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**FROM SMALL TO BIG MOLECULES: HOW DO WE PREVENT AND DELAY THE
PROGRESSION OF AGE-RELATED NEURODEGENERATION?**

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Running title: Use of nutraceuticals molecules to prevent age-related neurodegeneration

Abstract

Age-related neurodegeneration in the brain and retina is complicated. It comprises a series of events encompassing different modes of degeneration in neurons, as well as inflammation in glial cells. Systemic inflammation and risk factors can contribute to disease progression. Age-related conditions such as Alzheimer's disease (AD), Parkinson's disease (PD) and Age-related Macular Degeneration (AMD) affect patients for 5 to 20 years and are highly associated with risk factors such as hyperhomocysteinemia, hypercholesterolemia, hypertension, and symptoms of mood disorder. The long duration of the degeneration and the wide array of systemic factors provide the opportunity for nutraceutical intervention to prevent or delay disease progression.

Small molecules such as phenolic compounds are candidates for neuroprotection because they have anti-oxidant activities and can modulate intracellular signaling pathways. Bigger entities such as oligosaccharides and polysaccharides have often been neglected because of their complex structure. However, certain big molecules can provide neuroprotective effects. They may also have a wide spectrum of action against risk factors.

In this review we use an integrative approach to the potential uses of nutraceutical products to prevent age-related neurodegeneration. These include direct effects of phenolic compounds and polysaccharides on neurons to antagonize various neurodegenerative mechanisms in AD, PD and AMD, and indirect effects of these compounds on peripheral disease-related risk factors.

1. INTRODUCTION

Aging is a major risk factor contributing to the onset and progression of many neurodegenerative diseases. Although the symptoms, pathological changes and even the regions being affected during the neurodegenerative process are diverse, it is certain that these diseases share many common factors. Numerous studies demonstrate that oxidative stress, chronic inflammation, impairment of protein processing and degradation, and alterations of cellular survival pathways are common features of age-associated neurodegenerative diseases. These stress factors are therefore potential targets for disease prevention and intervention.

Nutraceutical intervention may be an effective mean for the prevention of age-associated neurodegenerative diseases. Certain diets reportedly reduce the risk of neurodegenerative diseases [1-4]. In this paper we review the current concepts of three age-related neurodegenerative diseases: Alzheimer's disease (AD), Parkinson's disease (PD), and Age-related Macular Degeneration (AMD), and summarize common therapeutic strategies. We also discuss the feasibility of several small phenolic compounds or big molecules such as oligosaccharides, polysaccharides and glycoconjugates from plant and marine sources as agents to intervene with the above illnesses.

2. AGE-RELATED NEURODEGENERATIONS: UNIQUE SYMPTOMS AND COMMON PATHOGENIC MECHANISMS

2.1 Unique features in Alzheimer's disease (AD), Parkinson's disease (PD), and Age-related Macular Degeneration (AMD)

AD is the leading cause of dementia. It is characterized by a decline in short-term memory and a slowly progressive loss of other cognitive functions. The unique pathological hallmarks of AD are the accumulation of extracellular senile plaques and intraneuronal neurofibrillary tangles (NFTs) in the hippocampus and cerebral cortex. Senile plaques and NFTs

are made up of aggregated amyloid- β (A β) peptide and hyperphosphorylated tau (p-tau) protein, respectively [5].

PD is characterized by movement difficulties including tremor, bradykinesia, and rigidity at early stages. At late stages, cognitive and behavioral impairment may arise. The substantia nigra in the midbrain is the major area affected, with massive loss of dopaminergic neurons accompanied by intracellular Lewy body inclusions. α -Synuclein is the major component of Lewy bodies [6].

AMD is one of the leading causes to severe visual impairment in the elderly [7, 8] and is ranked as the third cause of blindness [9]. It is categorized into dry or wet forms, which are characterized by derangement and detachment of the retinal pigment epithelium and visible choriocapillaris [10, 11], or abnormal in-growth of blood vessels into the retina concomitant with subretinal h emorrhage, respectively [12, 13]. AMD is a chronic degeneration of photoreceptors and retinal pigment epithelium of the macular region of the retina [14, 15]. Drusen in the macula are the major pathogenic factor. Drusen are yellow deposits containing oxidized products, immunoregulators, A β assemblies and cell debris [16].

2.4 Similarities in neurodegenerative mechanisms, risk factors and therapeutic strategies among AD, PD and AMD

The neurodegenerative mechanisms of AD, PD, AMD are found to be quite similar. Although debate continues on whether senile plaques, NFTs, Lewy bodies or drusen are responsible for the initiation of neurodegeneration in the diseases, large bodies of evidence from cell culture and animal studies show that these aggregated proteins are associated with neuroinflammation, oxidative stress and activation of stress or pro-apoptotic signaling pathways [17-19]. Targeting these common neurodegenerative mechanisms with the use of anti-oxidant,

anti-inflammatory drugs and specific stress signal inhibitors can therefore provide beneficial effects for disease prevention or treatment. Anti-oxidants are perhaps the most-investigated disease-modifying agents. In human subjects, anti-oxidant intervention with vitamin E is associated with better cognitive performance and may reduce the risk of AD [20-22]. For PD, anti-oxidants have shown protective effects in different experimental models [23-25]. Anti-oxidants may also benefit AMD. A diet with a high content of carotenoids such as vitamin A, lutein, and zeaxanthin has been recommended [26]. Together with supplements of antioxidants such as vitamin C and E, a cocktail of antioxidants reportedly prevents progression of AMD to late stage [27]. The use of anti-inflammatory drugs has been investigated in various diseases. Epidemiological studies suggest that non-steroid anti-inflammatory drugs (NSAIDs) may reduce the risk of AD [28]. However, the use of NSAIDs in AD is now quite controversial as several clinical trials demonstrate the ineffectiveness of NSAIDs for slowing the progression of AD [29, 30]. It is yet too early to conclude that anti-inflammatory drugs are ineffective for AD treatment or prevention as the dosage and duration of drug between epidemiological and clinical studies are different [31]. Nevertheless, down-regulation of cerebral inflammation is still a major target to retard disease progression [32, 33]. In PD, anti-inflammation has long been a major thrust in drug development [34]. In AMD, complement-mediated inflammation is involved in the pathogenesis, hence complement inhibition has been suggested as a potential pharmacological approach for disease treatment [35].

Age-related neurodegenerative diseases are often multifactorial and are associated with a number of risk factors. For example, AD is associated with smoking [36], diabetes mellitus [37] and hypertension [38]. PD is associated with hyperhomocysteinaemia [39] and exposure to pesticides [40]. AMD is associated with smoking, excessive light exposure and other attributed causes [41]. There are lots of overlapping of factors leading to disease progression and pathogenesis among these three neurodegenerative diseases. For example, cognitive impairment can occur in the late stage of PD [42]. Risk factors for AMD and AD are very similar [43, 44].

A β peptides have been found in AMD drusen [45, 46], and anti-A β therapy may be a strategy for AMD [47]. Some common risk factors for AD, PD and AMD are summarized in Table 1. In view of these, it is possible that some bioactive food compounds may reduce risk and modulate the pathogenesis of AD, PD and AMD indirectly.

3. NUTRACEUTICAL INTERVENTION FOR AGE-RELATED NEURODEGENERATIVE DISEASES

3.1 Polyphenols

Polyphenols is a class of highly bioactive compounds characterized by multiple hydroxyl groups attached to aromatic rings. Based on the number of phenol rings, how the rings are connected, and the chemical groups attached, polyphenolic compounds can be categorized into flavonoids, stilbenes, phenolic acids, phenolic alcohols, and lignans [48, 49]. They can either be naturally occurring as plant secondary metabolites, or synthesized by chemical means [49]. A number of *in vitro* and *in vivo* studies have demonstrated that these small molecules are able to modulate many pathways for disease progression and cellular survival in addition to their strong antioxidant, anti-inflammatory, and vasodilatory effects [25, 50]. All these properties can potentially combat common stress factors in many neurodegenerative diseases and thus be neuroprotective. In this section we mainly focus on the flavonoids and stilbenes because they have been well studied for their neuroprotective roles.

3.1.1 Flavonoids

Flavonoids are ubiquitous in plants and make up one of the largest subclasses of polyphenols [49]. They are characterized by a common structure (Figure 1a) formed by two benzene rings (rings A and B) interconnected by a 3-carbon oxygenated heterocycle (ring C) [48]. They can be further subdivided into flavonols, flavanols, flavones, isoflavones, flavanones, and anthocyanidins upon the saturation of ring C, the presence or absence of the 4-oxo-function, and the chemical substitutions on the B and C rings (Figure 1b) [51]. In food and beverages,

flavonoids are often glycosylated, linked to organic acids, and/or to one another [49]. The daily intake of flavonoids is highly variable among different ethnic groups, ranging from 20 to 1000 mg per day [52].

(A) Anti-oxidative effects of flavonoids and their structures

Many investigators have emphasized the antioxidant properties of flavonoids in relation to their neuroprotective effects. Accordingly, flavonoids can directly interact with reactive oxygen species (ROS) and reactive nitrogen species (RNS) [53], chelate transition metals such as iron and copper to suppress metal-catalyzed oxidative stress via the Fenton reaction [54], boost intracellular antioxidant enzyme activities [55], and preserve endogenous antioxidants [56, 57]. For example, a flavanol abundantly found in green tea, epigallocatechin-3-gallate (EGCG; Figure 2a), and a flavonol highly present in onions and apples, quercetin (Figure 2b), can directly quench singlet oxygen and scavenge hydroxyl radicals, superoxide radicals, and lipid peroxy radicals by donating hydrogen [51, 53, 55].

An analysis of structure and antioxidant activity relationships among various flavonoid subclasses reveals that certain structural features give rise to better antioxidant capabilities, including (1) the presence of ortho-dihydroxy groups in ring B, (2) the combination of 2,3 carbon-carbon double with the 4-oxo function in ring C, and (3) the possession of the 3-OH and 5-OH groups with the 4-oxo function on the A and C rings [51, 53]. Quercetin (Figure 2b) bears all the above features and is thus a strong antioxidant. In general, these characteristics allow greater electron delocalization and stability after donation of hydrogen. Regarding iron and copper chelating properties, three structural sites have been proposed to be responsible for forming inactive complexes with metals. These are (1) the ortho-hydroxy groups in ring B, (2) the 4 oxo-function together with 3-OH or 5-OH in rings A and C [51], and (3) the ortho-hydroxy group in gallic side chain as in EGCG [55, 58]. In addition, EGCG up-regulates the activities of the antioxidant enzymes catalase (for H₂O₂) and superoxide dismutase (for superoxide) in the

striatum of experimental mice [59], whereas quercetin can prevent the oxidation of the endogenous antioxidant glutathione in neurons [56, 57], thereby indirectly combating oxidative stress.

(B) Signaling pathways regulated by flavonoids

Besides antioxidant mechanisms, flavonoids function as regulators of many cellular pathways such as phosphoinositide-3-kinase (PI3K)-Akt/protein kinase B (Akt/PKB) and mitogen-activated protein kinase (MAPK) pathways for neuroinflammation, neuronal survival and vasodilation [50]. For instance, EGCG suppressed the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) and the release of nitric oxide (NO) and pro-inflammatory cytokines from astrocytes and microglia by inhibiting MAPK signaling cascades [60]. EGCG-mediated phosphorylation of protein kinase C (PKC) promotes survival of human neuroblastoma SH-SY5Y cells from A β and 6-hydroxydopamine (6-OHDA)-induced neurotoxicity, increases proteasomal removal of pro-apoptotic Bad protein, and shifts amyloid precursor protein (APP) processing to the non-amyloidogenic α -secretase pathway [61]. On the other hand, quercetin protects neurons against hydrogen peroxide and tumor necrosis factor- α (TNF- α)-induced neuronal death by inhibiting c-Jun N-terminal kinase (JNK) [50]. Naringenin (Figure 2c), a flavanone with high abundance in citrus fruits, protects neurons against bacterial endotoxin lipopolysaccharides (LPS) in combination with γ -interferon (IFN- γ)-induced glial activation by suppressing p38 and signal transducers and activators of transcription family of transcription factor 1 (STAT1) [62]. As for vasodilatory effects, Sorond *et al* demonstrated that consumption of a flavanol-rich cocoa drink for 1-2 weeks increased cerebral blood flow in the middle cerebral artery in healthy elderly subjects, presumably by increasing NO availability [63]. This may provide therapeutic benefits to AD and PD patients, in which a reduction in cerebral blood flow had been reported.

3.1.2 Stilbenes

The basic structure of stilbenes comprises a 1,2-diphenylethylene backbone with the two phenyl groups arranged in either *cis* or *trans* configuration (Figure 3). Both isomers can optically interconvert *via* a singlet-electron excited state, and the *trans* isomer is generally more stable [64]. Stilbenes exist as monomers, dimers, and oligomers [65]. Unlike flavonoids, in which the neuroprotective capacities of various subgroups have been investigated, research on stilbenes has mostly focused on resveratrol and its structural analogues.

(A) Resveratrol as a naturally occur stilbene derivative

Resveratrol (Figure 4a) is a stilbene derivative naturally synthesized on the skins of grapes in response to fungal invasion, but is also present in wine, peanuts, and berries [66]. It has been considered to be the chief ingredient responsible for the health-promoting effects of red wine, and a great number of *in vitro* and animal models have shown that it could potentially elicit multiple benefits in retarding neurodegenerative processes [23, 67-70], diabetes [71, 72], cancer [73-75], and cardiovascular diseases [76, 77]. In addition, several interesting articles have been published on the pharmacokinetics of orally administered resveratrol in humans [78-83]

(B) Anti-oxidative effects of resveratrol

Like the flavonoids, resveratrol bears good antioxidant, anti-inflammatory, vasoactive, and pro-survival effects, making it a candidate to counteract the common stress factors for age-related neurological disorders [25]. Resveratrol directly scavenges hydroxyl radicals, superoxide, and DPPH[•] radicals in cell-free systems [84, 85], and inhibits H₂O₂- or lipid peroxide-dependent peroxidation of membrane lipids in culture [86]. Based on a structural comparison of resveratrol and its analogues, it was deduced that the 4'OH served as the most important hydrogen donation site [85], and that monohydroxystilbenes such as piceatannol and oxyresveratrol, and polyhydroxystilbenes such as hexahydroxystilbene (also known as M8), were significantly more effective radical scavengers than resveratrol [66]. Since resveratrol is largely present in conjugated forms in the body [87], caution should be exercised when extrapolating such

structural relationship and radical scavenging activities *in vivo*. Intraperitoneal injection of resveratrol up-regulates endogenous antioxidant enzymes in the brain, including superoxide dismutase, peroxidase, and catalase [88].

(C) Anti-inflammatory effects of resveratrol

Resveratrol is a non-specific COX-1 and COX-2 inhibitor [19, 87]. COX-1 is constitutively active for prostaglandin E synthesis and its inhibition has been regarded as unfavourable, whereas selective suppression of COX-2 activity is the target of many NSAIDs [89]. Attempts have been made to chemically modify resveratrol by adding one or more hydroxyl groups so that it will act as a selective COX-2 inhibitor. For example, both piceatannol (Figure 4b) and hexahydroxystilbene (Figure 4c), which are monohydroxylated and polyhydroxylated stilbenes respectively, are selective COX-2 inhibitors and may be superior to resveratrol in fighting neuroinflammation [66].

(D) Beneficial effects of resveratrol on neurons of AD and PD

Resveratrol exhibits pro-survival effects both *in vitro* and *in vivo*. For example, it activates the sirtuin protein SIRT1, a NAD⁺-dependent histone deacetylase protein *in vitro* [90]. In mouse models of AD a calorie-restricted diet reduces AD pathogenesis *via* an increase in SIRT1 activity [87]. In yeast, induction of a homologue of SIRT1 (SIR2) helps to prolong lifespan. These reports suggest that SIRT1 is a key factor to prolong survival of neurons [61]. SIRT1 over-expression reduces A β pathology in APP-expressing neuronal cultures by hindering intracellular A β peptide synthesis [67, 91]. On the other hand, resveratrol stimulates the removal of intracellular A β in different cell lines through proteasomal degradation [24]. In models of PD, resveratrol inhibits dopamine-induced cell death in dopaminergic SH-SY5Y cells by up-regulating anti-apoptotic Bcl-2 and down-regulating caspase 3 [69, 92], and oral administration of resveratrol attenuates 6-OHDA-induced dopamine depletion and loss of dopaminergic neurons in rats [23].

(E) Regulation of cerebrovascular functions by resveratrol

In addition to its role in cardiovascular health resveratrol improves cerebral blood flow, which may alleviate complications in AD and PD. For example, Lu and colleagues have shown that a single intravenous injection of resveratrol (20 mg/kg) elevated hippocampal blood flow by NO-dependent mechanisms during cerebral ischemia induced by coronary artery ligation [93]. Oral administration of resveratrol to healthy human adults dose-dependently improved cerebral blood flow in the frontal cortex during specific cognitive performance tasks [94].

3.2 Big molecules as potential neuroprotective agents for aged-related neurodegeneration

Increasing lines of evidence have shown that big molecules such as polysaccharides and glycoconjugates exhibit diverse biological activities [95-97]. It is now known that the progression of neurodegenerative disease can be influenced by systemic as well as CNS factors. In this section, we focus on polysaccharides that have potential neuroprotective effects. We also include some synthetic derivatives of polysaccharides. Since the structures of these ‘big molecules’ are more complicated than those of small molecules, it is sometimes difficult to correlate their biological actions with their specific structures. We summarize the data regarding their direct protective effects on neurons, indirect effects on disease-related risk factors, and immunomodulation properties. We use several examples to illustrate how these big molecules could modulate the progression of neurodegenerative diseases directly and indirectly.

3.2.1 Direct effects on neurons

(A) Chitosan and its derivatives – oligosaccharides from marine sources

Chitosan and its derivatives are polysaccharides or glycans that exhibit direct protective effects on neurons. Chitosan can be produced by deacetylation of chitin, a natural occurring polysaccharide which is abundant in the exoskeleton of marine organisms such as crabs [98]. It has poor solubility. Hydrolysis converts it to chito-oligosaccharides (COSs).

COSs protect rat hippocampal neurons from glutamate-induced toxicity [99], which accelerates disease progression in different neurodegenerative diseases. COSs dose-dependently reduce the levels of apoptotic cell death-triggered by glutamate in cultured hippocampal neurons. COS treatment attenuates calcium influx and caspase-3 activation [99]. COSs might provide neuroprotection through their anti-oxidant actions. This is feasible because COSs have hydroxyl and superoxide radical scavenging properties [100]. They also reduce production of NO in a human melanoma cell line (B16F1) stimulated by LPS, and down-regulate the expression of the NF- κ B gene in B16F1 cells exposed to hydrogen peroxide [101]. In copper-treated primary cultures of cortical neurons, COSs reduce the levels of ROS. Copper-induced toxicity has been implicated in a number of neurodegenerative diseases, including AD [102].

Neuroinflammation is involved in AD, PD and AMD, and attenuation of inflammatory responses is a potential therapeutic strategy. Neuroinflammation can be induced by agents such as A β peptide and pro-inflammatory cytokines. Chitosan exhibits anti-inflammatory activities. Kim and colleagues reported that A β peptide and the cytokine interleukin-1 (IL-1) could induce cultured astrocytes to secrete the pro-inflammatory cytokines TNF- α and IL-6. This was attenuated by treatment with a water-soluble chitosan. The levels of iNOS were also attenuated in the chitosan-treatment groups [103].

Apart from non-specific actions against neurodegeneration (anti-oxidant, anti-neuroinflammation and anti-glutamate-induced toxicity), COSs and chitosan exhibit specific effects in particular neurodegenerative diseases. COSs and chitosan derivatives may elicit protective effects against AD by affecting the production of A β peptide and inhibiting acetylcholinesterase (AChE) activity. The production of A β from its precursor APP heavily depends on the activity of β -secretase, also known as β -amyloid cleavage enzyme (BACE-1). In vitro data suggest that COSs and chitosan derivatives are BACE-1 inhibitors [104, 105]. Joe and colleagues modified the structure of chitosan by performing amino-alkylation on chitosan and

replaced the hydroxyl group by an amino-alkyl group, and tested the resultant water soluble chitosan derivatives for BACE-1 inhibitory activity. Among the three derivatives tested, aminoethyl-chitosan was the strongest BACE-1-inhibitor. After structural comparison of the derivatives, they suggested that the free amino group at the C-2 and C-6 positions played an important role in the BACE-1 inhibitory activity [105]. The same group also conducted studies on COSs. They found that a 90% deacetylated COSs derivative provided the strongest BACE-1 inhibitory activity, and that deacetylation and sulfation at the C-2 position could affect the biological activities of COSs [104]. Lee and colleagues demonstrated the importance of deacetylation for anti-AChE activity. Acetylcholine (ACh) is an important neurotransmitter which is ablated in AD; ACh levels can be maintained by inhibiting its degrading enzyme AChE. COSs derivatives show different degrees of AChE inhibition. The degree of deacetylation had major effects on the anti-AChE properties, and can transform COS from a non-competitive to a competitive AChE inhibitor [106].

(B) *Lycium barbarum* polysaccharide – the ‘sugar’ from berry

The fruits of *Lycium barbarum*, which are also called Wolfberry, are common herbs and foods in Asian countries. *L. barbarum* polysaccharides (LBP) are a group of heterogenous proteoglycans made up of monosaccharides. The carbohydrate content of LBP comprises arabinose, rhamnose, xylose, galactose, glucose, glucuronic acid, galacturonic acid, and mannose [107, 108]. LBP can be purified and sub-fractionated by solvents. Different LBP fractions can have diverse biological effects [109, 110], although structure-function analysis has yet to be performed. The amino acid content of LBP may be important for its biological activities. Yu and colleagues showed that its anti-A β toxicity is lost when its amino acids are destroyed with strong acid [107].

The neuroprotective effects of LBP are not specific to a particular disease. Three characteristics of LBP may explain its biological effects on neurons. Firstly, the ability of LBP to

suppress the activation of stress kinases under pathological conditions. In vitro data from our laboratory showed that LBP has potent inhibitory effects on pro-apoptotic stress kinases such as c-Jun N-terminal kinase (JNK), double-stranded RNA-dependent protein kinase (PKR) and extracellular signal-regulated kinase (ERK) [97, 110, 111]. Activation of stress kinases are common mechanisms leading to neurodegeneration in AD, PD and AMD [112-114]. Suppression of the activities of these kinases is responsible for the protective effects of LBP against glutamate, A β peptide, dithiothreitol (DTT, an endoplasmic reticulum stress inducer), and homocysteine-induced toxicity of neurons [97, 110, 111, 115].

Secondly, the anti-oxidant properties of LBP may contribute to its neuroprotective effects. LBP can increase the activities of anti-oxidative enzymes in peripheral systems [116-118]. There are few studies on the effects of LBP on neurons. Li and colleagues reported that oral administration of LBP reduced neuronal damage and oxidative stress in a retinal ischaemic/reperfusion injury model. The levels of lipid peroxidation in the retina were markedly reduced in the LBP-treated group [119]. Since this model involves the disruption of the blood-retina barrier, it may not totally reflect the situation on human chronic neurodegenerative diseases. In chronic glaucoma experimental model which does not have leakage of blood-retina barrier, oral administration of LBP can rescue retinal cells from apoptotic cell death. It is uncertain if the protective effects of LBP in the chronic glaucoma model are through an anti-oxidative mechanism [120]. Nevertheless, oxidative damage in the retina is a common aspect of ocular neurodegeneration, hence the anti-oxidant effects of LBP has the potential to play a neuroprotective role in AMD.

Up-regulation of survival pathways is the third neuroprotective mechanism. In a cell culture model of AD, an alkaline fraction of LBP was protective against A β -induced toxicity through up-regulation of the Akt pathway [121]. In an ocular hypertension model which mimics

human glaucoma, oral administration of LBP to rats up-regulated the neuronal survival signal β B2-crystallin and prevented neuronal cell loss [122].

3.2.2 Indirect effects of big molecules- modulation on the disease risk factors and the immunity

As shown in Table 1, age-related neurodegenerative diseases share a number of risk factors. Modulation of these risk factors can delay disease onset or slow down their progression. In this section, we discuss the use of polysaccharides to antagonize deleterious effects of risk factors for AD, PD and AMD.

(A) Anti-depressive effects

Depression is common among AD and PD patients; it occurs in about 20 to 50% of AD patients and 45% of PD patients [123, 124]. Experimentally, daily injection of corticosterone elevates its plasma levels in rats and induces depression-like behaviors. Zhang et al. reported that oral administration of LBP attenuated the depression-like behavior, probably by promoting neurogenesis in the hippocampus [125]. Oligosaccharides from the medicinal herb *Morinda officinalis* also exhibit anti-depression properties. In a cell culture model of depression, polysaccharide from *M. officinalis* (MP-1) reduced the corticosterone-induced death of PC12 cells. MP-1 attenuated the overload of intracellular calcium ion and down-regulated the expression of mRNA for nerve growth factor (NGF) [126, 127]. Chemical analysis reveals that MP-1 is an insulin-type fructan with simple linear (2 \rightarrow 1)-linked structure, and that its glucose/fructose ratio is 1:21 [128].

(B) Hypoglycæmic effects

Elevated blood glucose levels in diabetes mellitus can accelerate the progression of neurodegeneration. The hypoglycæmic activities of tea polysaccharides have been reported. Diabetic mice treated with crude tea polysaccharides, or a tea polysaccharides fraction, had significantly lower fasting blood glucose and glycosylated serum protein than their control

counterparts. A 100-120 kDa fraction with galactopyranose in the backbone and arabinofuranose units in side branches accounted for the hypoglycæmic activity. It was suggested that the arabinogalactan proteins in this fraction were important for the biological activity [129]. Arabinogalactan proteins are proteoglycans with a high content of arabinose and galactose monosaccharides but less than 10% protein. LBP is also rich in arabinose and galactose and has hypoglycæmic effects [130]. An early study identified the structural characteristics of several arabinogalactan-protein extracted from the fruits of *Lycium chinense Mill* (a closed related species to *L. barbarum* [131]. It is possible that these arabinogalactan-proteins are responsible for the hypoglycæmic activity.

(C) Immunomodulation effects

The immune system can serve as a link between the periphery and the CNS. Systemic inflammation can affect the progression of neurodegenerative diseases [132, 133]. Polysaccharides that can modulate the immune responses and reduce inflammation may therefore be beneficial. We have demonstrated that LBP from *L. barbarum* can attenuate the activation of microglia in the retina in glaucoma [134]. Anti-inflammatory effects of polysaccharides from medicinal plants such as *Cryptopus volvatus* have been reported [135]. Many non-starch polysaccharides found in plants can elicit direct immunomodulatory effects. These polysaccharides bind to glycan-binding receptors expressed on dendritic cells, which are the immune cells in the peripheral circulation responsible for antigen presentation. Through this binding, the polysaccharides can modify signals from other pattern-recognition receptors, such as Toll-like receptors, on dendritic cells. This modification alters the effectiveness of both innate and adaptive immune responses [136]. Not all polysaccharides inhibit immune responses. We have shown that polysaccharides isolated from *Prunella vulgaris L.* can stimulate monocytes/macrophages and microglia to produce more free radicals and cytokines [137, 138]

4. THE BIOAVAILABILITY AND PERMEABILITY OF NUTRITIONAL MOLECULES AT THE BLOOD-BRAIN BARRIER

Many cell-culture and animal studies suggest the potential use of polyphenols such as flavonoids, stilbenes and polysaccharides in aged-related neurodegenerative diseases. However, there are debates on the effectiveness of these compounds in human subjects. Major concerns include bioavailability after gastrointestinal (GI) tract and liver metabolism and permeability across the blood-brain barrier (BBB).

It is important to note that the natural forms of plants flavonoids do not exist as shown in Figure 1b: they are often glycosylated, esterified, or polymerized, giving a huge variety of compounds that need further investigation [48, 49]. Nevertheless, it is generally believed that most flavonoids are hydrolyzed and conjugated by gut and liver enzymes before entering the circulation [50]. Except for the anthocyanins, the majority of circulating flavonoids do not occur as their plant forms, but as sulfates, glucuronides, and *O*-methylated derivatives [139]. These derivatives are likely to exhibit different bioactivities from their counterparts in plants, such as a reduction of their antioxidative activity [140, 141]. Many *in vitro* studies have focused on the neuroprotective properties of flavonoids that differ from their forms *in vivo*; caution must be exercised when extrapolating from these results. Both intact and/or derivative forms of flavonoids such as flavanols (e.g., tea catechins), flavanones (e.g., naringenin) and blueberry anthocyanins have been detected in the brain following oral and intravenous administration in animals, suggesting that they do pass through the BBB and can possibly take effect in the brain [142-144]. The degree of permeability is likely to be governed by several factors, including compound lipophilicity [145] and the action of specific transporters on the BBB [146]. However, the major questions which still need to be addressed are (1) whether levels attained *in vivo* are comparable to the effective dose used *in vitro*, and (2) if the *in vivo* forms also exert similar beneficial effects as their natural forms. Moreover, based on the numerous reports on the neuroprotective properties in animals [59, 147-151], it is possible that under an *in vivo* setting,

flavonoids, existing mostly as a mixture of metabolized forms, collectively protect the brain through a combination of many other important mechanisms that have not been identified. In future, it will be beneficial to develop ways to improve the oral bioavailability of flavonoids to maximize their benefits to the brain. For example, Scheepens et al have recently proposed the use of synergies between oral intakes of different polyphenols to boost bioavailability [152]. Additional studies are also need to investigate the usefulness of flavonoids to the human brain.

In a similar fashion to flavonoids, resveratrol is metabolized into various forms before entering the circulation. Natural resveratrol is mainly present in the glycosylated piceid form, which greatly enhances its stability against oxidative degradation and raises its solubility and absorption from the GI tract [153]. Following absorption, resveratrol is converted into *O*-glucuronides and *O*-sulfates by phase II drug-detoxifying enzymes in the liver [154]. In one human study led by Walle et al, following a 25 mg oral dose of resveratrol, as much as 70% of this dose was absorbed, with an increase of total resveratrol metabolites in the plasma reaching 2 uM within 1 hour, but the level of unmodified resveratrol was as low as 5 ng/ml [83]. Moreover, though it is still controversial whether orally administered resveratrol leads to its cerebral accumulation to an effective level, Wang *et al* have shown that an intraperitoneal injection of resveratrol (30 mg/kg body weight) in gerbils led to an increase of resveratrol metabolites (mostly as glucuronide conjugate form) in the brain, with the highest level, i.e. 400 ng/g of brain tissue, observed at the 4th hour, and rapidly declining thereafter [68]. This implies that resveratrol, particularly in glucuronide form, is capable of passing through the BBB, although the mechanism has yet been elucidated and it is unclear whether the level attained would be sufficient to protect the human brain. To date, there is only one report suggesting that orally administered resveratrol improves cerebral blood flow in human frontal cortices during cognitive tasks [94]. More work is needed to improve the CNS bioavailability of resveratrol and to clarify its effect on the human brain. In addition, we cannot rule out the possibility that resveratrol and its metabolites elicit protective effects in the brain which differ from those reported from cell culture studies.

Alternative route of drug administration can be a possible direction to improve the availability of flavonoids and resveratrol in the CNS. Recently, the nasal route of administration has gained increasing attention for brain uptake of drugs. Baicalin is a BBB-permeable natural flavonoid which has *in vivo* and *in vitro* neuroprotective effects against ischemic eye and brain damage [155, 156]. Studies on rats show that nasal administration can effectively increase the amount of baicalin detected in different brain regions compared with intravenous administration. More than half of the administered baicalin can be transported to the brain via the olfactory pathway in 8 hour [157]. Further research should be conducted in human to confirm the effectiveness of using nasal administration for delivery of drugs to the brain.

There is relatively little information on polysaccharides. Some researchers are skeptical that polysaccharides can be developed as CNS drugs because they are less likely to pass through the BBB. However, animal studies show that the feeding of polysaccharides can reverse neuropathological changes in the eye [119, 122], suggesting that it is possible for these big molecules to exhibit effects in the CNS. How can these big molecules modify the CNS environment? There are several possibilities: (1) polysaccharides might be transported into the CNS by unknown mechanism; (2) their metabolites might reach the CNS; (3) polysaccharides might provide their CNS neuroprotection by modulating biological events in the periphery. There is insufficient data to draw any conclusion as yet. Low-molecular weight heparin derivatives can pass through the BBB to produce their protective effects [20, 158]. These derivatives are produced by the depolymerization of the full-length heparin, which has a polysaccharide backbone structure [158]. Following on from this, we speculate that some neuroprotective full-length polysaccharides may be broken down into shorter BBB-permeable derivatives during GI tract metabolism. The example of heparin also sheds light on the possibility of synthesizing neuroprotective polysaccharide derivatives from natural plant or marine sources. If we can identify the structure that is critical for the neuroprotective function, it may be possible to

artificially break down the complex long-chain structure to enhance the BBB-permeability and at the same time preserve the neuroprotective properties.

Currently, most studies on neuroprotective polysaccharides fail to provide information on the chemical structure and thus create the major barrier for further characterization of the drug metabolism and pharmacokinetics (DMPK) profiles. We believe that this technical problem can be overcome. Early studies on the anti-cancer polysaccharides lentinan show that it is possible to isolate individual polysaccharide from herbs, characterize their structure and study its DMPK properties. An oral formulation of superfine dispersed lentinan is now under clinical trial to evaluate its safety and effectiveness in patients with various kinds of cancer [159, 160], suggesting that evaluation of the drug metabolism is practically feasible. We encourage researchers to conduct more chemical analysis on the potential neuroprotective polysaccharides. It will also be worth to study the effects of the metabolite of these compounds.

5. CONCLUSION

We have summarized current knowledge on some small molecules such as polyphenols and big molecules such as polysaccharides for their potential neuroprotective actions. In the small molecules section, we try to link the biological actions of some polyphenols with their structures. In the big molecule section, we use several examples to demonstrate that polysaccharides are able to modulate neuronal activities and disease-risk factors. Current data suggest that many polyphenols and polysaccharides are potent anti-oxidant, anti-inflammatory, and immunomodulation agents. Hence, they have potential uses in different age-related neurodegenerative diseases. More research is required to enhance the bioavailability and BBB-permeability of these compounds.

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Table 1: Risk factors for AD, PD and AMD.

	Alzheimer's disease	Parkinson's disease	Age-related macular degeneration
Age	Major risk factor		
Depression	Relation is not clear, but co-exists in many patients [123, 124]		X
Smoking	Yes [36]	X	Yes [161]
Diabetes	Yes [37]	Inconsistent data [162, 163]	Weak association [164]
Hyperhomocysteinaemia	Yes[165]	As a side effect of L-Dopa treatment [39]	X
Hypertension	Yes [38]	X [163]	Yes [133]

7. FIGURE LEGENDS

Figure 1. The chemical structures of the flavonoid backbone (Figure 1a) and various flavonoid subclasses (Figure 1b). A. Flavonoids are formed by two benzene rings (rings A and B) interconnected by a 3-carbon oxygenated heterocycle (ring C). B. Different flavonoid subclasses differ from one another by the saturation of ring C, the presence or absence of the 4-oxo-function, and the chemical substitutions on the B and C rings.

Figure 2. Chemical structures of epigallocatechin gallate (Figure 2a), quercetin (Figure 2b), and Naringenin (Figure 2c). A. Epigallocatechin gallate has a gallic group substitution at position 3. This group is thought to interact with iron to suppress iron-catalyzed oxidative stress *via* the Fenton reaction. B. Quercetin has strong antioxidant activity which can be attributed to the presence of (1) the ortho-dihydroxy groups in ring B, (2) the combination of 2,3 carbon-carbon double with the 4-oxo function in ring C, and (3) the possession of the 3-OH and 5-OH groups with the 4-oxo function on the A and C rings. The ortho-hydroxy groups in ring B and the 4-oxo function together with 3-OH or 5-OH in rings A and C are also responsible for the iron-chelating properties. C. Naringenin is a weaker antioxidant and iron chelator since it lacks many of the key structural features mentioned above.

Figure 3. The chemical structure of the stilbene backbone. Stilbenes can either be in *cis* or *trans* conformations. In general, the *trans* isomer is more energetically stable and more biologically active.

Figure 4. The chemical structures of resveratrol (Figure 4a), piceatannol (Figure 4b), and M8 (Figure 4c). Piceatannol is a monohydroxylated resveratrol derivative with an additional OH group at position 3', while M8 is a hexahydroxylated stilbene with additional OH groups at positions 3', 5' and 4.

8. References

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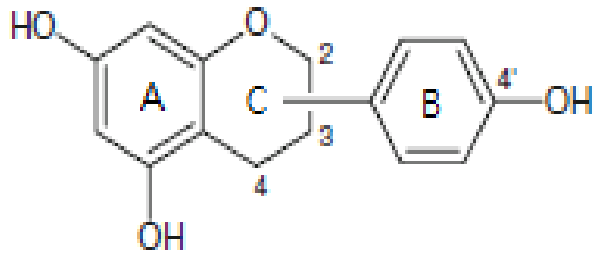
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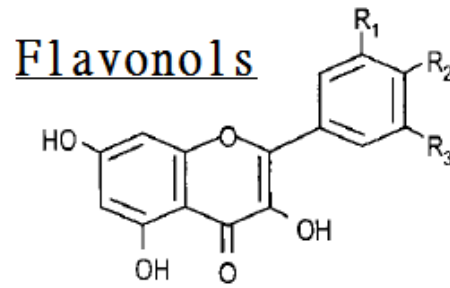
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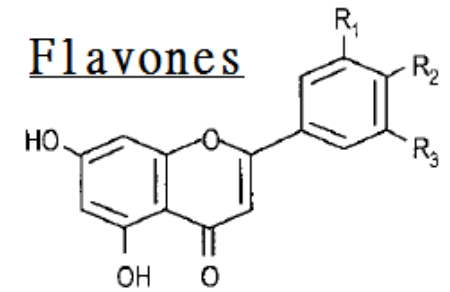
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A. Chemical structure of the flavonoid backbone

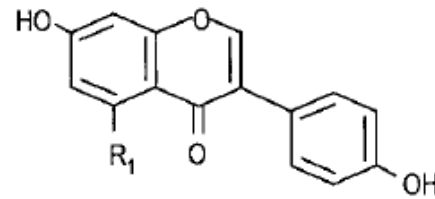


$R_2 = OH; R_1 = R_3 = H$: Kaempferol
 $R_1 = R_2 = OH; R_3 = H$: Quercetin

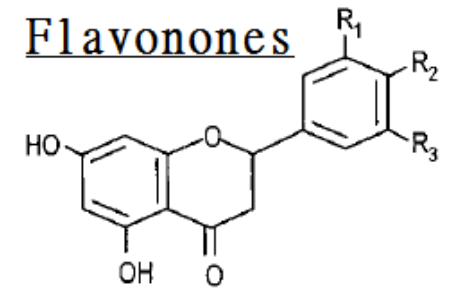


$R_1 = H; R_2 = OH$: Apigenin
 $R_1 = R_2 = OH$: Luteolin

Isoflavones

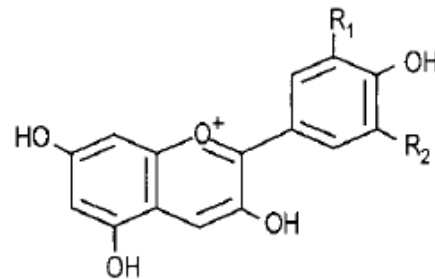


$R_1 = H$: Daidzein
 $R_1 = OH$: Genistein



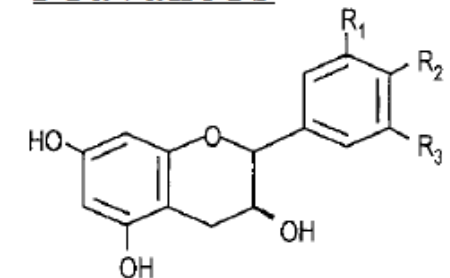
$R_1 = H; R_2 = OH$: Naringenin
 $R_1 = R_2 = OH$: Eriodictyol

Anthocyanidins



$R_1 = R_2 = H$: Pelargonidin
 $R_1 = OH; R_2 = H$: Cyanidin

Flavanols



$R_1 = R_2 = OH; R_3 = H$: Catechins
 $R_1 = R_2 = R_3 = OH$: Gallocatechin

Figure 1

b. Chemical structures of various flavonoid subclasses

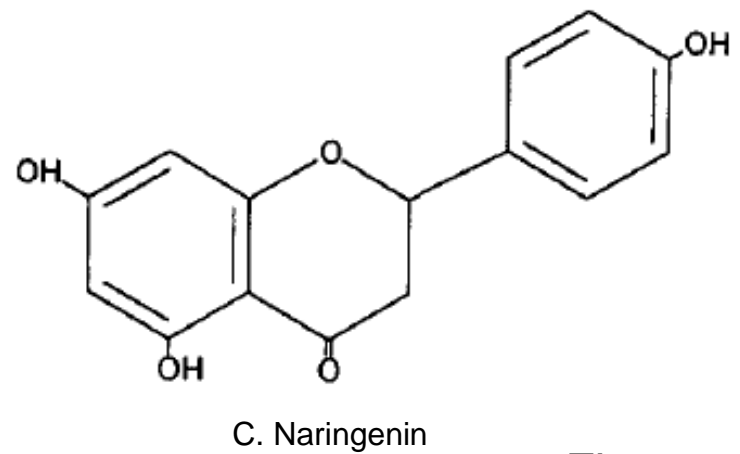
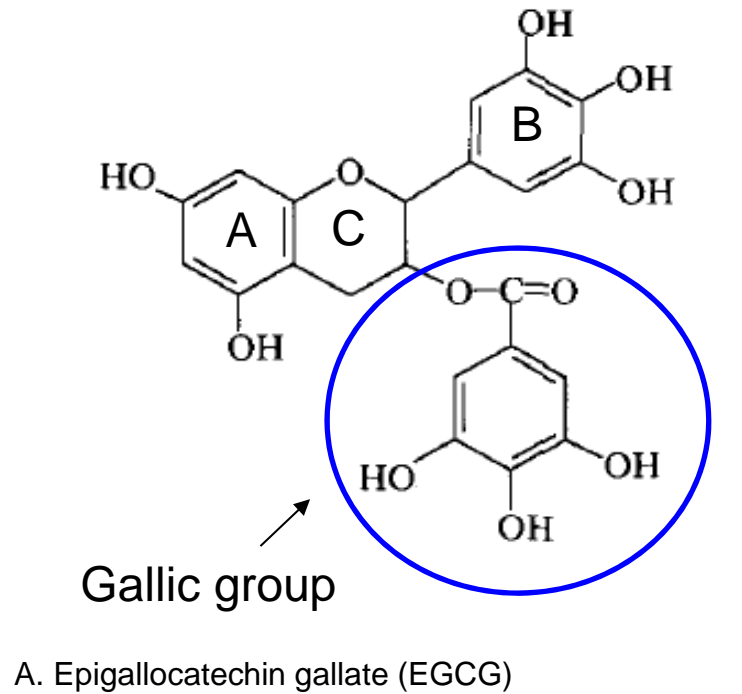
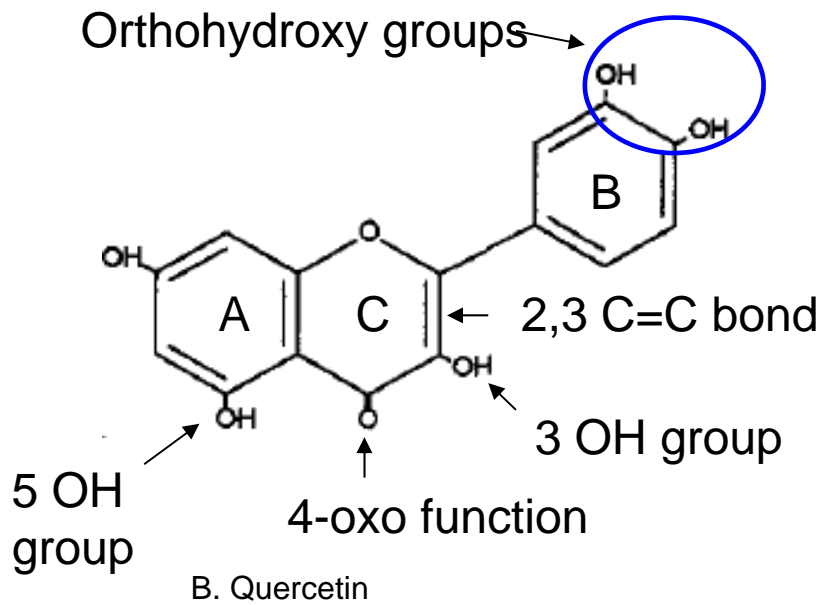
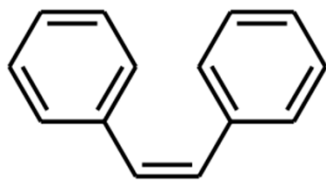
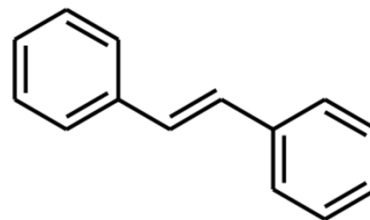


Figure 2

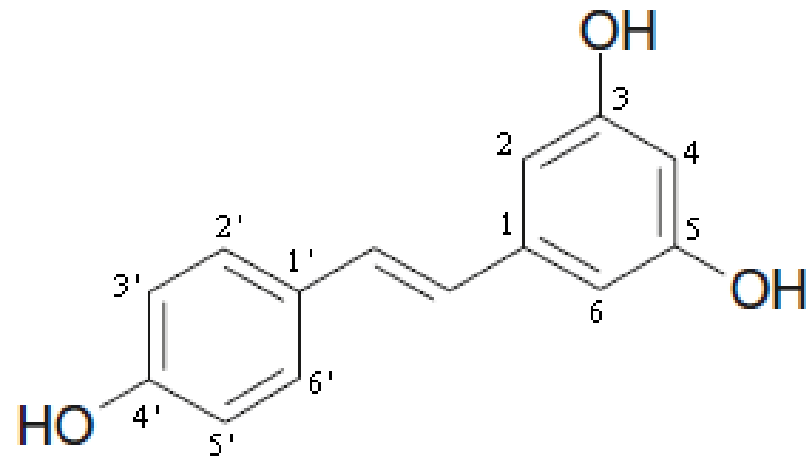


Cis-stilbene

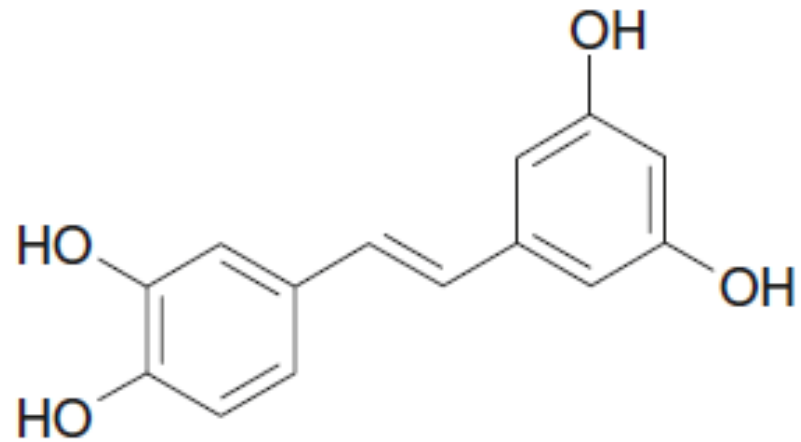


Trans-stilbene

Figure 3

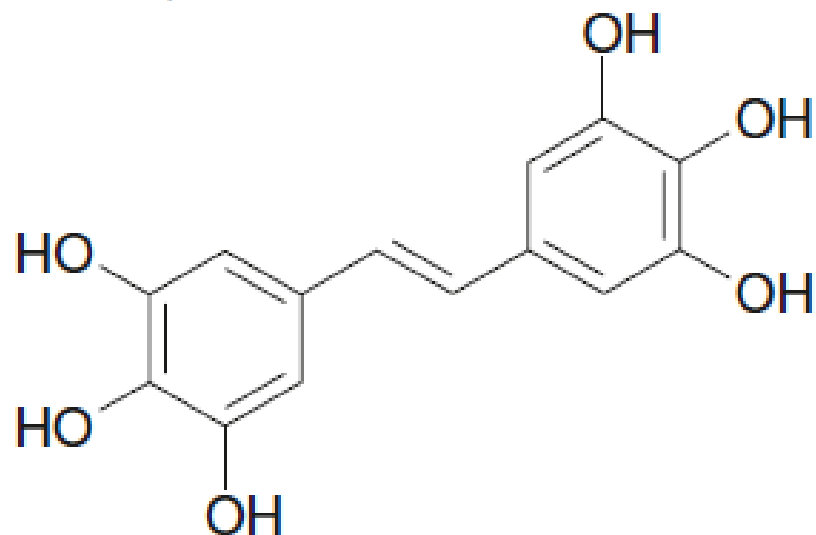


A. Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene)



B. Piceatannol (3,5,3',4'-tetrahydroxy-*trans*-stilbene)

Figure 4



C. M8 (3,4,5,3',4',5;-hexahydroxy-*trans*-stibene)

Figure 4