A $\beta$  amyloidosis and oxidative stress work to promote each other. These findings lead to the idea that amyloid-specific metal-complexing agents and antioxidants should be investigated as possible treatments for AD due to their potential effects in reducing oxidative stress via dissolution of redox-active metals and counteraction of free radicals [34].

A sufficient amount of evidence suggests, for example, that antioxidants from the diet can influence the occurrence of neurodegenerative disorders such as AD and Parkinson's disease (PD). In particular, the antioxidant flavanols-epicatechin and catechin have shown great promise. One study confirmed that consumption of the plant-derived flavanol (-) epicatechin enhances cognition in sedentary or wheel-running female C57BL/6 mice via positive effects on neuronal survival and plasticity. It also helped to enhance retention of spatial memory in these mice when administered in conjunction with exercise. The improvement in spatial memory resulted from increased angiogenesis and neuronal spine density, not from newborn cell survival in the dentate

gyrus of the hippocampus. In addition, microarray analysis showed upregulation of genes associated with learning and down-regulation of markers of neurodegeneration in the hippocampus [35]. Other studies have found that (-)-epigallocatechin-3-gallate (EGCG), an important type of catechin, helps to regulate the iron metabolism proteins APP and transferrin receptor (tR) due to its metal-chelating and radical-scavenging properties. The amount of APP protein in the cells was significantly reduced but the amount of mRNA encoding APP remained the same, suggesting a post-transcriptional effect. EGCG also reduced the formation of toxic beta-amyloid peptide in Chinese hamster ovary (CHO) cells that overexpressed the 'Swedish' mutation [36]. Further, EGCG has been found to hinder lipopolysaccharide (LPS)-activated microglial secretion of nitric oxide (NO) and tumor necrosis factor-alpha (TNF- $\alpha$ ) by down-regulating inducible NO synthase and TNF- $\alpha$  expression. It was also found that EGCG protects against microglial activation-induced neuronal injury in the human SH-SY5Y cell line and in primary rat mesencephalic cultures, suggesting that it may have powerful therapeutic effects in treating and/or preventing AD and PD by promoting neuronal health [37]. Both catechin and epicatechin have been found to have anti-fibrillogenic properties as well in that they have been shown to reduce already existing alphaS fibrils in addition to causing a reduction in the formation of alphas fibrils in brain cells [38]. Another study determined that administration of the antioxidant quercetin preserves the activity of antioxidant enzymes (to counter oxidative stress due to free radicals) and reduces the formation of cellular edema in rat neuronal cells [39]. The Personnes Agees Quid study [40] found that people who drank 3-4 glasses of wine per day developed dementia 80% less three years later than people who drank less or did not drink at all even after corrections had been made for confounding factors [41]. In addition, a follow-up study 5 years later suggested an inverse relationship between flavanoid intake and the risk of dementia in subjects over the age of 65. The sources of flavanols included fruits, vegetables, wine, and tea [42]. Further, consumption of two more cups of tea per day helped to reduce the risk of PD [43]. Other sources of flavanol such as ginkgo biloba extract Egb 761 have been shown to improve cognitive function in AD patients [44-46]. The neuroprotective effects of these flavanoids and polyphenols have been suggested using mostly animal models. Rats that consumed a diet rich in antioxidants from sources such as blueberries, strawberries, and spinach experienced less decline in cognitive function [26, 47]. Overall, the consumption of foods and beverages rich in polyphenols has been shown to increase the antioxidant levels in serum and, therefore, it is thought that they have a beneficial effect against oxidative damages [44-45].

Many studies have demonstrated in animal models that tea may have a role in reducing PD though this has not been demonstrated in regards to AD. However, *in vitro* studies have shown that green tea extract may protect neurons from A $\beta$  amyloid-induced damages [48-50]. Recently, APP proteolysis and A $\beta$  metabolism have been targeted for potential use in AD therapy. APP can be processed by a nonamyloidogenic pathway involving the cleavage of APP to soluble APP by  $\alpha$ -secretase activity or it can be processed by amyloidogenic  $\beta$  and  $\gamma$ -secretases. EGCG, a main phenolic constituent may promote the nonamyloidogenic  $\alpha$ -secretase pathway and epicatechin (EC) may reduce the formation of A $\beta$  amyloid fibrils [51]. However, the presence of another catechin epigallocatechin (EGG) in conjunction with EC increases A $\beta$  peptide production by 20-30% in SweAPPN2a neuronal cells and 10-15% in TgAPPsw-derived neuronal cells. The presence of these two catechins together inhibits the ability of EGCG to reduce A $\beta$  amyloid peptide generation [52].

## Cardiovascular Risk Factors

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It is clearly evident that maintaining healthy cerebrovasculature decreases the risk of VaD. Recently, more data suggest that healthy cerebrovasculature also reduces the risk of AD because most risk factors for vascular disease have been found to influence AD risk [1]. The inhabitants of the Melanesian island of Kitava demonstrate this trend. They do not salt their food and their quasi-vegan diet contains only a small amount of animal product in the form of potassium-rich fish. Due to this very low-salt diet, the Kitavans remain thin and free from hypertension and stroke as well as maintain insulin sensitivity throughout their lives [53-55]. Excellent cerebrovascular health is attributed to their lack of strokes. Another point of great interest is that in addition to

good cardiovascular health, senile dementia is virtually absent in the Kitavan society, even though many Kitavans live to reach a very old age [56]. Further, similar trends were noted among the sub-Saharan African population early in the 20th century. Hypertension, stroke, and senile dementia were all rarely present in this population [57]. Therefore, a link seems to exist between excellent cerebrovascular health and not developing dementia [1].

Other evidence shows that cerebral ischemia exerts a pro-inflammatory effect that up-regulates the metabolic cycle that may result in AD, or it directly kills neurons and makes them more susceptible to stimuli that would kill them [58-61]. Chronic hypoperfusion in rodents has been shown to enhance the expression of APP in affected brain regions in rodents [62-64]. Up-regulation of  $\beta$ -secretase and down-regulation of  $\alpha$ -secretase have also been reported following ischemic brain injury [65-66]. The low concentrations of NO produced by a healthy cerebrovascular endothelium act in a protective way toward parenchymal brain cells [67-68]. Nitric oxide has been documented to up-regulate the expression of alpha-secretase and down-regulate the expression of  $\beta$ -secretase in cultured neuroblastoma cells. These actions suggest that cerebrovascular NO might act to suppress the production of A $\beta$  in the absence of superoxide [69].

Flavanols in unprocessed cocoa powder, mostly epicatechin, act directly on endothelium to stimulate eNO activity, thereby causing increased cerebral blood flow [70-72]. The Kuna Indians off the coast of Panama drink about 900 mg of cocoa a day and are the only civilization that consumes salt and is still hypertension-free, suggesting that cocoa has profoundly beneficial cardiovascular effects [73-75]. Data also suggests that the increased cardiovascular health of the Kuna Indians is not genetic but environmental because the effects are not sustained in those members of the population who have moved to urban areas. In one study that investigated cocoa flavanols and vasodilatation [75-76], 27 healthy individuals were studied before and after ingestion of 920 mL of flavanol-rich cocoa over a 5-day period in 4 equal doses. Each cocoa dose contained a total of 821 mg of flavanols. To monitor blood flow, pulse wave amplitude readings were taken in the fingertip using peripheral arterial tonometry. After 4 days of cocoa ingestion, a 29% increase in amplitude resulted when measured in the morning 12 hours after the last dose of cocoa. On the 5th day, another dose of cocoa led to a 33% increase after 90 minutes [75]. Evidence shows that the mechanism that causes this vasodilator response is NO-dependent because a nitric oxide synthase (NOS) inhibitor NG-nitro-L-arginine methyl ester (L-NAME) administered after 4 days of cocoa ingestion completely reversed the increase in vasodilatation. Thus, reversal of the response clearly involves a mechanism that inhibits NOS. The agent in the cocoa responsible for the vasodilator response was isolated by setting up a control in which subjects ingested a flavanol-poor cocoa drink. The vasodilator response was notably smaller in these subjects, suggesting that the vasodilator response is in fact due to flavanols [73, 76]. Further evidence that flavanols play a role in producing vasodilatation includes a number of different studies. Researchers found that red wine elicits NO-dependent relaxation in rabbit and rat aorta and red wine polyphenol extract increases the production of NOS as well as NO in human umbilical vein endothelium [77-79].

This NO-dependent vasodilator response can be classified as a measure of enhanced endothelial function, an ability that declines as a result of increasing age but is a major cardiovascular risk factor and predictor of future cardiovascular events. Thus, growing evidence suggests that flavanols may have beneficial effects on endothelial function. In one study, the vasodilator response in 15 young healthy subjects was compared to that of 19 older healthy subjects. Baseline readings from the subjects were obtained following the ingestion of cocoa for 4-6 days. A second reading was taken at the end of this period, 90-180 min after ingestion of the last cocoa dose. Blood pressure, flow mediated dilation, and pulse wave amplitude readings were obtained. Twelve of the young subjects and 9 of the older subjects were then administered L-NAME intravenously. The results of this study suggest that cocoa enhanced with flavanols improved measures of endothelial function to a greater degree in healthy elderly people than in the younger people. The elderly saw greater increases in flow-mediated dilation and peripheral vasodilatation after administration of the cocoa-rich flavanols as well as greater increases in blood pressure as a result of administration of the NOS inhibitor L-NAME. These findings suggest that flavanols may



be useful in counteracting decreases in endothelial function associated with aging [80].

Furthermore, flavanols can reverse endothelial dysfunction due to insults such as smoking. A study conducted by Heiss determined that a single-dose of flavanol-rich cocoa can acutely reduce endothelial dysfunction. After ingestion of flavanol-enriched cocoa for 7 days, FMD responses increased significantly. Thus, it has been shown that daily consumption of flavanol-rich cocoa not only prevents endothelial dysfunction, but can also effectively reverse endothelial dysfunction in a sustained and dose-dependent manner [81]. In addition to resulting in cardiovascular disease, aging is a common risk factor for cerebrovascular diseases such as stroke and dementia. One out of 10 adults over the age of 65 is afflicted, as are half of all adults above the age of 85. Most of the elderly population develops dementia as a result of AD or VaD [82-83]. Evidence suggests that dementia is 9 times more likely to occur in the first year after cerebral infarct; the chances of developing AD during this time increase by 50% [84-85]. Epidemiologically, AD and VaD share many risk factors such as age, ApoE4 genotype, hypertension, arteriosclerosis, diabetes mellitus, smoking, and atrial fibrillation [86]. In addition to this overlap, the neuropathology of these two diseases also relates. Neurofibrillary plaques and tangles exist in VaD and vascular pathology is present in AD. A number of cerebromicrovascular abnormalities show up in AD pathology as well as vascular lesions, cerebral amyloid angiopathy, microvascular degeneration, and periventricular white matter lesions [82, 87]. The vascular abnormalities seen in AD are consistent with impairment of the BBB, decreased microvascular density, vascular distortions, functional alteration, damaged cerebral endothelial function, and arteriolar changes such as lipohyalinosis [82].

### **The Effect of Flavanols upon Cerebral Blood Flow**

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A few studies have documented the use of polyphenols to increase cerebral blood flow. Galli found that fruit polyphenols decrease the susceptibility of rat brains to the damage caused by oxidative stress as aging occurs [88]. In a French study, it was found that an inverse relationship exists between the ingestion of flavanoids and the development of dementia, a finding that might be explained by the concept that flavanols improve vascular function and increase cerebral blood flow [89]. Further, there is much speculation that decreased cerebral blood flow leads to the development of dementia.

The Rotterdam study in which the cerebral blood flow of 1730 subjects over the age of 55 was monitored over a 6-year period concluded that cerebral hypoperfusion precedes and may contribute to the onset of clinical dementia [90]. Other studies have also concluded using single-photon emission computed tomography (SPECT) that the cerebral blood flow is much lower in certain brain regions (mainly the prefrontal and inferior parietal cortices) of those who progressed rapidly to AD [91-92]. Moreover, another cocoa study determined that there is an increase in cerebral blood flow through the middle cerebral artery after ingestion of 900 mg of cocoa daily for a week. This effect of cocoa was sustained [76]. Finally, a study that employed functional magnetic resonance imaging based on blood oxygenation level-dependent (BOLD) contrast to explore the effect of flavanols on the human brain found an increase in the BOLD signal intensity in response to a cognitive task following ingestion of 150 mg of flavanol-rich cocoa for 5 days. In addition, a pilot study that was conducted to evaluate the relationship between cerebral blood flow and a single acute dose of cocoa consisting of 450 mg of flavanols concluded that flavanol-rich cocoa can increase cerebral blood flow to gray matter, suggesting the potential of flavanols as a treatment for vascular impairment, dementia, strokes, and the maintenance of cardiovascular health [93].

### **Link between Brain Vascular Atrophy, Alzheimer's Disease, and Flavanols**

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Through a number of studies it has been determined that polyphenols may be used to delay the onset of neurodegenerative diseases as discussed earlier and that flavanols, a type of polyphenols, may be used to improve cardiovascular health, including cerebrovascular health. Further, evidence exists that brain vascular atrophy leads to MCI; MCI often converts into the AD form of dementia [94]. Because flavanols can be used to prevent or delay the onset of brain vascular atrophy through the benefits they impart cardiovascularly, they

should also be effective in delaying the conversion of MCI into AD. MCI consists of memory complaints and objective evidence of cognitive impairment but no evidence of dementia and, as such, is considered a stage between normal aging and dementia. Conversion to AD is associated with the worsening of executive functions and functional status [94]. In one particular study, MRIs of patients progressing from MCI to AD were studied throughout the duration of the conversion, and it was determined that 3 years before the diagnosis of AD, deficits included primarily grey matter loss in the medial temporal lobes, including the amygdala, anterior hippocampus, entorhinal cortex, and partially in the fusiform gyrus. However, 1 year before the diagnosis of AD, cerebral atrophy had progressed and spread to the middle temporal gyrus, the posterior regions of the temporal lobe, and the entire extent of the hippocampus. By the time AD was diagnosed, atrophy had further spread throughout the middle temporal lobes, the temporoparietal association lobes, as well as the frontal lobes [95]. Moreover, the Sydney Stroke Study found that post-stroke dementia and MCI are very common in older individuals through the study of MRI brain scans, further suggesting a link between brain vascular atrophy and dementia [96].

Lacunar infarcts and deep white matter changes characterize subcortical ischemic vascular disease (SIVD). From 36% to 50% of vascular dementia is attributed to SIVD. In rats, it has been determined that aging produces changes in blood flow that makes the brain more susceptible to insults such as oxidative stress and other changes involved in AD. Impaired delivery of oxygen due to decreased blood flow to neurons leads to further cognitive detriments. The effects are cyclic in that insults such as amyloids promote further changes in blood hemorheology and decreased blood flow. Hippocampal and cortical atrophy resulting from a mixture of ischemic and degenerative pathologies rather than the presence of lacunes is the main factor leading to dementia in SIVD and AD [97].

## Conclusion

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Overall, a great deal of evidence suggests that flavanols increase blood flow and perfusion of the brain. In addition, a number of experimental data also suggest that flavanols may delay the onset of neurodegenerative diseases such as AD through a number of different mechanisms. In particular, it has been determined that the natural antioxidant flavanols decrease the incidence of vascular atrophy and offer many cardiovascular benefits in addition to counteracting oxidative stress via their antioxidant properties. Further, brain vascular atrophy and the development of MCI are directly linked. In turn, MCI is often a precursor for the development of AD. Therefore, it seems that the next most likely step for investigation should be the effects of flavanols on AD development and progression in humans via consideration of the flavanols' vascular benefits and the mechanisms by which they impart these benefits. It looks promising that flavanols may be natural agents that have potential in effectively treating and/or preventing AD by a number of mechanisms. A discovery such as this would greatly benefit millions of people and help in warding off the dementia epidemic that is upon us.

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