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Neuroprotective properties of resveratrol and derivatives

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Stilbenoid compounds consist of a family of resveratrol derivatives. They have demonstrated promising activities *in vitro* and *in vivo* that indicate they may be useful in the prevention of a wide range of pathologies, such as cardiovascular diseases and cancers, as well have anti-aging effects. More recently stilbenoid compounds have shown promise in the treatment and prevention of neurodegenerative disorders, such as Huntington's, Parkinson's, and Alzheimer's diseases. This paper primarily focuses on the impact of stilbenoids in Alzheimer's disease and more specifically on the inhibition of β-amyloid peptide aggregation.

Keywords: stilbenoid; Alzheimer's disease; β-amyloid peptide; inhibition of aggregation

Introduction

Natural products are an abundant source of polyphenolic compounds, including a less common group, the stilbenoids. These constitute a large class of resveratrol derivatives—including monomers, dimers, and oligomers—resulting from different oxidative condensations of the individual monomers. Stilbenoids are naturally occurring in several plant families, such as Cyperaceae, Dipterocarpaceae, Gnetaceae, and Vitaceae.[1,2] Grapes, which include the wine grape, *Vitis vinifera* L., are viewed as the most important dietary sources of these substances.[3,4] Numerous labs have been involved in the chemical characterization of stilbenes, primarily those found in grapes, red wine, and vine stems.

The impetus for the numerous research studies involving the chemical characterization of stilbenoids is their many promising biological activities, particularly those of resveratrol. The biological activities of resveratrol, and several of its derivatives, include the prevention or direct interference of numerous degenerative processes, such as neurodegenerative diseases.[5]

Due to the increase in the aging population, neurodegenerative diseases continue to involve a greater percentage of the population. These disorders, which result from the deterioration of neurons, are classified into two pathological classes: movement disorders such as Parkinson's disease (PD), and cognitive deterioration and dementia, such as Alzheimer's disease (AD).

AD is the most common type of neurodegenerative disorder, accounting for 65% of all dementias, with a prevalence estimated to be between 1 and 5% among people age 65 years and older.[6] Histopathological evaluations reveal that one of the major characteristics of AD is the excessive accumulation of two types of proteins: tau proteins and β-amyloid peptide (βA).[7] βA originates from the proteolytic cleavages of the transmembrane amyloid precursor protein (APP).[8] βA accumulation leads to the formation and deposit of amyloid plaques and neurofibrilary tangles, which promote inflammation and activate neurotoxic pathways, leading to dysfunction and death of brain cells.[9]

Recently, numerous studies have shown that a wide range of polyphenols have neuroprotective effects both *in vitro* and *in vivo*.[10–20] Among these polyphenols, resveratrol and several of its derivatives have demonstrated some of the most promising anti-neurodegenerative activities.[12–19] In this paper, we present investigations on the role of stilbenoids in neurodegenerative diseases, with an emphasis on

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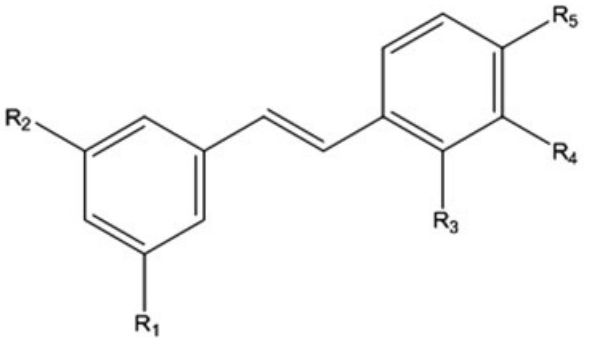


Compound Name	R^1	R^2	R^3	R^4	R^5
Resveratrol	OH	OH	H	H	OH
Piceid	OGlc	OH	H	H	OH
Piceatannol	OH	OH	H	OH	OH
Resveratroloside	OH	OH	H	H	OGlc
Pterostilbene	OMe	OMe	H	H	OH
Oxyresveratrol	OH	OH	OH	H	OH
Gob C	OH	OH	H	H	OGlc
Gob D	OH	OH	H	OMe	OGlc

Figure 1. Structures of stilbene monomer derivatives.

the studies demonstrating their ability to inhibit βA fibril formation in AD.

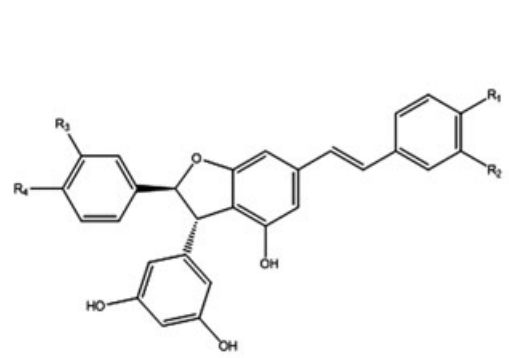
Resveratrol derivatives

Stilbenoids are defined by their structural skeleton, which comprises two aromatic rings joined by an ethylene bridge (C_6–C_2–C_6). From this relatively simple structure, a large array of compounds has been synthesized by plants. The stilbene monomers are primarily modified via the number and the position of hydroxyl groups, substitutions with methyl and methoxy groups, sugars, and differences due to the *cis* and *trans* configurations (Fig. 1). In addition to stilbene monomers, many dimers and oligomers have also been identified. These compounds are the result of the oxidative condensations of the resveratrol monomer. The dimers are divided into two major groups: group A, with compounds having five-membered oxygen heterocyclic ring, such as the viniferins (Fig. 2), and group B, without the oxygen containing ring, such as pallidol (Fig. 3). Finally, stilbene trimers and, more recently, tetramers, such as hopeaphenol, are known. Due to the multiple variations that can be achieved, it is reasonable to assume there are considerably more stilbene oligomers to be found in plants that exist as minor constituents (Fig. 4).[21,22]

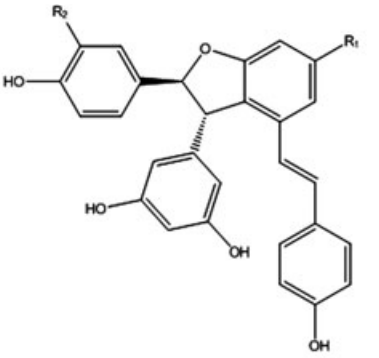
Stilbenoids and neurodegenerative diseases

While numerous stilbenes exit, the majority of studies have involved resveratrol, which has shown to have antiaging effects in several organisms, including yeasts, nematodes, mice, and rats. Resveratrol has also been shown to have specific activities that can delay or alter the progression of neurological disorders, such as brain ischemia, Huntington's disease (HD), PD, and AD.[23]

In a study involving rat hippocampal neurons, voltage-activated potassium currents were inhibited by resveratrol, suggesting that it may be useful for treating ischemic brain injury.[24] Resveratrol also demonstrated protective effects in a PD model, using midbrain dopaminergic neurons, against several type of insults that have shown a correlation to PD pathogenesis. These included the cytotoxic effects induced by 1-methyl-4-phenyl pyrimidium, sodium azide, thrombin, and DNA damage.[25] In two HD models, resveratrol rescued mutant polyglutamine-specific cell death in neuronal cells derived from HdhQ111 knock-in mice and in transgenic *Caenorhabditis elegans*.[26] In a brain ischemia model, administration of resveratrol to gerbils during the early stage of cerebral ischemia protected against neuronal death in the



	R^1	R^2	R^3	R^4
Gnetin C	OH	H	H	OH
Gneafricanin A	OH	OMe	OMe	OH
Gnemenoside A	OGlc	H	H	OGlc



	R^1	R^2
Scirpusin A	OH	OH
ε-Viniferin	OH	H
ε-Viniferin glucoside	OGlc	H

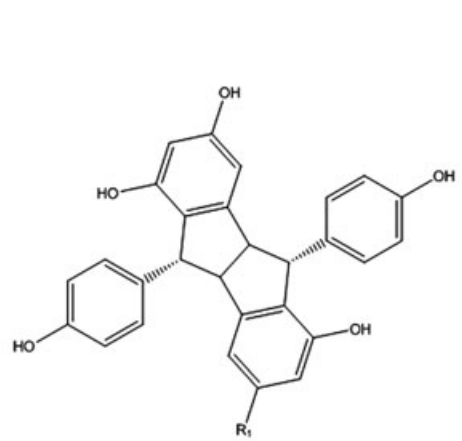
Figure 2. Structures of stilbene dimer derivatives (group A).

hippocampal CA1 area and concomitantly inhibited glial cell activation.[27] Moreover, in this *in vivo* model, results showed that resveratrol, after formation of glucuronide conjugates, enters the bloodstream and could cross the blood–brain barrier. Required concentration of resveratrol to have neuroprotective actions were in range of 10–100 μM.[27] Different mechanisms, such as antioxidant and regulation of gene transcription, have been suggested to be involved in the protective actions of resveratrol.

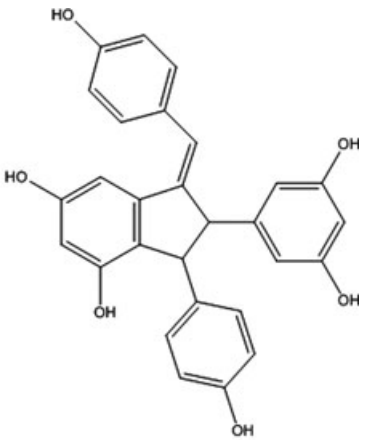
Stilbenoids and Alzheimer's disease

The majority of neurodegenerative studies is currently focused on AD, most likely due to the fact that AD is the most common type of neurodegenerative disorder. So far, the effects of resveratrol and several others stilbenes in AD models suggest that stilbenes may be very effective modulators of AD development and progression.[28]

For example, in an APP695-transfected mouse neuroblastoma N2a cells, resveratrol could reduce the secretion of βA; in this study, the treatment of cells with selective proteasome inhibitors significantly blocked the resveratrol-induced decrease of βA levels.[14] These results suggest the antiamyloid activity of resveratrol is proteasome dependant. In another study using hippocampal primary neurons, resveratrol significantly attenuated the βA-induced



Compound Name	R^1
Pallidol	OH
Pallidol glucoside	OGlc



Parthenocissin A

Figure 3. Structures of stilbene dimer derivatives (group B).

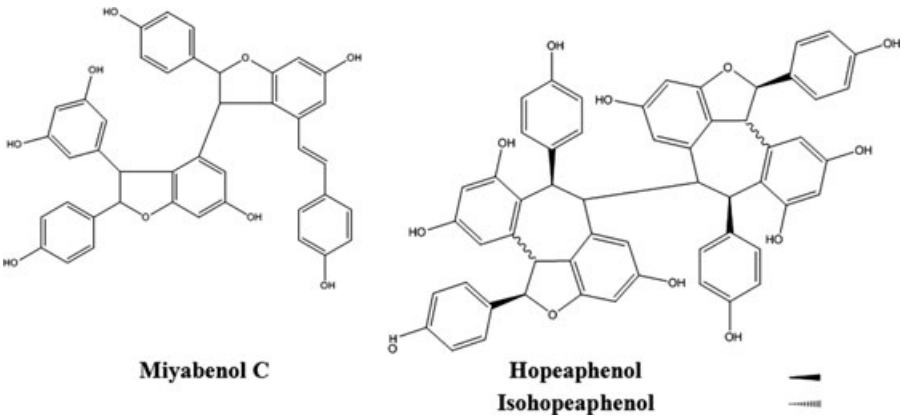


Figure 4. **Structures of some stilbenoid oligomers.**

cell death in a concentration dependant manner.[15] This study suggested that the protein kinase C pathway was involved in the neuroprotective action of resveratrol.[15] Jeon *et al.* reported that resveratrol, oxyresveratrol, and scirpusin A have potent inhibitory activities on β-secretase with IC_{50} values at 15, 7.6, and 10 μM, respectively.[16] Among the secretases, β-secretase is one of the most attractive targets for the inhibition of amyloid production. Finally, in PC12 neural cells, resveratrol protected against the βA peptide-induced toxicity by influencing apoptotic signaling pathways, reducing changes in mitochondrial membrane potential and inhibiting the accumulation of intracellular reactive oxygen intermediates.[13]

Recently, a therapeutic approach that interferes directly with the neurodegenerative process in AD, especially the accumulation and the aggregation of βA, is considered one of the most promising targets to alter the progression of the disease, rather than merely treating the symptoms.[29] Several studies suggest that polyphenols could prevent AD or delay its onset by directly inhibiting the formation of βA fibril deposits in the brain.[17–20] Indeed, pathologic and biochemical studies suggest that βA fibrils are reactive oxygen species generators, whereas monomeric βA acts as natural antioxidant that prevents neuronal cell death caused by oxidative stress.[30–32] Using *in vitro* assays, we recently reported that resveratrol derivatives inhibit the aggregation of the peptide and destabilize the preformed oligomers and fibrils.[17–19] Initial screening of 9 monomers, 6 dimers, and 3 stilbenoid oligomers for inhibition was performed at a concentration of 10 μM and their inhibiting effect was compared to that of curcumin as the positive control.[20] Five stilbenoids exhibited peptide aggregation inhibition activity equal to or better than that of curcumin. These were further tested to determine their IC_{50} values. The IC_{50} values of all compounds are summarized in Table 1. Among all the

Table 1. **Inhibition of βA fibril formation**[a]

Compound	Inhibition %	IC_{50} (μM)
Curcumin	**45 ± 9**	**10 ± 2**
Stilbene Monomers		
Moracin M	9 ± 7	–
Resveratrol	**63 ± 6**	**6 ± 2**
Piceid	**62 ± 6**	**6 ± 2**
Piceatannol	25 ± 9	–
Pterostilbene	35 ± 7	–
Oxyresveratrol	32 ± 7	–
Gob C	11 ± 6	–
Gob D	28 ± 5	–
Stilbene Dimers		
Gnetin C	39 ± 5	–
Gneafricanin A	40 ± 6	–
Gnemenoside A	**46 ± 7**	**10 ± 2**
Scirpusin A	**80 ± 9**	**0.7 ± 0.3**
ε-Viniferin	25 ± 9	–
ε-Viniferin glucoside	**93 ± 3**	**0.2 ± 0.3**
Stilbene Oligomers		
Myabenol C	15 ± 5	–
Hopeaphenol	13 ± 6	–
Isohopeaphenol	21 ± 9	–

[a]Bold values indicate the molecules exhibiting inhibitory activity equal to, or greater than, the postive control, curcumin.

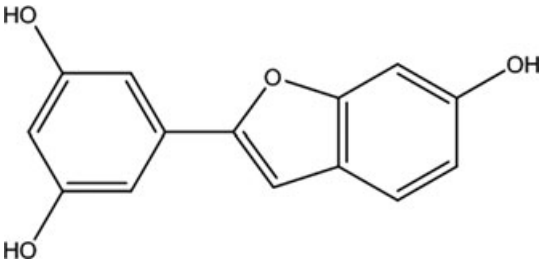


Figure 5. **Structures of moracin M.**

compounds tested, resveratrol, piceid, and the dimers, scirpusin A and ε-viniferin glucoside, exhibited an efficient inhibition of βA aggregation.

Resveratrol and its glucoside both inhibited the aggregation of the peptide, more so than the other stilbene monomers tested. Examination of inhibitory data for stilbene monomers suggests several potential structure-activity relationships. Additional substitutions on the aromatic rings reduced the protective activity against aggregation. Methoxy or glucosyl derivatives and derivatives with an additional hydroxyl group were weaker inhibitors, suggesting that hydrogen bonds might play an important role in the binding process. Finally, the benzofuranyl group in moracin M led to a decrease in activity, potentially due to the greater rigidity of its structure (Fig. 5).

Of the six stilbene dimers, three had an inhibitory activity equal to or greater than curcumin, which was found to be 10 ± 2 μM. Two dimers had considerable inhibitory activity: scirpusin A (0.7 ± 0.3 μM) and ε-viniferin glucoside (0.2 ± 0.3 μM). These two compounds differed only by two substituents. Scirpusin A had an additional hydroxyl group and ε-viniferin glucoside has a glucose unit (Fig. 2). It is very difficult to draw any conclusions on the structure-activity relationship using this limited data set. Nevertheless, their strong inhibitory activity *in vitro* warrants further investigation into their potential as therapeutic agents in AD treatment and prevention.[18]

Unlike the stilbene dimers, the stilbene oligomers (trimers and tetramers), were weak inhibitors. These results suggest that spatial constraints are critical in the binding process. However, other oligomers need to be tested to confirm that bulk compounds are not active since results indicated that the inhibitory effect depends not only on the specific ring substituents, but may also depend on the overall 3-D structure.[18]

Conclusion

A limited number of therapeutic options are available to treat neurodegenerative diseases; however, these are primarily treating symptoms and not interfering with the disease process. This paper demonstrates that resveratrol derivatives are highly promising molecules that could be used to both prevent and/or treat neurodegenerative diseases such as AD. Indeed, resveratrol derivatives may effectively modulate multiple mechanisms of the neurodegenerative disease pathology. For example, in AD, resveratrol inhibits activity on β-secretase, the generation of the reactive oxygen intermediates, and the aggregation of βA peptide. Moreover, other resveratrol derivatives, such as the dimers scirpusin A and ε-viniferin glucoside, could be potent preventive and therapeutic agents. However, the efficacy and utility of resveratrol derivatives in treating neurodegenerative pathology also depends on their bioavailability and activity *in vivo*. Future research is warranted to address these issues.

Conflicts of interest

The authors declare no conflicts of interest.

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