

**Review Article**

A Mini Review on the Protective Effect of Lignans for the Treatment of Neurodegenerative Disorders

Mamali Das and Kasi Pandima Devi*

Department of Biotechnology, Alagappa University, Tamil Nadu, India

Received Date: 22 December 2018**Accepted Date:** 28 January 2019**Published Date:** 19 February 2019**Citation**

Das M, Devi KP (2019) A Mini Review on the Protective Effect of Lignans for the Treatment of Neurodegenerative Disorders. J Nutr Food Lipid Sci 2019(1): 40-53.

Correspondence should be addressed to Kasi Pandima Devi, India
E-mail: devikasi@yahoo.com**Copyright**

Copyright © 2019 Kasi Pandima Devi et al. This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and work is properly cited.

Abstract

Nature is a rich source of numerous bioactive compounds that are categorized as secondary metabolites. Lignans are group of such compounds, generally called phytoestrogens widely present in many plants and vegetables, grains, seeds, nuts and tea. They have been used as folk medicine for the treatment of several clinical conditions like asthma, cardiovascular diseases, atherosclerosis, colitis and many more. Structurally, lignans are characterized by two phenylpropane groups attached by a carbon bond. They have been divided in to several types on the basis of structure of their carbon skeleton, the way of cyclization and oxygen incorporation in the skeleton. Lignans from numerous plant species such as *Kadsura polysperma*, *Kadsura ananosma*, *Schisandra wilsoniana*, *Schisandra chinensis*, *Schisandra arisanensis*, *Manglietiastrum sinicum*, *Pycnanthus angolensis*, *Cleistanthus indochinensis*, *Sargentodoxa cuneata*, *Tabebuia chrysotricha*, *Lindera glauca*, *Tilia amurensis* and many more have been found to be beneficial for cancer, hepatitis, microbial and fungal infection. Neurodegenerative Diseases (NDD) represent a class of disorder each of which corresponds to a specific pathological condition while their molecular pathways have been found to be interlinked. Lignans isolated from particular species like *Myristica fragrans*, *Adelostemma gracillimum*, *Schisandra chinensis*, *Torreya nucifera*, *Larrea tridentate*, *Eucommia ulmoides*, *Caulis clematidis*, *Saururus chinensis*, *Zea mays* are helpful for NDDs including Alzheimer's disease, Parkinson's disease, glaucoma, amyotrophic lateral sclerosis, Huntington's disease and Japanese encephalitis. In this review the individual lignans will be summarized in relation to their neuroprotective and cognitive enhancement activities.

Keywords

Alzheimer's Disease; Amyotrophic Lateral Sclerosis; Glaucoma; Huntington's Disease; Japanese Encephalitis; Lignan; Neolignan; Neurodegenerative Diseases; Parkinson's disease

Introduction

The word lignans depicting a group of dimerized phenylpropanoids in which the two carbons namely C6-C3 are attached by its central carbon (Figure 1) was first introduced by Haworth in 1936 [1]. The natural derivatives of lignans are named as neolignans [2]. This polyphenolic phytoestrogen is found in more than 60 families of vascular plants such as rye, barley and fresh fruits and vegetables and predominantly in the hulls of flax and sesame seeds [3].

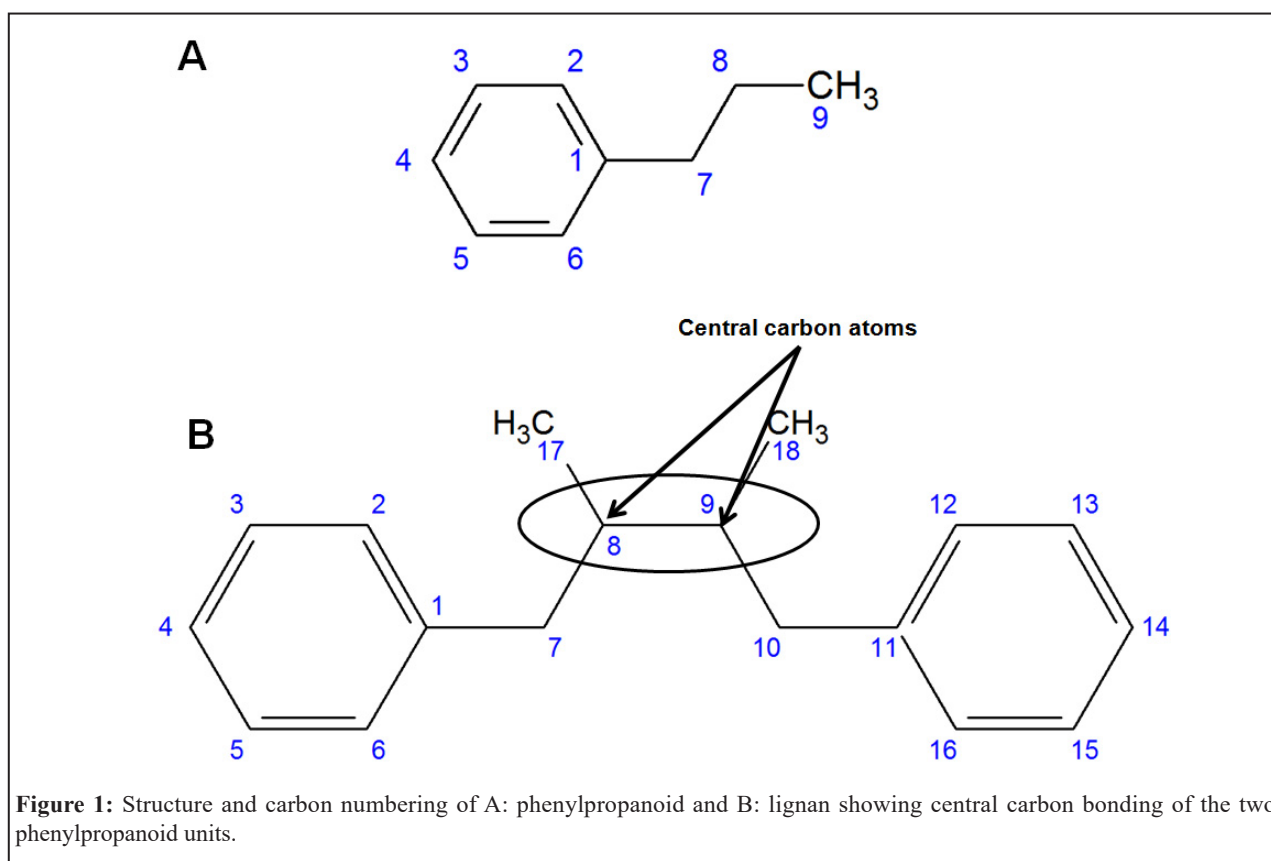


Figure 1: Structure and carbon numbering of A: phenylpropanoid and B: lignan showing central carbon bonding of the two phenylpropanoid units.

Neurodegenerative Diseases (NDD) refer to a progressive loss in particular regions of the brain from which there is no recovery. Cells, which are the fundamental units of life hold numerous quality control schemes to spot out and remove dysfunctional toxic cellular components like organelles and proteins. It is a fact that, at steady state, misfolded proteins are continuously formed inside the cell and are thus fixed by several in built mechanisms like chaperones, ubiquitin proteasome system and autophagy. These systems hold the key for a healthy cellular atmosphere, thus any altered cellular condition resulting in expression and aggregation of toxic proteins that overcome these quality control systems eventually result in death of the concerned and neighboring cells in a progressive manner. This phenomenon becomes the basis of NDD like Alzheimer's (AD), Parkinson's (PD), Huntington's Diseases (HD), Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS). These NDD possess unique clinical manifestations for each, although the molecular pathways are quite similar. Huge research on these aspects revealed lot of critical information regarding the particular molecules associated with these diseases such as Amyloid- β (A β) in AD [4,5], α -synuclein in PD [6], huntingtin protein in HD [7], and transactive response DNA-binding protein 43 (TDP-43) in FTD and ALS [8]. Further it is evidenced that these NDDs arise due to involvement of multiple pathways such as abnormal protein metabolism, unregulated free radical production and metal and pesticide

exposure. Several lignans are historically proven useful for many pathological conditions like cancer and NDDs and in this mini review, we have gathered the comprehensive information on those lignans and their sources. Pathology of the various NDDs and the feasibility of lignans for treating various NDDs are also discussed.

Lignans: Source, Chemistry and Pharmacological Properties

Source

Lignans, a group of non-flavonoid polyphenols acting as antioxidants and defense molecules against bacterial and fungal pathogens are wide spread in plant kingdom particularly in plant-based foods, including seeds, fruits and vegetables and have recently attracted significant scientific attention due to their wide biological activities. These compounds are created naturally by peroxidases and laccases enzymes which induce structural diversity and bioactivities to them [9,10]. Generally, the lignans content of food does not exceed 0.2 mg/g while some foods like flaxseed [11] and sesame seeds [12,13] have 3.35 mg/g and 3.73 mg/g respectively.

The type and amount of lignans present in various plants differ from one to the other. They are found in the bran of whole

grains and seed coat of seeds. Among the dietary components, barley, oats, buckwheat, millet, wheat, sesame seeds, rye and flax contain quite high levels of lignans [14]. Legumes and nuts also have considerably good amount of lignans while fruits and vegetables such as grapes, kiwi, oranges, pineapple, asparagus, wine, coffee and even tea cannot be ignored [15-18]. Animal foods on the other hand are poor in lignans whereas exceptionally very less enterolignans like enterodiol and enterolactone are found in milk products which are produced due to the action of gut inhabiting bacteria [19].

Chemistry and Pharmacological properties of the different sub-groups of lignans

Basically lignans have two phenylpropane units joined by a C-C bond between the central atoms of the respective side chains. Lignans have been divided into 8 subgroups such as aryltetralins, aryl-naphthalene, furans, furofurans, dibenzylbutanes, dibenzylbutyrolactols, dibenzocyclooctadienes and dibenzylbutyrolactones based on the carbon skeleton, cyclization and the way oxygen is incorporated in the skeleton. Lignans occur in nature as glycosylated derivatives while their free forms are very rare. Out of the most common lignans secoisolariciresinol, lariciresinol, pinoresinol, matairesinol and 7-hydroxmatairesinol are found abundantly in nature. This section will elaborate on the different subgroups of lignans and their biological properties.

Dibenzocyclooctadienes: More than 130 dibenzocyclooctadiene lignans have been isolated from two plant genera *Schisandra* and *Kadsura* of family Schisandraceae. CD spectroscopy revealed the structures and configurations of 14 new dibenzocyclooctadiene lignans and ananolignans isolated from the seeds of *K. ananosma*, where two ananolignans showed the most promising *in vitro* neuroprotection against oxidative stress [20]. More recently, an investigation on *S. wilsoniana* fruits led to identification of dibenzocyclooctadiene lignans and marlignans whose cytotoxicity and anti-HIV-1 were evaluated and interestingly they displayed EC_{50} of 3-6 mg/mL [21]. Similarly, Schinlignan G a compound isolated from *S. chinensis* [22] exhibited potent anti-hepatitis B virus activity with IC_{50} of 5 mg/mL. Tiegusanin G isolated from the aerial parts of the same plant [23] showed anti-HIV-1 activity with an EC_{50} 8mM. In the same way neglschisandrin isolated from *S. neglecta* exhibited minor cytotoxicity towards A549 cell line with EC_{50} values of 12 mg/mL [24]. Several arisanschinins from *Schisandra arisanensis* fruits, displayed moderate *in vitro* anti proliferation in phytohemagglutinin induced Peripheral Blood Mononuclear Cells (PBMC) [25]. New dibenzocyclooctadiene lignans called schisanchinins were isolated from ethyl acetate extract of *Schisandra chinensis* (Turcz.) Bail fruits where both

of them inhibited NO release by LPS-activated microglia cells [26]. Dibenzocyclooctadiene lignans from aerial parts of *S. lancifolia* showed weak anti-HIV-1 activity [27]. Manglisin B, isolated from the mature carpels of *Manglietiastrum sinicum*, was shown to exhibit antimicrobial activities against *Staphylococcus aureus* [28].

Arylnaphthalenes and aryltetralins: Ovafofinins from the stem of *Eurya japonica* (Theaceae) [29] showed strong antioxidant activities while cyclolignene derivatives from the roots of *Pycnanthus angolensis* (Myristicaceae) showed mild antimicrobial activities against several drug-resistant *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* [30]. Among Cleistanxin and neocleistanxin from the fruits of *Cleistanthus indochinensis* (Euphorbiaceae) the former had strong activity against KB, MCF-7, MCF-7R, and HT29 cancer cell lines while the later had mild cytotoxicity [31]. Four new aryl-naphthalene lignans from the aerial parts of *Acanthus mollis* (Acanthaceae) showed significant growth inhibition of the of crown gall tumors on potato discs and antiproliferative activity against *Paracentrotus lividus* [32]. An aryltetralin lignans 4-acetyl-4-demethyl-podophyllotoxin obtained from roots and rhizomes of *Sinopodophyllum emodi* (Berberidaceae) [33] displayed strong cytotoxicity against KB and Hela cell lines with IC_{50} 0.05 and 0.08 mM respectively. Sargentosides isolated from ethanol extracts (60%) of *Sargentodoxa cuneata* (Lardizabalaceae) [34] and aryltetralin-type lignans glycosides from the branches of *Tabebuia chrysotricha* (Bignoniaceae), showed mild DPPH radical-scavenging activity [35]. Similarly, lignans from the trunk of *Lindera glauca* (Lauraceae) called Linderanosides were selectively cytotoxic towards A498 cells [36]. Methanolic extract of *Tilia amurensis* Rupr. (Tiliaceae) trunk evidenced two new lignans glycosides called tiliamurosides A and B where the latter had significantly cytotoxic towards SK-MEL-2, SK-OV-3, HCT-15 and A549 cells [37]. The maple sap of *Acer saccharum* also known as sugar maple or rock maple produced Saposide A which was moderately antioxidative [38]. Similarly, glycoside 7-O-[(3,4-di-O-acetyl)- α -L-arabinopyranosyl] diphyllin, an aryl-naphthalene lignans lactone obtained from *Phyllanthus poilanei* was cytotoxic against the HT-29 cells with IC_{50} 0.17 mM [39] while ester of the same lignan isolated from *Dodecadenia grandiflora* (Lauraceae) leaves showed significant antihyperglycemic activity in Streptozotocin-induced (STZ) diabetic rats, when compared to metformin [40].

Dibenzylbutanes, dibenzylbutyrolactols and dibenzylbutyrolactones: A dibenzylbutane lignan kadsurindutin E isolated from ethyl alcohol soluble fraction of *Kadsura coccinea* roots inhibited NO production in BV-2 cells with IC_{50} 24 mM [41]. Similarly, 2 new lignans isolated from

ethanol extract of *Machilus robusta* (Lauraceae) bark exhibited anti-HIV replication activity with IC_{50} 2.5 and 2 mM [42]. Methanol extract of ethyl alcohol phase from the trunk of *Abies holophylla* (Pinaceae) containing epoxy lignans, holophyllol A, B and C exhibited NO production inhibitory activity in BV-2 cells [43]. *In vitro* anti-leishmanicidal activity against axenic amastigote forms of *Leishmania* was observed in ethyl alcohol extract of leaves of *Piper sanguineispicum* Trel. (Piperaceae) and later they were identified as sanguinolignans [44].

Furofurans: Epimagnolin B, a furofuran lignan from the flower buds of *Magnolia fargesii* (Magnoliaceae) was observed to inhibit NO and PGE₂ production and subsequent suppression of iNOS and COX-2 through the inhibition of I- κ B- α degradation and nuclear translocation of p65 subunit of NF- κ B [45]. Sesamin-2,20-diol a new sesamin type furofuran lignan obtained from the aerial parts of *Isodon japonicus* (Lamiaceae) [46] and rare lignans like zanthopodocarpins A and B isolated from *Zanthoxylum podocarpum* bark showed relatively mild inhibition of LPS induced NO production in RAW264.7 cells [47]. Out of four furofuran lignans such as Dipsalignan A, B, C and D isolated from *Dipsacus asper* Wall (Caprifoliaceae) roots; Dipsalignan D had weak HIV-1 anti-integrase activity [48]. Khainoside A obtained from the leaves of *Vitex glabrata* (Verbenaceae) showed strong anti-proliferative activity in estrogen-induced cells [49]. Roots of *Zanthoxylum planispinum* (Rutaceae) a shrub used as traditional medicine for snake bite, toothache and roundworms afforded two dilignans called bizanthplanispines A and B which was recently found to inhibit proliferation of HeLa cells with IC_{50} 22 and 26 mg/mL respectively [50].

Furans: Seven epoxy lignans, like ribesins A, B, C and D and three tetrahydrofuran- type sesquiligans, like ribesins E, F and G, were found from *Ribes nigrum* (Grossulariaceae) leaves where Ribesins D and G were potential superoxide anion scavengers [51]. In the same way eight new tetrahydrofuran lignans extracted from *Schisandra sphenanthera* (Schisandraceae) roots had anti-oxidative haemolysis of human RBCs [52]. Similarly, tetrahydrofuranoid lignans isolated from *Arctium lappa* L. (Asteraceae) fruit were found to be hepatoprotective against D-galactosamine-induced cytotoxicity in HL-7702 hepatic cells [53]. Linderuca A, B and C obtained from methanol extract of *Lindera glauca* (Lauraceae) twigs showed significant inhibition of NO production with IC_{50} of 12, 9.4, and 9.9 mM respectively [54]. In addition, out of Manglisin B, C, D and E isolated from *Manglietiastrum sinicum* (Magnoliaceae) mature carpels Manglisin B and D showed modest antimicrobial activities against four *Staphylococcus aureus* strains with MIC 0.03 - 0.13 mM [28]. Four new spirocyclic lignans, such as ramonanins A, B, C and D were isolated from *Guaiacum officinale* (Zygophyllaceae) heartwood exhibited apoptosis mediated cytotoxicity against human breast cancer cell lines [55].

Benzofurans: Dihydrobenzofuran neolignans such as 30-methoxymiliumollin and miliumollinone obtained from leaves of *Miliusa mollis* Pierre (Annonaceae), exhibited weak cytotoxicity against NCI-H187, KB and MCF7 cells [56]. Similarly, *Vitex rotundifolia* fruits methanol extract showed Nitric Oxide (NO) production inhibition in RAW264.7 cells [57]. Akequintosides B from *Akebia quinata* (Lardizabalaceae) showed slight inhibition of IL-6 production in TNF- α stimulated MG-63 cells [58]. Meliasendanins B, C and D from *Melia toosendan* (Meliaceae) fruits had moderate ABTS radical-scavenging activity [59]. Euryalin B obtained from seeds of *Euryale ferox* (Nymphaeaceae) exhibited strong effect against DPPH radical [60]. Callislignan A from the leaves of *Callistemon lanceolatus* (Myrtaceae) showed moderate antibacterial activity against *S. aureus* and MRSA SK1 [61]. Saposide B from the maple sap of *Acer saccharum* [38] and Boehmenan X from the bark of *Durio carinatus* [62] exhibited antioxidant activity on superoxide dismutase.

Alkyl aryl ethers: Three Myrifralignans reported from the seeds of *Myristica fragrans* Houtt (Myristicaceae) showed Nitric Oxide (NO) inhibitory potential in LPS stimulated RAW264.7 cells [63]. Fruits of *Broussonetia papyrifera* (Moraceae) afforded [61] chushizisins A, B, C and D out of which compound A, B and D had DPPH radical-scavenging activity. Callislignan B from the leaves of *Callistemon lanceolatus* exhibited antibacterial activity against *S. aureus* [64]. Ligraminols from *Acorus gramineus* (Araceae) showed weak inhibitory activity against A549 proliferation [65]. *Acorus gramineus Soland* (Araceae) afforded surinamensinols A and B which had antiproliferative activities against several human cancer cell lines [66]. Moderate radical-scavenging activity was observed by neolignans from the roots of *Nannoglottis carpesioides* (Asteraceae) [67].

Benzodioxanes: Benzodioxane Neolignans (BNs) has been well recognized for exhibiting interesting biological activities [68]. Methanol extract of *Miliusa fragrans* leaves afforded five BNs out of which (+)-4-Odemethyleusiderin displayed inhibitory activity against cancer cells as well as herpes simplex virus [69]. Similarly, (7R,8R)-5-O-Demethylbilagrewin an aromatic compound isolated from the *Santalum album* (L.) (Santalaceae) heartwood exhibited cytotoxicity against HL-60 cells [70].

Neurodegenerative Disorders and their Pathology

Alzheimer Disease (AD) and pathology

AD is a menacing progressive neurodegenerative disorder that is regarded as one of the most serious health problems worldwide. Affected individuals initially face difficulty in remembering newly learned information, suffer from disorientation, mood changes, confusion but later develop more serious memory loss

and behavior changes, suspicions about own relatives, associates and caregivers. AD brain shows clear deposition of Aβ and neurofibrillary tangles. Two major forms of AD include Early-Onset Familial AD (EOFAD) and Late-Onset AD (LOAD). EOFAD which represents less than 5% is rare but highly penetrant which arise due to mutations in different genes which transmit in an autosomal dominant fashion whereas the latter one arises without any familial link [71]. Till now, more than 160 mutations in genes such as Aβ Precursor Protein (APP) on chromosome 21 [72], Presenilin 1 (PSEN1) on chromosome 14 [73], and Presenilin 2 (PSEN2) on chromosome 1 [74] have been reported to cause EOFAD. On contrary LOAD which appears at age 65 or older represents the vast majority of all AD cases. It has been suggested that the ε4 allele of the apolipoprotein E gene on chromosome 19q13 exerts a risk for LOAD while the minor allele, ε2 has some protective effect [75]. Although there is no cure for AD there are drug and non-drug procedures that may manage the symptoms. Cholinesterase inhibitors such as donepezil, revastigmine and galantamine are being used for memory enhancement. A number of herbal remedies are promoted as memory enhancers to delay or prevent AD.

Several hypotheses have been proposed regarding AD pathology such as cholinergic, tau and amyloid hypothesis. The cholinergic

hypothesis directs about a sharp decline in the level of Acetylcholine (ACh) which is a major neurotransmitter, due to its hydrolysis by Acetylcholinesterase (AChE) [76]. Amyloid hypothesis proposes the formation and deposition of amyloid beta (Aβ) protein in the brain of AD patients which is produced from Amyloid Precursor Protein (APP), a transmembrane glycoprotein involved in multiple biological processes like protein trafficking, neurogenesis and synaptogenesis and of course evolutionarily conserved [77]. The deposited Aβ also called senile or neuritic plaques are commonly surrounded by microglial cells and reactive astrocytes which are involved in neuroinflammatory cascade. Evidences are growing regarding cross linking of cholinergic and Aβ pathways [78]. Tau is an axonal phosphoprotein that stabilizes microtubule through binding with tubulin and promotes neurite outgrowth [79]. In the neurons, during the early developmental stages, it predominantly occurs in hyperphosphorylated condition but in adults, it is found in dephosphorylated form, which is essential for cytoskeletal integrity [80]. Glycogen synthase kinase-3β (GSK-3β) controls tau phosphorylation and its abnormal hyperphosphorylation makes it inaccessible for proteases and thus binding to tubulin, resulting in structural and functional disruption of synaptic metabolism (Figure 2) [81]. The degree of cognitive impairment in AD is significantly correlated with the presence of neurofibrillary tangles [82]. A consecutive study

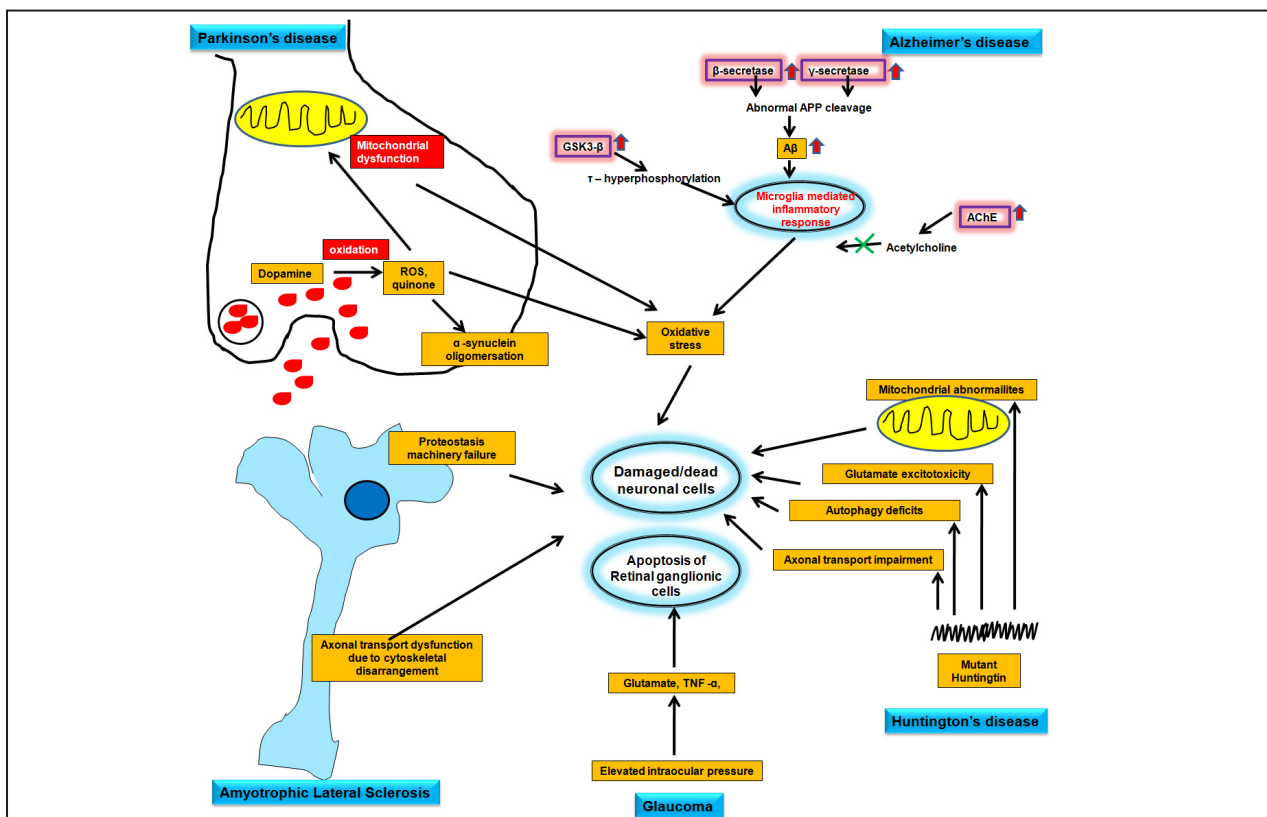


Figure 2: Mechanism underlying the pathology of neurodegenerative diseases like Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, Amyotrophic lateral sclerosis and glaucoma.

[83] shows that a protein kinase p38 γ phosphorylates tau at the threonine-205 to protect it from A β aggregation induced damage and the activity of this enzyme is mostly lost with AD progression. Vascular amyloid deposition or congophilic angiopathy is another pathological characteristic of AD where A β accumulates in the leptomeningial walls and within the gray matter of the cerebral cortex. Severe congophilic angiopathy leads to vascular rupture leading to accumulation of blood in the brain tissues causing hemorrhages [84]. Granulovacuolar degeneration and eosinophilic perineuronal lesions or Hirano Bodies are other pathological lesions found in AD which are relatively less understood [85].

Parkinson's Disease (PD) and pathology

PD the second of common neurodegenerative diseases is an extrapyramidal progressive motor dysfunction, affecting the midbrain region called the substantia nigra pars compacta. It affects 1 % of people over 60, 3.4 % over 70, and 4% over 80 years of age [86,87]. Tremor, rigidity and postural stability and bradykinesia are the preliminary symptoms of PD while depression, dementia, sleep abnormalities and autonomic failure become evident during its later stage [88]. The key symptoms of PD are correlated to the deficiency in the neurotransmitter dopamine. Therefore, the current treatment of PD involves drugs such as L-3,4-dihydroxyphenylalanine (L-DOPA) which is a precursor of dopamine, monoamine oxidase inhibitors, and dopamine receptor agonists which facilitate dopaminergic neurotransmission. Unfortunately, none of the currently available therapies can delay PD associated degeneration while constant use of L-DOPA frequently causes psychiatric reactions. Hence most of the ongoing PD related research is to modify the disease course by neuroprotection.

Two prominent pathological hallmarks displayed in postmortem brains of PD patients are the presence of Lewy bodies, aggregated α -synuclein [89] and reactive microgliosis. Mostly 90-95% of PD is sporadic while its rare familial forms involving mutations in a number of genes have also been described. Missense mutations in the α -synuclein gene have been linked to PD [90]. Mutations in the parkin genes lead to mitochondrial dysfunction, oxidative stress, and cell death [91-93]. Mutations in the DJ-1 gene makes the cells vulnerable to oxidative stress and leads to early onset autosomal recessive PD [94]. Majority of PD cases are sporadic and environmental factors play a critical role in PD etiology. Consistent uses of herbicides or pesticides [95] and exposure to organic solvents like carbon monoxide, and carbon disulfide [96] increase the risk of PD.

Amyotrophic Lateral Sclerosis (ALS) and pathology

ALS or Lou Gehrig's disease cause premature death of neurons that control voluntary muscles thereby causing paralysis.

Clinically it is characterized by progressive degeneration of motor neurons in the brain and spinal cord. Though the occurrence of ALS is low (0.005%) when compared to other dementia, its prevalence increases in people with age 55-75 years. Genetic factors such as MAPT (Microtubule-Associated Protein Tau) and mutations in genes SOD1 and ALS2 genes are majorly responsible for most Familial ALS (FALS) cases [97]. These mutations account for about 20% of FALS cases while up to 10% of the sporadic ALS there was no familial segregation [98].

Major neuropathological features of ALS include protein misfolding, oxidative stress, glutamatergic excitotoxicity and cytoskeletal dysfunctions leading to severe neurodegeneration. Further, intracellular inclusions such as Bunina bodies, perikaryal inclusions of neurofilament and Lewy body-like cytoplasmic inclusions are prominent microscopic features. Though in majority of ALS cases, brain does not exhibit prominent abnormalities, spinal cord frequently reveals atrophic anterior nerve roots and precentral gyrus [99]. Some ALS cases also display atrophy of the frontal or temporal cortex or both [100-102]. In some cases, the corticospinal tract displays grey matter abnormalities [103-105].

Huntington Disease (HD) and pathology

Huntington Disease (HD) is an autosomal dominant, progressive neurodegenerative disease characterized by abnormal movements (chorea), cognitive loss and psychiatric sickness. HD is caused by an extended repeat of CAG (usually more than 40) in the gene which encodes the huntingtin protein located in chromosome 4. Subsequently it results in atrophied striatum, cortical and extrastriatal regions. Mutant huntingtin which has been implicated in the toxicity of HD form aggregates by its N-terminal cleavage, further oligomerize and form inclusions. This in turn adversely affects a number of intracellular processes such as mitochondrial and transcriptional system of several genes, disrupted calcium signaling, abnormal protein interactions, alterations in proteosomal function and finally autophagy [106]. Overall, the pathological factors affect the brain causing cell loss and gliosis with the striatum being most affected.

Glaucoma and pathology

Glaucoma is considered as a set of optical nerve disorders that are associated with structural changes in the optic nerve head which lead to blindness. Primary Open-Angle Glaucoma (POAG) and Primary Angle-Closure Glaucoma (PACG) are the most common forms of glaucoma [107]. The junction between the iris and cornea (forming an angle) serve as drainer of aqueous humor from the anterior chamber of the eye [108] and in POAG, the trabecular meshwork becomes unblocked by iris tissue leading to opening of the angle and subsequent intraocular pressure gets transmitted to the axons of retinal

ganglia at the optic nerve which imparts a mechanical stress and finally cell death [109]. In PACG exactly the opposite happens when the peripheral iris blocks normal aqueous humor flow [110] which lead to increased intraocular pressure and optic nerve damage. Symptomatically glaucoma is characterized by a sudden and painful loss of vision [111], blurred vision and rainbows around lights accompanied with nausea and vomiting [112].

Effect of Lignans for the Treatment of Neurodegenerative Disorders

Lignans with anti-AD effect

Alzheimer's Disease (AD) which cause progressive degeneration of neurons (involve multiple roadways such as A β toxicity microglia activation and release of inflammatory cytokines like IL-1 β , TNF- α , NO and NF-kB [113]. Several lignans has been proved to target many of these pathways and thus seemed beneficial in both *in vitro* and *in vivo* conditions. Macelignan from *Myristica fragrans*, was found to mitigate glutamate induced neurotoxicity via anti-oxidant and anti-inflammatory properties along with reduced ROS production in murine hippocampal HT22 cells. This study also evidenced that macelignan mediates inhibition of Lipopolysaccharides (LPS)-induced neuroinflammation in primary culture of rat microglial cells through reduced TNF- α and IL-6 [114]. Subsequent *in vivo* report says that this lignans ameliorate LPS induced neuroinflammation in rats through its molecular mechanism extended to MAPK signalling and nuclear factor kB (NF-kB) [115]. Based on a review clarifying the accumulation of toxic ceramides in liver that cause neurodegenerative diseases such as AD due to improper lipid metabolism caused by diabetes type 2 [116], macelignan when administered to diabetic rats interestingly reduced phosphorylation of eukaryotic initiation factor, ER stress, glucose- regulated protein and CCAAT/ enhancer-binding protein homologous protein [117]. Another report suggests four new lignans from crude extract of *Adelostemma gracillimum* (Apocynaceae) root had protective effect against N-methyl-D-aspartate (NMDA)-induced cytotoxicity in rat primary cortical neurons [118]. Similarly, five novel lignans from *Rubus idaeus* rhizome methanol extract protected human neuroblastoma cells SHSY5Y cells from H₂O₂ induced neurodegeneration through its *in vitro* antioxidative property [119]. Similarly studies on the effect of lignans from stem of *Schisandra chinensis* rattan on amyloid- β ₁₋₄₂ induced microglia activation showed that they ameliorate microglia activation through activation of NF-kB/MAPK signaling pathway [120]. Schisandrins B obtained from the fruit of the same plant mitigated A β ₁₋₄₂ induced DNA methylation in

SHSY5Y cells evidenced by decreased mRNA and protein expression of DNA methyltransferases DNMT3A and DNMT1 [121]. In the same way honokiol attenuated A β ₁₋₄₂ oligomer induced memory impairment in AD model mice via reduced mitochondrial apoptosis and inhibition of NFk β signaling [122]. A study using hippocampal neurons from rats demonstrated that nordihydroguaiaretic acid protects hippocampal neurons against amyloid beta-peptide toxicity through ROS suppression and reduced calcium accumulation [123]. Similarly, several other lignans in methanolic extract like arctiin, (-)-traxillagenin, (-)-arctigenin, traxillaside, and 3(-)-4'-demethyltraxillagenin isolated from the bark of *Torreya nucifera* (Taxaceae) were found to be very potent neuroprotectors against glutamate-induced toxicity in rat cortical primary cells [124]. In a similar manner some lignans such as triclin, salcolin, and tetrahydro-4,6-bis(4-hydroxy-3-methoxyphenyl)-1H,3H-furo[3,4-c] furan-1-one isolated from the ethanolic extract of *Zea mays* stems revealed both anti-inflammatory as well as neuroprotective effect in LPS RAW 264.7 cells and glutamate-induced HT22 cells respectively [125]. Consecutively Flax Lignans (FLL) has also been in the queue of holding neuroprotective potential which has been supported by few studies. FLL reduced intracellular Ca²⁺ and balanced expression of Bcl-2 and Bax, further reduced the upregulation of GluN2B subunit containing NMDA receptor in NMDA exposed cells [126]. Since NMDA receptor plays a role in the mechanism of synaptic transmission, the FLL can improve the learning abilities and memory of AD patients. Four polysperlignans another class of dibenzocyclooctadiene lignans isolated from *K. polysperma* stem when tested on A β or H₂O₂ induced neurotoxicity on PC12 cells had statistically significant neuroprotective effects [127]. In the same way strong antioxidant activity was observed in H₂O₂ treated PC12 cells by chushizisins obtained from fruits of *Broussonetia papyrifera* [61].

Lignans with anti-PD effect

A group of investigators claimed that schisantherin A (a dibenzocyclooctadiene lignan) from *Schisandra chinensis* fruit protects against 6-hydroxydopamine (6-OHDA) (a PD model) induced dopaminergic neuronal damage in Zebrafish and cytotoxicity in SHSY5Y cells by regulating intracellular ROS accumulation and inhibiting NO production [128]. Weng et al., showed that 6 days daily intraperitoneal injection of 10 mg/kg magnolol reversed the neuronal damage associated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced dopaminergic neurotoxicity (the toxin which produces symptoms like PD) in male C57BL/6 mice [129].

In another study 20 mg/Kg sesamin, the lignin present in more amount in sesame oil not only improved motor imbalance but

also lowered malondialdehyde, caspase 3 activity, α -synuclein expression and ROS [130]. Another report by Kiyofuji et al., evidenced that supplementation of 10 μ M macelignan (a nutmeg lignan) to the mice midbrain slice cultures treated with IFN- γ and LPS showed dramatic effect on inflammation induced degeneration of dopaminergic neurons through expression of arginase-1 [131]. Induction of arginase-1 by the lignin is a good treatment approach for PD because studies have shown that the plaque removal will be better in cells which are positive for arginase-1. In another study, supplementation of 25 μ M (-)-sesamin ameliorated 6-OHDA induced neurotoxicity in PC12 cells via reduced ERK1/2 and Bad (Bcl-2-associated death promoter) phosphorylation. Additionally, oral administration of 30 mg/kg body weight of sesamin showed increased dopamine, 3,4-dihydroxyphenylacetic acid, norepinephrine, as well as homovanillic acid in the substantia nigra-striatum of 6-OHDA-induced PD in rat model [132].

Lignans effective for other neurodegenerative disorders

Mutations in copper/zinc-superoxide dismutase (SOD1) has been found to be associated with familial ALS and a sharp increase in TNF α in the CNS of G93A-SOD1 mice (transgenic expressing mutant SOD1 enzymes) proposed a possible target for the therapeutic leads against ALS. Nordihydroguaiaretic Acid (NDGA), a lignan from *Larrea tridentate* showed 10% increase in lifespan of G93A-SOD1 mice model of ALS. It antagonized TNF- α and 5-lipoxygenase and thus reduced neuronal damage [133]. A similar work done by Boston et al., revealed that subcutaneous injection of 1 mg of NDGA/day for 30 days in mice, caused persistent increase of glutamate uptake in spinal cord synaptosomes but when given to the SOD1-G93A transgenic mouse model of ALS at later stage it did not extend their life span [134].

Glaucoma a progressive neurodegenerative disease characterized by degeneration of retinal ganglion cells and axons requires development of potent neuroprotective leads for effective treatment. Glaucoma exhibit strong similarities with AD and PD including the selective loss of neuronal populations and trans synaptic degeneration [135]. Several lignans has been reported of having neuroprotection against glaucoma such as lignans from *Eucommia ulmoides* extract showed neuroprotection against glaucoma-associated optic neuropathy in glaucomatous rats by activating AMPK (AMP-activated protein kinase) signaling, which restores the energy balance of the cells [136].

Plant lignans has also been found to be effective for HD related oxidative damage. Recent studies show that NDGA improves

ATP generation and mitochondria structure in oxidative stress-induced neuronal cells. In addition, it restores mitochondria structure mitochondrial membrane potential and synaptic structure in the striatum of R6/2 mice [137]. Some of the plant lignans are even proved to be beneficial for virus borne neurodegenerative diseases like Japanese Encephalitis (JE). For instance, Swarup et al., found that arctigenin provides complete protection against JE in BALB/c infected with Japanese Encephalitis Virus (JEV). Several factors contributed for the neuroprotective effect of the lignan including reduced caspase-3 activity, ROS, RNS, proinflammatory cytokines and viral load [138]. In the same way dihydrobenzofuran neolignans from *Clematidis armandii* showed potent anti-neuroinflammatory activity by suppressing TNF- α release in LPS-stimulated BV-2 cells [139]. Apoptotic neuronal cells contribute to neuronal loss in neurodegenerative diseases where some lignans like sauchinone from (*Saururus chinensis*) has been reported to protect C6 rat glioma cells from staurosporine induced apoptosis via decreased caspase-3 activity [140]. Some of the lignans like petasignolide A from *Petasites japonicus* [141] and 9-hydroxypinoresinol were found to be protective against kainic acid induced seizure in mice [142]. Figure 3 shows the structure of lignans effective for these neurodegenerative diseases.

Conclusion

Plant secondary metabolites represent a huge group of bioactive molecules and lignans are one of such molecules which have been used as folk medicine from time immemorial. Based on their structure lignans have been divided in to dibenzocyclooctadienes, aryl naphthalenes, aryl tetralins, dibenzylbutanes, dibenzylbutyrolactols, dibenzylbutyrolactones, furofurans and furans. Similarly, neolignans which are the natural derivatives of lignan have been divided into Benzofurans, alkyl aryl ethers and benzodioxanes. In this review the individual lignans were summarized in relation to their neuroprotective and cognitive enhancement activities. Lignans from many plant species were found to be beneficial for cancer, hepatitis, microbial and fungal infections while specific lignans like macelignan, schisandrin B, arctiin, (-)-traxillagenin, traxillaside, 3(-)-4'-demethyltraxillagenin, flax lignans, schisantherin A, (-)-sesamin, nordihydroguaiaretic acid and sauchinone were helpful for NDDs including Alzheimer's disease, Parkinson's disease, glaucoma, amyotrophic lateral sclerosis, Huntington's disease and Japanese encephalitis. These molecules prevent neurodegeneration through their antioxidative and anti-inflammatory effect; they also intervene the molecular pathways like DNA methylation, caspase 3, ERK etc. that lead to cellular apoptosis (Figure 4). Literature survey proposed that lignans can serve as efficient neuroprotective molecules in cell line

as well as animal models, where as extensive clinical studies remain to be carried out to prove their efficiency.

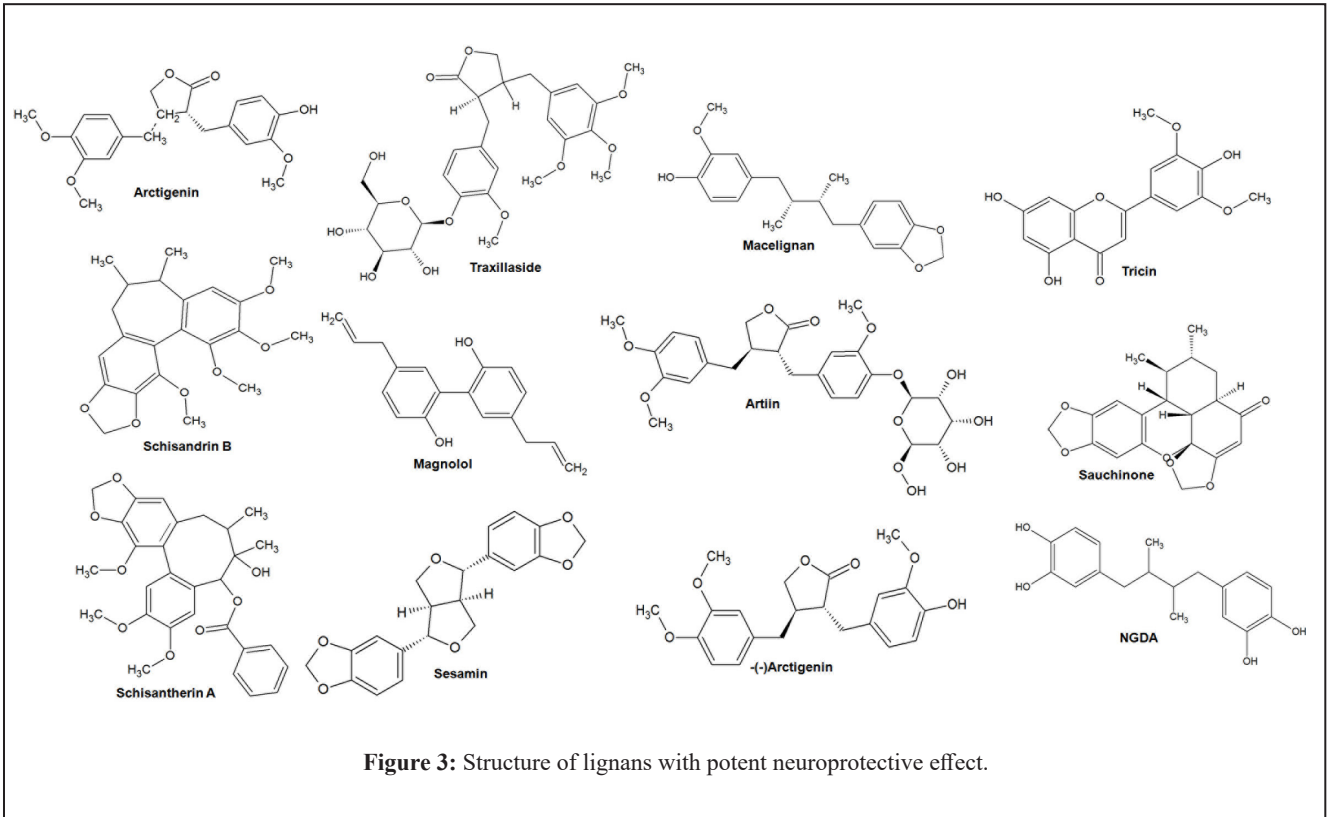


Figure 3: Structure of lignans with potent neuroprotective effect.

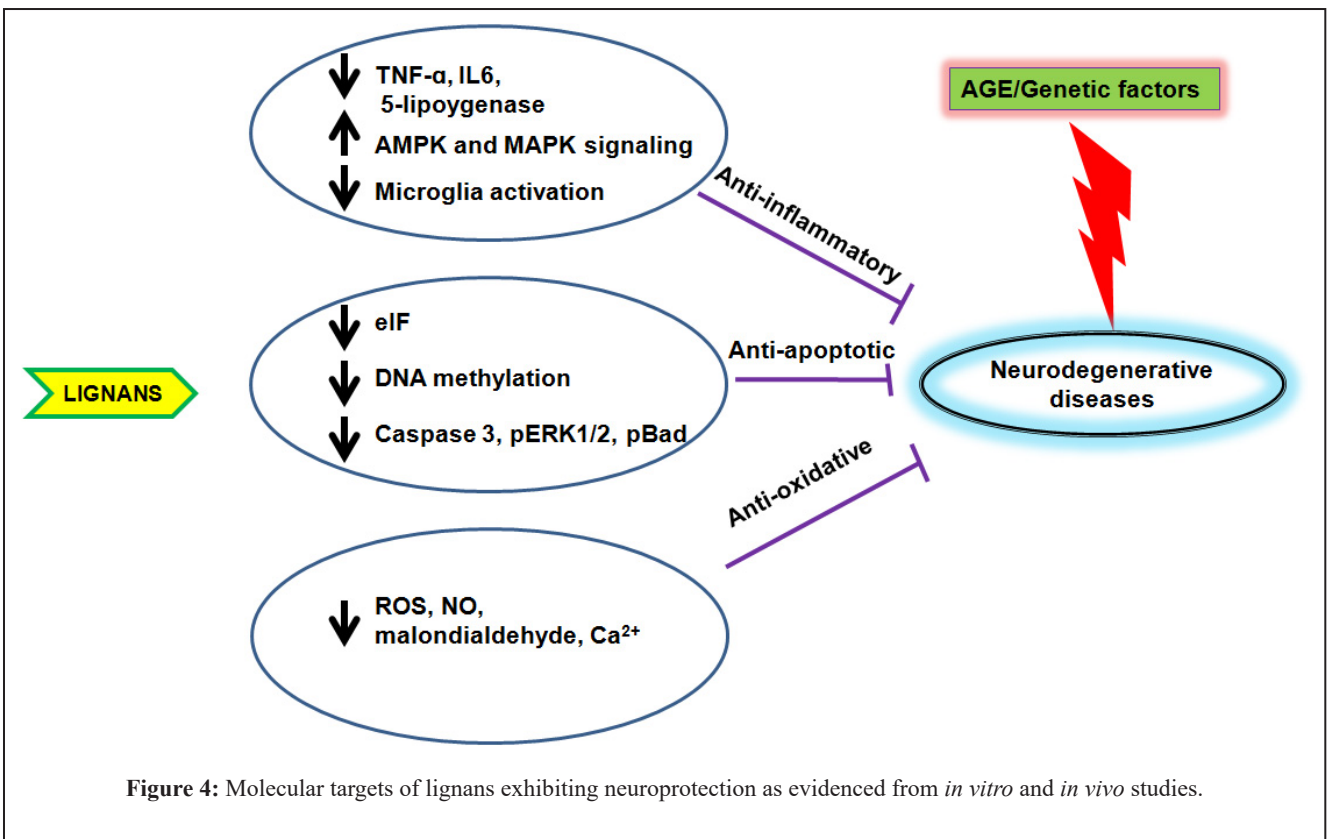


Figure 4: Molecular targets of lignans exhibiting neuroprotection as evidenced from *in vitro* and *in vivo* studies.

Acknowledgement

The authors gratefully acknowledge the Bioinformatics Infrastructure Facility provided by the Alagappa University (funded by Department of Biotechnology, Government of India; Grant No. BT/B1/25/015/2012) and RUSA 2.0 [F. 24-51/2014-U, Policy (TN Multi-Gen), Dept of Edn, GoI].

References

- Haworth RD (1936) Natural resins. *Annu Rep Prog Chem* 33: 266-279.
- Umezawa T (2003) Diversity in lignan biosynthesis. *Phytochem Rev* 2: 371-390.
- Gordaliza M, García PA, Del Corral JM, Castro MA, Gómez-Zurita MA (2004) Podophyllotoxin: distribution, sources, applications and new cytotoxic derivatives. *Toxicol* 44: 441-459.
- Hardy JA, Higgins GA (1992) Alzheimer's disease: the amyloid cascade hypothesis. *Science* 256: 184-185.
- Ferreri AJ, Illerhaus G, Zucca E, Cavalli F, International Extranodal Lymphoma Study Group (2010) Flows and flaws in primary central nervous system lymphoma. *Nat Rev Clin Oncol* 7: 125-126.
- Taylor JP, Hardy J, Fischbeck KH (2002) Toxic proteins in neurodegenerative disease. *Science* 296: 1991-1995.
- Krainc D (2010) Clearance of mutant proteins as a therapeutic target in neurodegenerative diseases. *Arch Neurol* 67: 388-392.
- Rademakers R, Neumann M, Mackenzie IR (2012) Advances in understanding the molecular basis of frontotemporal dementia. *Nat Rev Neurol* 8: 423-434.
- Penttinen P, Jaehrling J, Damdimopoulos AE, Inzunza J, Lemmen JG, et al. (2007) Diet-derived polyphenol metabolite enterolactone is a tissue-specific estrogen receptor activator. *Endocrinology* 148: 4875-4886.
- Adlercreutz H (2007) Lignans and human health. *Crit Rev Clin Lab Sci* 44: 483-525.
- Muir AD, Westcott ND (2003) *Flax, The Genus Linum*. 1stedn, Taylor & Francis Group, London, UK.
- Peñalvo JL, Haajanen KM, Botting N, Adlercreutz H (2005) Quantification of lignans in food using isotope dilution gas chromatography/mass spectrometry. *J Agric Food Chem* 53: 9342-9347.
- Peterson J, Dwyer J, Adlercreutz H, Scalbert A, Jacques P, et al. (2010) Dietary lignans: physiology and potential for cardiovascular disease risk reduction. *Nutr Rev* 68: 571-603.
- Smeds AI, Eklund PC, Sjöholm RE, Willför SM, Nishibe S, et al. (2007) Quantification of a broad spectrum of lignans in cereals, oilseeds, and nuts. *J Agric Food Chem* 55: 1337-1346.
- Kuhnle GG, Dell'Aquila C, Aspinall SM, Runswick SA, Mulligan AA, et al. (2009) Phytoestrogen content of cereals and cereal-based foods consumed in the UK. *Nutr Cancer* 61: 302-309.
- Milder IE, Arts IC, van de Putte B, Venema DP, Hollman PC (2005) Lignan contents of Dutch plant foods: a database including lariciresinol, pinoresinol, secoisolariciresinol and matairesinol. *Br J Nutr* 93: 393-402.
- Peñalvo JL, Adlercreutz H, Uehara M, Ristimaki A, Watanabe S (2008) Lignan content of selected foods from Japan. *J Agric Food Chem* 56: 401-409.
- Kuhnle GG, Dell'Aquila C, Aspinall SM, Runswick SA, Mulligan AA, et al. (2008) Phytoestrogen content of foods of animal origin: dairy products, eggs, meat, fish, and seafood. *J Agric Food Chem* 56: 10099-10104.
- Gagnon N, Côtés C, da Silva D, Kazama R, Benchaar C, et al. (2009) Ruminal metabolism of flaxseed (*Linum usitatissimum*) lignans to the mammalian lignan enterolactone and its concentration in ruminal fluid, plasma, urine and milk of dairy cows. *Br J Nutr* 102: 1015-1023.
- Yang JH, Zhang HY, Wen J, Du X, Chen JH, et al. (2011) Dibenzocyclooctadiene lignans with antineurodegenerative potential from *Kadsura ananosma*. *J Nat Prod* 74: 1028-1035.
- Yang GY, Wang RR, Mu HX, Li YK, Li XN, et al. (2013) Dibenzocyclooctadiene lignans and norlignans from fruits of *Schisandra wilsoniana*. *J Nat Prod* 76: 250-255.
- Ikeya Y, Taguchi H, Yosioka I, Iitaka Y, Kobayashi H (1979) The constituents of *Schizandra chinensis* Baill. II. The structure of a new lignan, gomisin D. *Chem Pharm Bull* 27: 1395-1401.
- Li XN, Pu JX, Du X, Yang LM, An HM, et al. (2009) Lignans with anti-HIV activity from *Schisandra propinqua* var. *sinensis*. *J Nat Prod* 72: 1133-1141.
- Chen M, Xu X, Liao Z, Dong L, Li L, et al. (2008) Neglschisandrins AB: Two New Dibenzocyclooctene Lignans from *Schisandra neglecta*. *Molecules* 13: 548-555.
- Cheng YB, Chang MT, Lo YW, Ho CJ, Kuo YC, et al. (2009) Oxygenated lignans from the fruits of *Schisandra arisanensis*. *J Nat Prod* 72: 1663-1668.
- Hu D, Yang Z, Yao X, Wang H, Han N, et al. (2014) Dibenzocyclooctadiene lignans from *Schisandra chinensis* and their inhibitory activity on NO production in lipopolysaccharide-activated microglia cells. *Phytochemistry* 104: 72-78.
- Yang GY, Fan P, Wang RR, Cao JL, Xiao WL, et al. (2010) Dibenzocyclooctadiene lignans from *Schisandra lancifolia* and their anti-human immunodeficiency virus-1 activities. *Chem Pharm Bull* 58: 734-737.
- Ding JY, Yuan CM, Cao MM, Liu WW, Yu C, et al. (2014) Antimicrobial constituents of the mature carpels of *Manglietiastrum sinicum*. *J Nat Prod* 77: 1800-1805.
- Yang Kuo LM, Zhang LJ, Huang HT, Lin ZH, Liaw CC, et al. (2013) Antioxidant lignans and chromone glycosides from *Eurya japonica*. *J Nat Prod* 76: 580-587.

30. Nono ECN, Mkounga P, Kuete V, Marat K, Hultin PG, et al. (2010) Pycnanthulignenes A- D, antimicrobial cyclolignene derivatives from the roots of *Pycnanthus angolensis*. *J Nat Prod* 73: 213-216.
31. Thanh VT, Pham VC, Mai HD, Litaudon M, Guéritte F, et al. (2012) Cytotoxic lignans from fruits of *Cleistanthus indochinensis*: synthesis of cleistantoxin derivatives. *J Nat Prod* 75: 1578-1583.
32. Teponno RB, Kusari S, Spiteller M (2016) Recent advances in research on lignans and neolignans. *Nat Prod Rep* 33: 1044-1092.
33. Sun YJ, Li ZL, Chen H, Liu XQ, Zhou W, et al. (2011) Three new cytotoxic aryltetralin lignans from *Sinopodophyllum emodi*. *Bioorg Med Chem Lett* 21: 3794-3797.
34. Zeng X, Wang H, Gong Z, Huang J, Pei W, et al. (2015) Antimicrobial and cytotoxic phenolics and phenolic glycosides from *Sargentodoxa cuneata*. *Fitoterapia* 101: 153-161.
35. Takahashi S, Kawakami S, Sugimoto S, Matsunami K, Otsuka H (2015) Lignan glycosides and phenolic compound glycosides from the branches of *Tabebuia chrysotricha*. *AJPS* 6: 676-684.
36. Suh WS, Kim KH, Kim HK, Choi SU, Lee KR (2015) Three new lignan derivatives from *Lindera glauca* (Siebold et Zucc.) Blume. *Helv Chim Acta* 98: 1087-1094.
37. Kim KH, Moon E, Kim SY, Choi SU, Lee KR (2012) Lignan constituents of *Tilia amurensis* and their biological evaluation on antitumor and anti-inflammatory activities. *Food Chem Toxicol* 50: 3680-3686.
38. Yoshikawa K, Tani S, Baba C, Hashimoto T (2013) Phenylpropanoid, sapinol A, lignan and neolignan sophorosides, saposides A and B, isolated from Canadian sugar maple sap. *Molecules* 18: 9641-9649.
39. Ren Y, Lantvit DD, Deng Y, Kanagasabai R, Gallucci JC, et al. (2014) Potent cytotoxic aryl-naphthalene lignan lactones from *Phyllanthus poilanei*. *J Nat Prod* 77: 1494-1504.
40. Kumar M, Rawat P, Rahuja N, Srivastava AK, Maurya R (2009) Antihyperglycemic activity of phenylpropanoyl esters of catechol glycoside and its dimers from *Dodecadenia grandiflora*. *Phytochemistry* 70: 1448-1455.
41. Fang L, Xie C, Wang H, Jin DQ, Xu J, et al. (2014) Lignans from the roots of *Kadsura coccinea* and their inhibitory activities on LPS-induced NO production. *Phytochemistry Lett* 9: 158-162.
42. Li Y, Cheng W, Zhu C, Yao C, Xiong L, et al. (2011) Bioactive neolignans and lignans from the bark of *Machilus robusta*. *J Nat Prod* 74: 1444-1452.
43. Kim CS, Kwon OW, Kim SY, Lee KR (2013) Bioactive lignans from the trunk of *Abies holophylla*. *J Nat Prod* 76: 2131-2135.
44. Cabanillas BJ, Le Lamer AC, Castillo D, Arevalo J, Rojas R, et al. (2010) Caffeic acid esters and lignans from *Piper sanguineispicum*. *J Nat Prod* 73: 1884-1890.
45. Kim JY, Lim HJ, Lee da YK, Kim JS, Kim DH, et al. (2009) *In vitro* anti-inflammatory activity of lignans isolated from *Magnolia fargesii*. *Bioorg Med Chem Lett* 19: 937-940.
46. Hong SS, Lee C, Lee CH, Park M, Lee MS, et al. (2009) A new furofuran lignan from *Isodon japonicus*. *Arch Pharmacol Res* 32: 501-504.
47. Zhou XJ, Chen XL, Li XS, Su J, He JB, et al. (2011) Two dimeric lignans with an unusual α, β -unsaturated ketone motif from *Zanthoxylum podocarpum* and their inhibitory effects on nitric oxide production. *Bioorg Med Chem Lett* 21: 373-376.
48. Sun X, Ma G, Zhang D, Huang W, Ding G, et al. (2015) New lignans and iridoid glycosides from *Dipsacus asper* Wall. *Molecules* 20: 2165-2175.
49. Chouhan HS, Sridevi K, Singh NK, Singh SK (2012) Anti-inflammatory activity of ethanol extract of *Vitex glabrata* leaves. *Pak J Pharm Sci* 25: 131-134.
50. Su GY, Wang KW, Wang XY, Wu B (2015) Bioactive lignans from *Zanthoxylum planispinum* with cytotoxic potential. *Phytochemistry Lett* 11: 120-126.
51. Sasaki T, Li W, Zaike S, Asada Y, Li Q, et al. (2013) Antioxidant lignoids from leaves of *Ribes nigrum*. *Phytochemistry* 95: 333-340.
52. Jiang K, Song QY, Peng SJ, Zhao QQ, Li GD, et al. (2015) New lignans from the roots of *Schisandra sphenanthera*. *Fitoterapia* 103: 63-70.
53. Yang YN, Huang XY, Feng ZM, Jiang JS, Zhang PC (2014) Hepatoprotective activity of twelve novel 7'-hydroxy lignan glucosides from *Arctii fructus*. *J Agric Food Chem* 62: 9095-9102.
54. Kim KH, Moon E, Ha SK, Suh WS, Kim HK, et al. (2014) Bioactive lignan constituents from the twigs of *Lindera glauca*. *Chem Pharm Bull* 62: 1136-1140.
55. Chavez KJ, Feng X, Flanders JA, Rodriguez E, Schroeder FC (2011) Spirocyclic lignans from *Guaiacum* (Zygophyllaceae) induce apoptosis in human breast cancer cell lines. *J Nat Prod* 74: 1293-1297.
56. Sawasdee K, Chaowasku T, Lipipun V, Dufat TH, Michel S, et al. (2013) Neolignans from leaves of *Milium mollis*. *Fitoterapia* 85: 49-56.
57. Lee C, Lee JW, Jin Q, Lee HJ, Lee SJ, et al. (2013) Anti-inflammatory constituents from the fruits of *Vitex rotundifolia*. *Bioorg Med Chem Lett* 23: 6010-6014.
58. Jin HG, Kim AR, Ko HJ, Lee SK, Woo ER (2014) Three new lignan glycosides with IL-6 inhibitory activity from *Akebia quinata*. *Chem Pharm Bull* 62: 288-293.
59. Wang L, Li F, Yang CY, Khan AA, Liu X, et al. (2014) Neolignans, lignans and glycoside from the fruits of *Melia toosendan*. *Fitoterapia* 99: 92-98.
60. Song CW, Wang SM, Zhou LL, Hou FF, Wang KJ, et al. (2011) Isolation and identification of compounds responsible for antioxidant capacity of *Euryale ferox* seeds. *J Agric Food Chem* 59: 1199-1204.

61. Mei RQ, Wang YH, Du GH, Liu GM, Zhang L, et al. (2009) Antioxidant lignans from the fruits of *Broussonetia papyrifera*. *J Nat Prod* 72: 621-625.
62. Rudiyansyah, Lambert LK, Garson MJ (2010) Lignans and triterpenes from the bark of *Durio carinatus* and *Durio oxleyanus*. *J Nat Prod* 73: 1649-1654.
63. Cao GY, Xu W, Yang XW, Gonzalez FJ, Li F (2015) New neolignans from the seeds of *Myristica fragrans* that inhibit nitric oxide production. *Food Chem* 173: 231-237.
64. Rattanaburi S, Mahabusarakam W, Phongpaichit S, Carroll AR (2012) Neolignans from *Callistemon lanceolatus*. *Phytochemistry Lett* 5: 18-21.
65. Kim KH, Kim HK, Choi SU, Moon E, Kim SY, et al. (2011) Bioactive lignans from the rhizomes of *Acorus gramineus*. *J Nat Prod* 74: 2187-2192.
66. Kim KH, Moon E, Kim HK, Oh JY, Kim SY, et al. (2012) Phenolic constituents from the rhizomes of *Acorus gramineus* and their biological evaluation on antitumor and anti-inflammatory activities. *Bioorg Med Chem Lett* 22: 6155-6259.
67. Xue CB, Chai DW, Jin XJ, Bi YR, Yao XJ, et al. (2011) Triterpenes and neolignans from the roots of *Nannoglottis carpesioides*. *Phytochemistry* 72: 1804-1813.
68. Pilkington LI, Barker D (2015) Synthesis and biology of 1, 4-benzodioxane lignan natural products. *Nat Prod Rep* 32: 1369-1388.
69. Sawasdee K, Chaowasku T, Lipipun V, Dufat TH, Michel S, et al. (2013) New neolignans and a lignan from *Miliusa fragrans*, and their anti-herpetic and cytotoxic activities. *Tetrahedron Lett* 54: 4259-4263.
70. Matsuo Y, Mimaki Y (2010) Lignans from *Santalum album* and their cytotoxic activities. *Chem Pharm Bull* 58: 587-590.
71. Tanzi RE (1999) A genetic dichotomy model for the inheritance of Alzheimer's disease and common age-related disorders. *J Clin Invest* 104: 1175-1179.
72. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, et al. (1991) Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 349: 704-706.
73. Sherrington R, Rogaev EI, Liang YA, Rogaeva EA, Levesque G, et al. (1995) Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 375: 754-760.
74. Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, et al. (1995) Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* 376: 775-778.
75. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, et al. (1993) Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA* 90: 1977-1981.
76. Hebert LE, Scherr PA, Beckett LA, Albert MS, Pilgrim DM, et al. (1995) Age-specific incidence of Alzheimer's disease in a community population. *JAMA* 273: 1354-1359.
77. Muller-Hill B, Beyreuther K (1989) Molecular biology of Alzheimer's disease. *Annu Rev Biochem* 58: 287-307.
78. Kar S, Slowikowski SP, Westaway D, Mount HT (2004) Interactions between β -amyloid and central cholinergic neurons: implications for Alzheimer's disease. *J Psychiatry Neurosci* 29: 427-441.
79. Mandelkow EM, Mandelkow E (2012) Biochemistry and cell biology of tau protein in neurofibrillary degeneration. *Cold Spring Harb Perspect Med* 2: 006247.
80. Ribaut-Barassin C, Dupont JL, Haeberlé AM, Bombarde G, Huber G, et al. (2003) Alzheimer's disease proteins in cerebellar and hippocampal synapses during postnatal development and aging of the rat. *Neuroscience* 120: 405-423.
81. Mietelska-Porowska A, Wasik U, Goras M, Filipek A, Niewiadomska G (2014) Tau protein modifications and interactions: their role in function and dysfunction. *Int J Mol Sci* 15: 4671-4713.
82. Braskie MN, Klunder AD, Hayashi KM, Protas H, Kepe V, et al. (2010) Plaque and tangle imaging and cognition in normal aging and Alzheimer's disease. *Neurobiol Aging* 31: 1669-1678.
83. Ittner A, Chua SW, Bertz J, Volkerling A, van der Hoven J, et al. (2016) Site-specific phosphorylation of tau inhibits amyloid- β toxicity in Alzheimer's mice. *Science* 354: 904-908.
84. Prelli F, Castano E, Glenner GG, Frangione B (1988) Differences between vascular and plaque core amyloid in Alzheimer's disease. *J Neurochem* 51: 648-651.
85. Hirano A (1994) Hirano bodies and related neuronal inclusions. *Neuropathol Appl Neurobiol* 20: 3-11.
86. de Lau LM, Breteler MM (2006) Epidemiology of Parkinson's disease. *Lancet Neurol* 5: 525-535.
87. Olanow CW, Stern MB, Sethi K (2009) The scientific and clinical basis for the treatment of Parkinson disease. *Neurology* 72: 1-136.
88. Chaudhuri KR, Schapira AH (2009) Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* 8: 464-474.
89. Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M (1998) α -Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proc Natl Acad Sci USA* 95: 6469-6473.
90. Farrer MJ (2006) Genetics of Parkinson disease: paradigm shifts and future prospects. *Nat Rev Genet* 7: 306-318.
91. Gandhi S, Wood-Kaczmar A, Yao Z, Plun-Favreau H, Deas E, et al. (2009) PINK1-associated Parkinson's disease is caused by neuronal vulnerability to calcium-induced cell death. *Mol Cell* 33: 627-638.
92. Gegg ME, Cooper JM, Chau KY, Rojo M, Schapira AH, et

- al. (2010) Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy. *Hum Mol Genet* 19: 4861-4870.
93. Grünewald A, Gegg ME, Taanman JW, King RH, Kock N, et al. (2009) Differential effects of PINK1 nonsense and missense mutations on mitochondrial function and morphology. *Exp Neurol* 219: 266-273.
94. Bonifati V, Rizzu P, Van Baren MJ, Schaap O, Breedveld GJ, et al. (2003) Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science* 299: 256-259.
95. Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, et al. (2011) Rotenone, paraquat, and Parkinson's disease. *Environ Health Perspect* 119: 866-872.
96. Corrigan FM, Wienburg CL, Shore RF, Daniel SE, Mann D (2000) Organochlorine insecticides in substantia nigra in Parkinson's disease. *J Toxicol Environ Health A* 59: 229-234.
97. Kunst CB (2004) Complex genetics of amyotrophic lateral sclerosis. *Am J Hum Genet* 75: 933-947.
98. Gros-Louis F, Gaspar C, Rouleau GA (2006) Genetics of familial and sporadic amyotrophic lateral sclerosis. *BBA-Molecular Basis of Disease* 1762: 956-972.
99. Majoor-Krakauer D, Willems PJ, Hofman A (2003) Genetic epidemiology of amyotrophic lateral sclerosis. *Clin Genet* 63: 83-101.
100. Kato S (2003) Amyotrophic lateral sclerosis, Neurodegeneration. *The Molecular Pathology of Dementia and Movement Disorders*.
101. Ellison D, Love S, Chimelli LM, Harding B, Lowe JS, et al. (2012) *Neuropathology: A Reference Text of CNS Pathology*. 3rd edn, Elsevier Health Sciences, The Netherlands.
102. Chang JL, Lomen-Hoerth C, Murphy J, Henry RG, Kramer JH, et al. (2005) A voxel-based morphometry study of patterns of brain atrophy in ALS and ALS/FTLD. *Neurology* 65: 75-80.
103. Abrahams S, Goldstein LH, Suckling J, Ng V, Simmons A, et al. (2005) Frontotemporal white matter changes in amyotrophic lateral sclerosis. *J Neurol* 252: 321-331.
104. Murphy JM, Henry RG, Langmore S, Kramer JH, Miller BL, et al. (2007) Continuum of frontal lobe impairment in amyotrophic lateral sclerosis. *Arch Neurol* 64: 530-534.
105. Roccatagliata L, Bonzano L, Mancardi G, Canepa C, Caponnetto C (2009) Detection of motor cortex thinning and corticospinal tract involvement by quantitative MRI in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis* 10: 47-52.
106. Zuccato C, Valenza M, Cattaneo E (2010) Molecular mechanisms and potential therapeutic targets in Huntington's disease. *Physiol Rev* 90: 905-981.
107. Quigley HA, Broman AT (2006) The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 90: 262-267.
108. Quigley HA (1993) Open-angle glaucoma. *N Engl J Med* 328: 1097-1106.
109. Sigal IA, Ethier CR (2009) Biomechanics of the optic nerve head. *Exp Eye Res* 88: 799-807.
110. Distelhorst JS, Hughes GM (2003) Open-angle glaucoma. *Am Fam Physician* 67: 1937-1944.
111. Wolfs RC, Grobbee DE, Hofman A, de Jong PT (1997) Risk of acute angle-closure glaucoma after diagnostic mydriasis in nonselected subjects: The Rotterdam Study. *Invest Ophthalmol Vis Sci* 38: 2683-2687.
112. Ringeisen AL, Harrison AR, Lee MS (2011) Ocular and orbital pain for the headache specialist. *Curr Neurol Neurosci Rep* 11: 156-163.
113. Zhao R, Hu W, Tsai J, Li W, Gan WB (2017) Microglia limit the expansion of β -amyloid plaques in a mouse model of Alzheimer's disease. *Mol Neurodegener* 12: 47.
114. Jin DQ, Lim CS, Hwang JK, Ha I, Han JS (2005) Anti-oxidant and anti-inflammatory activities of macelignan in murine hippocampal cell line and primary culture of rat microglial cells. *Biochem Biophys Res Commun* 331: 1264-1269.
115. Ma J, Hwang YK, Cho WH, Han SH, Hwang JK, et al. (2009) Macelignan attenuates activations of mitogen-activated protein kinases and nuclear factor kappa B induced by lipopolysaccharide in microglial cells. *Biol Pharm Bull* 32: 1085-1090.
116. De La Monte SM (2012) Metabolic derangements mediate cognitive impairment and Alzheimer's disease: role of peripheral insulin resistance diseases. *Panminerva Med* 54: 171-178.
117. Han KL, Choi JS, Lee JY, Song J, Joe MK, et al. (2008) Therapeutic potential of peroxisome proliferators-activated receptor- α/γ dual agonist with alleviation of endoplasmic reticulum stress for the treatment of diabetes. *Diabetes* 57: 737-745.
118. Zhang J, Guo S, Chan KW, Tong EP, Fu G, et al. (2016) New lignans with neuroprotective activity from *Adelostemma gracillimum*. *Phytochem Lett* 16: 1-7.
119. Xu Y, Li LZ, Cong Q, Wang W, Qi XL, et al. (2017) Bioactive lignans and flavones with *in vitro* antioxidant and neuroprotective properties from *Rubus idaeus* rhizome. *J Funct Foods* 32: 160-169.
120. Yang B, Han W, Han H, Liu Y, Guan W, et al. (2018) Lignans from *Schisandra chinensis* rattan stems suppresses primary A β 1-42-induced microglia activation via NF- κ B/MAPK signaling pathway. *Nat Prod Res* 23: 1-4.
121. Zhang M, Zheng HX, Gao YY, Zheng B, Liu JP, et al. (2017) The influence of Schisandrin B on a model of Alzheimer's disease using β -amyloid protein A β 1-42-mediated damage in SH-SY5Y neuronal cell line and underlying mechanisms. *Toxicol Environ Health A* 80: 1199-1205.

122. Wang M, Li Y, Ni C, Song G (2017) Honokiol attenuates oligomeric amyloid β 1-42-induced Alzheimer's disease in mice through attenuating mitochondrial apoptosis and inhibiting the nuclear factor Kappa-B signaling pathway. *Cell Physiol Biochem* 43: 69-81.
123. Goodman Y, Steiner MR, Steiner SM, Mattson MP (1994) Nordihydroguaiaretic acid protects hippocampal neurons against amyloid β -peptide toxicity, and attenuates free radical and calcium accumulation. *Brain Res* 654: 171-176.
124. Jang YP, Kim SR, Kim YC (2001) Neuroprotective dibenzylbutyrolactone lignans of *Torreya nucifera*. *Planta medica* 67: 470-472.
125. Jung YJ, Park JH, Cho JG, Seo KH, Lee DS, et al. (2015) Lignan and flavonoids from the stems of *Zea mays* and their anti-inflammatory and neuroprotective activities. *Arch Pharmacol Res* 38: 178-185.
126. Li XB, Yang ZX, Yang L, Chen XL, Zhang K, et al. (2012) Neuroprotective effects of flax lignan against NMDA-induced neurotoxicity in vitro. *CNS Neurosci Ther* 18: 927-933.
127. Dong K, Pu JX, Zhang HY, Du X, Li XN, et al. (2012) Dibenzocyclooctadiene lignans from *Kadsura polysperma* and their antineurodegenerative activities. *J Nat Prod* 75: 249-256.
128. Zhang LQ, Sa F, Chong CM, Wang Y, Zhou ZY, et al. (2015) Schisantherin A protects against 6-OHDA-induced dopaminergic neuron damage in zebrafish and cytotoxicity in SH-SY5Y cells through the ROS/NO and AKT/GSK3 β pathways. *J Ethnopharmacol* 170: 8-15.
129. Weng CC, Chen ZA, Chao KT, Ee TW, Lin KJ, et al. (2017) Quantitative analysis of the therapeutic effect of magnolol on MPTP-induced mouse model of Parkinson's disease using *in vivo* 18F-9-fluoropropyl-(+)-dihydrotrabenazine PET imaging. *PLOS ONE* 12: 0173503.
130. Baluchnejadmojarad T, Mansouri M, Ghalami J, Mokhtari Z, Roghani M (2017) Sesamin imparts neuroprotection against intrastriatal 6-hydroxydopamine toxicity by inhibition of astroglial activation, apoptosis, and oxidative stress. *Biomed Pharmacother* 88: 754-761.
131. Kiyofuji K, Kurauchi Y, Hisatsune A, Seki T, Mishima S, et al. (2015) A natural compound macelignan protects midbrain dopaminergic neurons from inflammatory degeneration via microglial arginase-1 expression. *Eur J Pharmacol* 760: 129-135.
132. Park HJ, Zhao TT, Lee KS, Lee SH, Shin KS, et al. (2015) Effects of (-)-sesamin on 6-hydroxydopamine-induced neurotoxicity in PC12 cells and dopaminergic neuronal cells of Parkinson's disease rat models. *Neurochem Int* 83-84: 19-27.
133. West M, Mhatre M, Ceballos A, Floyd RA, Grammas P, et al. (2004) The arachidonic acid 5-lipoxygenase inhibitor nordihydroguaiaretic acid inhibits tumor necrosis factor α activation of microglia and extends survival of G93A-SOD1 transgenic mice. *J Neurochem* 91: 133-143.
134. Boston-Howes W, Williams EO, Bogush A, Scolere M, Pasinelli P, et al. (2008) Nordihydroguaiaretic acid increases glutamate uptake *in vitro* and *in vivo*: therapeutic implications for amyotrophic lateral sclerosis. *Exp Neurol* 213: 229-237.
135. Gupta N, Yücel YH (2007) Glaucoma as a neurodegenerative disease. *Curr Opin Ophthalmol* 18: 110-114.
136. Li CP, Qiu GZ, Liu B, Chen JL, Fu HT (2016) Neuroprotective effect of lignans extracted from *Eucommia ulmoides* Oliv. on glaucoma-related neurodegeneration. *Neurol Sci* 37: 755-762.
137. Lee J, Kosaras B, Del Signore SJ, Cormier K, McKee A, et al. (2011) Modulation of lipid peroxidation and mitochondrial function improves neuropathology in Huntington's disease mice. *Acta Neuropathol* 121: 487-498.
138. Swarup V, Ghosh J, Mishra MK, Basu A (2008) Novel strategy for treatment of Japanese encephalitis using arctigenin, a plant lignan. *J Antimicrob Chemother* 61: 679-688.
139. Xiong J, Bui VB, Liu XH, Hong ZL, Yang GX, et al. (2014) Lignans from the stems of *Clematis armandii* ("Chuan-Mu-Tong") and their anti-neuroinflammatory activities. *J Ethnopharmacol* 153: 737-743.
140. Song H, Kim YC, Moon A (2003) Sauchinone, a lignan from *Saururus chinensis*, inhibits staurosporine-induced apoptosis in C6 rat glioma cells. *Biol Pharm Bull* 26: 1428-1430.
141. Cui HS, Kim MR, Sok DE (2005) Protection by petasignolide A, a major neuroprotective compound in the butanol extract of *Petasites japonicus* leaves, against oxidative damage in the brains of mice challenged with kainic acid. *J Agric Food Chem* 53: 8526-8532.
142. Cui HS, Sok DE, Min BS, Kim MR (2007) Protective action of 9-hydroxypinoresinol against oxidative damage in brain of mice challenged with kainic acid. *J Pharm Pharmacol* 59: 521-528.