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Review paper

Phenolic phytochemicals for treatment of Alzheimer's condition - a review

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Abstract

The progressive neurodegenerative disease, Alzheimer's disease, affects daily life due to severe memory loss and declining cognitive function. Alzheimer's disease has several hypotheses for its pathophysiology, and on the basis of those hypotheses, researchers are exploring a variety of pathologic targets to find a cure or symptomatic treatment. It has long been known that plants are effective in treating dementia, amnesia, and Alzheimer's disease. A lot of preclinical and clinical studies on plant-based drugs have shown promising results in treating the disease.

In this review, we will focus on plants rich in phenolic phytochemicals and the benefit of those phytochemicals in Alzheimer's disease treatment.

Key words: Alzheimer's disease, phenolic phytochemicals, neurodegenerative disease

Introduction

The most common neurodegenerative disorder, Alzheimer's disease, is the most prevalent cause of dementia in the elderly population, and the fifth most common cause of death in high-income countries. It is believed that Alzheimer's disease progresses primarily due to beta-amyloid protein aggregation, neurofibrillary tangles, neuroinflammation, and neurotoxicity (Dos Santos et al., 2018).

This pathology affects mainly the neocortex, which is associated with cognitive functions. Alzheimer's disease is also characterized by a deficit in cholinergic neurotransmission, especially affecting cholinergic neurons in the basal forebrain (Mukherjee et al., 2007).

In Alzheimer's disease, neurotoxicity is believed to be due to mitochondrial dysfunction and oxidative stress (Mathew et al., 2014; Tewari et al., 2018).

Metal ions such as Cu^{2+} and Zn^{2+} have been shown to be heavily concentrated in the neocortex of Alzheimer's patients. Aβ seems to have a high affinity for Cu^{2+} and Zn^{2+}, which might mediate its aggregation and toxicity, and this metal binding to Aβ, might cause the production of reactive oxygen species, which are involved in neurodegeneration (Natarajan et al., 2013).

Aβ could cause serious oxidative damage from the over-production of reactive oxidative species (ROS) and damage mitochondrial oxygen consumption directly reducing ATP production. Another pathological characteristic of Alzheimer's disease has been the reduction in mitochondrial mass and function.

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Research on new strategies for earlier diagnosis is among the most active areas in Alzheimer's science. Hope that future treatments could target the disease in its early stages, before irreversible brain damage or mental decline occurs. Therapy in the later stages of Alzheimer's disease is not very effective and this is most likely caused by massive neuronal death, which precedes the symptoms of dementia (Sheinerman and Umansky, 2012). Statistical studies have shown that, if scientists today can delay Alzheimer's disease onset by five years, the number of affected patients will be reduced by nearly half in less than a generation. Even better, if the onset of Alzheimer's disease can be delayed by a decade or so, more than 90 percent of current patients could die of old age rather than of this disease (Gaudreault and Mousseau, 2019).

Five drugs are available for the management of Alzheimer's disease which are approved by the US Food and Drug Administration (FDA) and they are used to relief only symptomatic treatments by stabilizing temporary cognitive symptoms such as loss of memory and disorientation (Awasthi et al., 2017). Cholinesterase inhibitors are three of the five drugs available and these are donepezil, galantamine, and rivastigmine. The fourth drug is memantine, which functions by regulating the activity of a different chemical messenger in the brain, which plays a part in memory and learning. Both groups of drugs can help the management of symptoms in Alzheimer's disease but work in different pathways. The fifth medication is a combination of one of the cholinesterase inhibitors (donepezil) with memantine, Namzaric, and was approved in 2014 and it is the only advancement since 2003 (Kong and Pohl, 2018). However, these drugs have emphasized side effects like nausea, vomiting, food aversion, headache, constipation, and dizziness, and the need for new and improved therapy with fewer side effects and better outcomes is enormous (Awasthi et al., 2017).

Diverse therapeutic approaches are studied for the prevention and modification of Alzheimer's disease progression like: anti-amyloid deposition strategy (up-regulation of α-secretase and down-regulation of β- and γ-secretase, targeting amyloid transport, targeting amyloid clearance, targeting Tau protein), acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitors, oxidative stress reduction, antioxidant pathways, metal chelation, anti-inflammation, receptor antagonists, mitochondrial dysfunction, genetic mutations, stem cell gene therapies, MAO-B inhibitors etc. (Awasthi et al., 2017; Kong and Pohl, 2018; Mi et al., 2019; Sanka et al., 2018).

In this review, we aim to show relevant *in vitro*, *in vivo* studies focused on the potential uses of different phenolic phytochemicals in the treatment of Alzheimer's disease because many natural molecules showed properties that are important in alleviating Alzheimer's disease (Benny and Thomas, 2018; Gaudreault and Mousseau, 2019).

Plants and their phytochemicals in Alzheimer's treatment

Herbal medicines have shown promising results in treating and preventing various diseases, including Alzheimer's. Many of nature's secondary metabolites are involved in adjusting metabolic pathways and are effective against a variety of diseases, including neurodegenerative disorders (Hussain et al., 2019). Based on their chemical structures and characteristics pharmacologically important phytochemicals can be classified into one of three categories: alkaloids, terpenoids and polyphenols as shown in Table 1 (Huang et al., 2016). In this review we will focus on polyphenols and their role in Alzheimer's disease treatment.

Phenolic phytochemicals

Phenolic phytochemicals are the largest category of phytochemicals and the most widely distributed (King and Young, 1999). Phytochemicals can be classified into the three main classes of polyphenols based on their chemical structure: (1) phenolic acids (hydroxybenzoic and hydoxycinnamic acids), (2) flavonoids (e.g., flavones, flavonols, flavan-3-ols, isoflavones, flavanones, and anthocyanidins or anthocyanins), and (3) other phenolics (e.g., stibenes, lignans, tannins, xanthones, lignins, chromones, and anthraquinones), as shown in Table 2 (Martinez et al., 2017).

Table 1. Phytochemical's classification

Phytochemicals		
Alkaloids	*Terpenoids*	*Phenolic phytochemicals*
Pyrrolidines	Monoterpens	Flavonoids
Pyrrolizidines	Diterpenes	Lignans
Isoquinolines	Sesquiterpenes	Stilbenes
Indoles	Sesterpenes	Phenolic acids
Quinolines	Triterpenes	Xanthones

Table 2. Main classes of phenolics

Simple phenols	*Polyphenols*	*Other phenolics*
1.Phenolic acids	***1.Flavonoids***	**Stilbenes**
Hydroxycinnamic acids	**Flavonols**	Resveratrol
Caffeic acid	Rutin	Piceatannol
Curcumin	Quercetin	**Lignans**
Ferulic acid	Kaempferol	lyoniside
Cholinergic acid Cinnamic acid	**Isoflavones**	Nudiposide
Coumaric acid	Genistein	
Hydroxybenzoic acids	**Flavones**	
Syringic acid	Luteolin	
Gallic acid	Apigenin	
Vanillic acid	**Flavan-3-ols**	
	Catechin	
Ellagic acid	Epicatechin	
Protocatechuic acid	Glycitein	
2.Coumarins	Equol	
bergapten	**Flavonones**	
imperatorin	Naringin	
pimpinellin	Hesperidin	
umbelliferone	**Anthocyanidins and anthocyanins**	
herinarin	Cyanidin	
	Malvidin	
	2.*Tannins*	
	Gallotannins	
	Ellagitannins	
	Procyanidins A, B	
	Tannic acid	

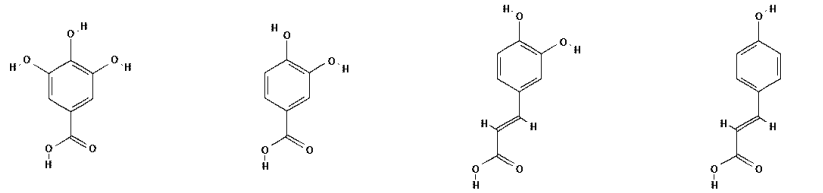
Several scientific studies have shown the beneficial activities of the polyphenols against Alzheimer's disease-like decreasing the cell damage caused by free radicals, neuroprotective effects (e.g. polyphenols resveratrol and tiron have shown neuroprotective effects through inactivation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) induced by superoxide anion radical, AChE inhibitory activity (example rosmarinic acid exhibited inhibitory activity towards AChE 85.8%) and β-amyloid aggregation (polyphenolic glycosides such as: naringenin, rutin, and apigenin) (Natarajan et al., 2013; Scotti and Scotti, 2017).

Polyphenols like quercetin, resveratrol, curcumin, and (-)-epigallocatechin gallate etc., have shown to exhibit multiple pharmacological effects like anti-inflammatory activity, cholinesterase inhibition, blocking of Aβ, and tau aggregation (Natarajan et al., 2013).

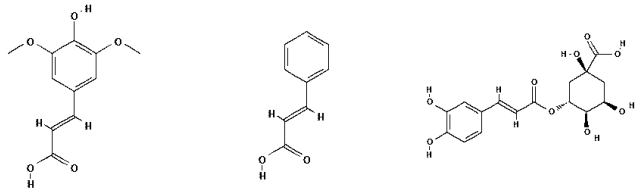
Phenolic acids

Phenolic acids chemically are characterized by a carboxyl group linked to the benzene ring and are derived from two main phenolic compounds, benzoic and cinnamic acids. Those compounds of this group are classified in to two groups hydroxycinnamic and hydroxybenzoic acids (Durazzo et al., 2019).

Hydroxybenzoic acids have a general structure of the C6–C1 type derived directly from benzoic acid.



Gallic acid Protocatechuic ac. Caffeic acid p-Coumaric acid



Sinapic acid Cinnamic acid Chlorogenic acid

Fig. 1. Phytochemicals isolated from *Caesalpinia crista*

The main hydroxybenzoic acids found in plants are vanillic, syringic p-hydroxybenzoic acid, protocatechuic acids, gallic acid, and ellagic acid. Hydroxybenzoic acids are part of structures like lignins and tannins. Gallic acid participates in the formation of gallotannins (Caballero et al., 2003).

In *Paeonia suffruticosa* were identified phenols like gallic acid and flavonoids quercetin, kaempferol, catechin, and *Caesalpinia crista* phenols like gallic acid, protocatechuic acid, catechin, chlorogenic acid, epicatechin, caffeic acid, vanillin, p-coumaric acid, sinapic acid, rutin hydrate, myricitin, cinnamic acid, quercetin, and kaempferol has shown to have aggregation inhibitory property in addition to the cholinergic activity (Fig. 1) (Keri et al., 2018; Li et al., 2018; Scotti and Scotti, 2017).

In addition to hydroxycinnamic acids, phenolic compounds with C6–C3 carbon skeletons, also known as phenylpropanoids, include curcuminoids, coumarins, and chromones (Durazzo et al., 2019).

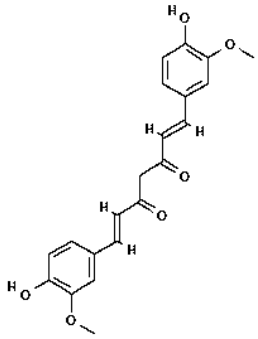


Fig. 2. Curcumin isolated from *Curcuma longa*

The most widely studied among the curcuminoids is curcumin. Curcumin which is the main constituent found in *Curcuma longa* has shown to be an effective metal chelator that readily chelates Cu^{2+} and curcumin-Cu^{2+} is more active than the parent compound in scavenging ROS by catalyzing the dismutation of superoxide anion radical or by donating the electron (Fig. 2) (Durazzo et al., 2019).

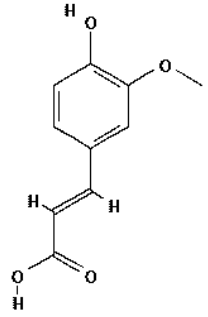
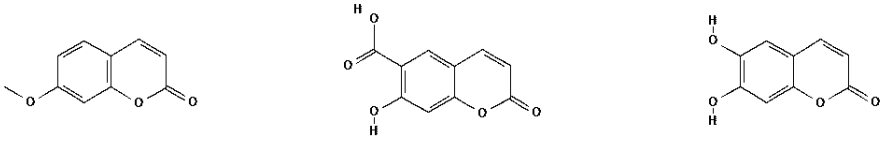
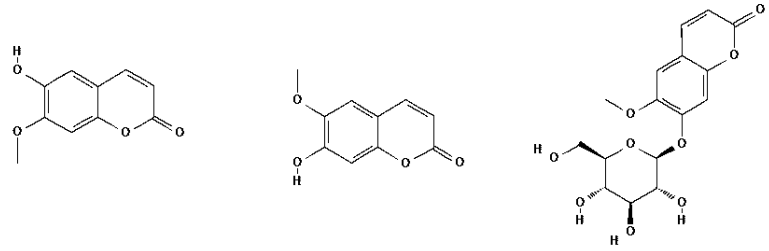


Fig. 3. Ferulic acid isolated from *Nepeta* spp.

Promising results for treating Alzheimer's disease have also been demonstrated by ferulic acid, which is an antioxidant and anti-inflammatory compound derived from plants such as *Nepeta* spp. (Fig. 3). Ferulic acid has been shown to improve cognitive function and ameliorate β-amyloid-induced reduction in ACh levels in the cortex, and the β-amyloid-induced inflammatory responses in the hippocampus in mice (Natarajan et al., 2013).



7 -methoxy coumarin Umbelliferone 6-carboxylic ac. Esculetin



Isoscopoletin Scopoletin Scopolin

Fig. 4. Phytochemicals isolated from *Angelica decursiva* and *Artemisia capillarie*

Coumarins

Coumarin and its derivatives are an important group of natural compounds. Coumarins are structurally constructed by benzene ring fused at the α-pyrone ring that serves as the structural nucleus. Coumarins can be chemically classified as: simple coumarins, complex coumarins, and various coumarins (Matos et al., 2015).

Coumarins bergapten, imperatorin, pimpinellin, and umbelliferone isolated from the roots of *Zosima absinthifolia* have been shown to possess remarkable antioxidant and anticholinesterase activities. Activity against AChE was especially expressed by umbelliferone, and against BChE more prominent was pimpinellin, whereas strong antioxidant effects were noticed from pimpinellin, and bergapten (Karakaya et al., 2019).

From *Angelica decursiva* and *Artemisia capillaries*, were isolated 2'-isopropyl psoralene, 7-methoxy coumarin (herinarin), umbelliferone 6-carboxylic acid, scopoletin, isoscopoletin, scoparone, scopolin, and esculetin and they were evaluated for their inhibitory activity against AChE, BChE, and BACE1 (beta secretase 1) enzyme activity (Fig. 4). As a result of the study umbelliferone 6-carboxylic acid and esculetin have shown the best potency to inhibit AChE, BChE, and BACE1. As shown in this study, esculetin is highly effective in inhibiting AChE and BChE due to its catechol group whereas the presence of carboxyl or catechol groups in esculetin and umbelliferone 6-carboxylic acid increases BACE1 inhibition. Whiles, the sugar moiety and methoxylation of the coumarins investigated reduces the activity against AChE and BChE (Ali et al., 2016).

From *Marantochloa purpurea* was obtained dihydropyranocoumarin derivative pteryxin and studies have shown to be effective in AChE and BChE inhibition (Fig. 5). Pteryxin was found to be more potent in the inhibition of BChE than galanthamine and can be a promising compound as BChE inhibition therapy in the treatment of Alzheimer's disease (Orhan et al., 2017).

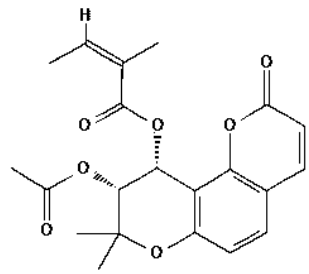


Fig. 5. Pteryxin isolated from *Marantochloa purpurea*

From *Toddalia asiatica* were isolated nine coumarins such as: phellopterin, isopimpinellin, artanin, fraxinol, toddalolactone, toddaculin, toddacoumaquinone, toddanone, and toddalenone. Those coumarins were tested for AChE activity, protection against neuronal cell damage induced by H_2O_2, and anti-Aβ aggregation. Seven out of

nine coumarins were shown to have a multifunctional effect in inhibiting the pathogenesis of Alzheimer's disease. The highest AChE inhibitory activity was shown by fraxinol due to the presence of hydroxyl group at position 6. The presence of di-hydroxyl or carbonyl groups at position 6 in the long alkyl chain, resulted in enhanced activity at toddalolactone and toddanone, comparable to toddaculin. Toddanone, phellopterin, and todalenone are the most active in the inhibition of self-induced Aβ aggregation and this is due to lipophilicity and also the presence of the furan ring might increase the binding activity. According to this study, substituents on positions 6, 7, and 8 of coumarin ring influenced anti-AChE function and anti-Aβ aggregation (Fig. 6). Phellopterin has shown to be the most potent compound in neuroprotective activity against H_2O_2 and Aβ1–42-induced neuronal cell death (Takomthong et al., 2020).

Flavonoids

Flavonoids are the largest group of plant phenols and great variability of structural basis make it possible to further sub-divided them into isoflavones, flavones, flavanones, flavanols, flavan-3-ols (found in tea), and anthocyanidins (found in fruits). Flavonoids are compounds of low molecular weight and they usually can be found bound to sugar molecules (Pollastro et al., 2018; Wightman, 2017). Flavonoids because of their potential AChE inhibitory activity allied to the well-known antioxidant activity and low toxicity, are currently considered an important source of anti-Alzheimer's disease compounds (Dos Santos et al., 2018). The flavonoid fraction in gingko extracts gives *Gingko biloba* its antioxidant and ROS scavenging properties (Jivad and Rabiei, 2014). EGb 761 is a standardized extract of *Gingko biloba* and other constituents and it contains approximately 24% flavone glycosides like quercetin, kaempferol, and isorhamnetin. EGb761 has shown efficacy against impaired memory, often present in patients with dementia, however, the drug was not beneficial in advanced cases of dementia (EGb 761: Ginkgo biloba extract, Ginkor, 2003).

Quercetin and ginkgetin, inhibit cyclooxygenase (COX) and lipoxygenase (LOX), thus leading to a decrease in prostaglandin levels and thereby decreased pro-inflammatory and procoagulant properties. These flavonoids are strong scavengers of ROS and possibly vasodilatory, thus contributing to the reduction of oxidative damage in the CNS (Howes and Houghton, 2012).

Quercetin, was shown to inhibit Aβ-induced cell apoptosis in cultured human neuroblastoma SH-SY5Y cells and also stimulated neuronal outgrowth and proliferation of synapses in hippocampal neurons (Howes and Houghton, 2012). *Ginkgo biloba* extract inhibited the formation of oligomers thus contributing to the modulation of APP processing, preventing fibrils, and Aβ aggregation (Scotti and Scotti, 2017)

In addition to being rich in terpenes, *Salvia* officinalis is also rich in flavonoids, making it a promising candidate for the treatment of Alzheimer's disease. The most frequent polyphenols isolated from *Salvia officinalis* are rosmarinic acid, apigenin, cirsimaritin, ellagic acid, genkwanin, hispidulin, luteolin, quercetin, and rutin. A study has reported significant improvements in secondary memory performance and attention accuracy after administration of standardized *Salvia officinalis* extract in older adults (Fig. 7) (Hasanein et al.,2017).

Flavonolignan extracted from *Silybum marianum*, silibinin also known as silybin, has shown to inhibit AChE and Aβ peptide aggregation at Alzheimer's disease treatment (Fig. 8) (Scotti and Scotti, 2017).

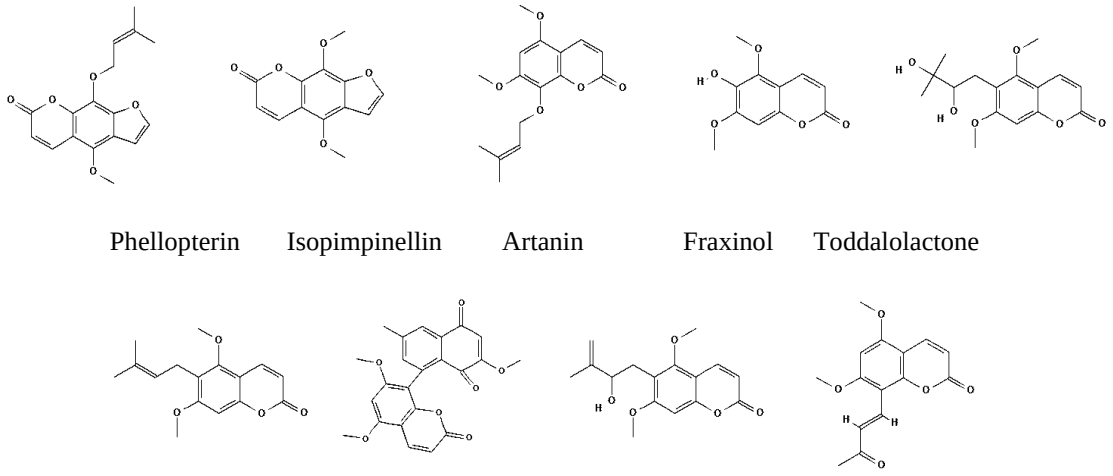
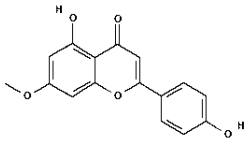
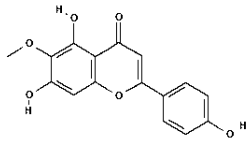


Fig. 6. Phytochemicals isolated from *Toddalia asiatica*





Genkwanin Hispidulin

Fig. 7. Phytochemicals isolated from *Salvia officinalis*

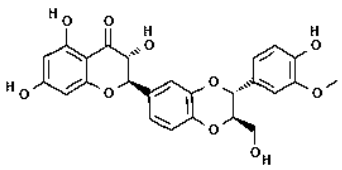


Fig. 8. Silibinin isolated from *Silybum marianum*

Camellia *sinensis* or green tea extracts rich in flavonoids such as quercetin, gossypetin, myricetin, quercitrin, isoquercitrin, and rutin are known for antioxidant properties and are currently used for Alzheimer's disease therapy (Fig. 9) (Natarajan et al., 2013). *Camellia sinensis* is also rich in gallocatechin gallate and theaflavin and has shown that could completely inhibit Aβ aggregation (Phan et al., 2019).

From *Zizyphus jujube* has been extracted different types of flavonoids like rutin, quercetin, kaempferol. Medicinal properties of jujube are mainly due to the antioxidant properties of these compounds (Jivad and Rabiei, 2014; Kumar et al., 2017; Singhal et al., 2012).

Icariin, a flavonoid isolated from *Epimedium* spp. has been shown to possess antioxidant effect dose-dependently resulting in protective effect on neurons damaged by ischemia. Also, some recent studies using rats and 5xFAD mice showed that when icariin was given subcutaneously in rats and 5xFAD mouse, resulted in less neuron damage compared to untreated groups and is suggested that the underlying mechanism is inhibition of tau protein hyperphosphorylation (Fig. 10).

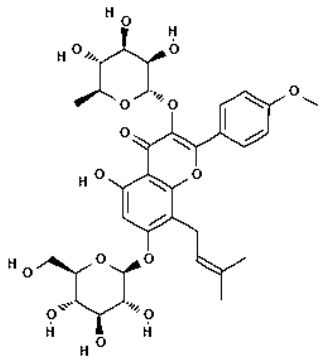
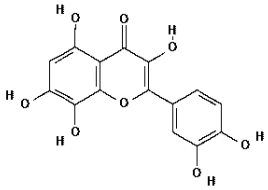
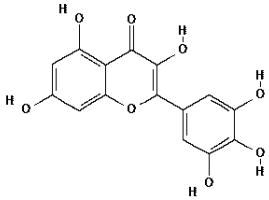
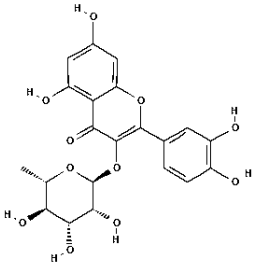
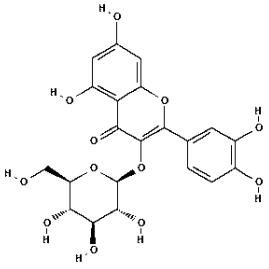


Fig. 10. Icariin isolated from *Epimedium* spp.









Gossypetin Myricetin Quercitrin Isoquercitrin

Fig. 9. Phytochemicals isolated from *Camellia sinensis*

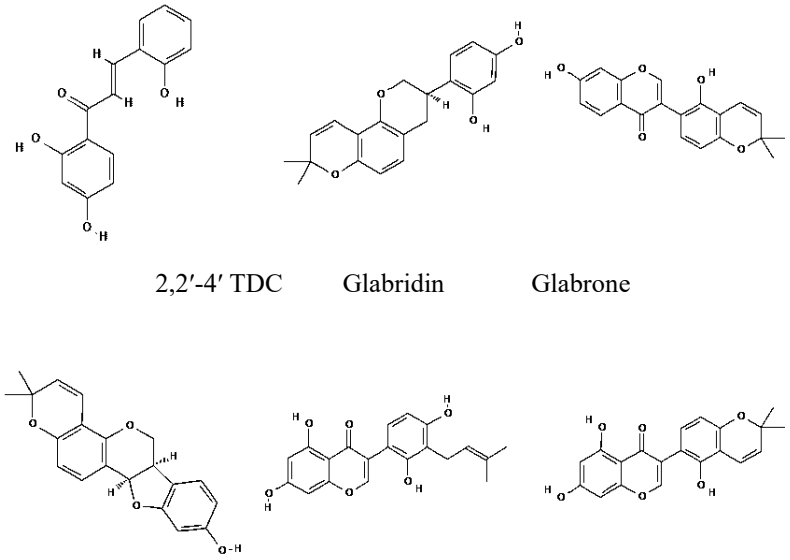


Fig. 11. Phytochemicals isolated from *Glycyrrhiza* spp

AChE inhibitory effects, associated with the alleviation of memory impairment in Alzheimer's, have been noted from the ethanolic extract of *Epimedium koreanum*, but no studies have yet been conducted to determine the nature of the compounds responsible (Howes and Houghton, 2012).

Isoflavonoid and flavonoid constituents in *Glycyrrhiza* genus include 2,2′-4′ trihydroxychalcone (TDC), glabridin, shinpterocarpin, glabrone, licoisoflavones A and B, galbrene, and due to their antioxidative, anti-inflammatory properties, several species of *Glycyrrhiza* were investigated for possible therapeutic effects against neurodegenerative disorders. For example, flavonoid of *Glycyrrhiza glabra*, TDC exhibited antioxidant, anti-inflammatory effect, and on the other hand extract from *Glycyrrhiza inflata* prevents tau misfolding *in vitro*. Thus, the extract of this genus may be effective against Alzheimer's disease (Fig. 11) (Tewari et al., 2018; Natarajan et al., 2013).

Luteolin flavonoid found in *Lavandula officinalis*, increased effects on the central nervous system area by causing calming and soothing effects through GABA receptor (Jivad and Rabiei, 2014).

In *Cannabis sativa* have been identified more than 20 flavonoids that belong mainly to two classes, flavones, and flavonols, also three prenylated aglycone flavanones named cannflavin A, B, and C. Studies have shown that cannflavin A has a neuroprotective role against Aβ-mediated neurotoxicity, associated with an inhibition of Aβ fibrillization (Fig. 12) (Pollastro et al., 2018; Eggers et al., 2019).

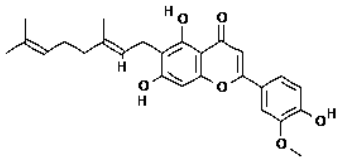


Fig. 12. Cannflavin A isolated from *Cannabis sativa*

Neocorylin, isoflavone isolated from the extract of *Psoralea corylifolia* seeds exhibited an inhibitory effect on baculovirus expressed BACE1 under *in vitro* conditions, and also prenylated flavones isolated from methanol extracts of *Morus lhou* showed significant BACE1 inhibitory activity (Natarajan et al., 2013).

Tiliroside, 3-methoxy quercetin, quercitrin, and quercetin isolated from *Agrimonia pilosa* has been shown to express AChE inhibitory activity (Fig. 13) (Natarajan et al., 2013).

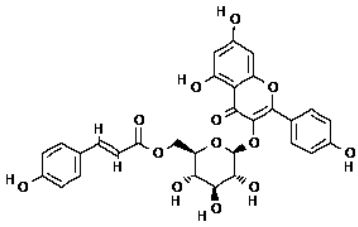


Fig. 13. Tiliroside isolated from *Agrimonia Pilosa*

Tannins

Tannins are water-soluble polyphenols, with many health-related beneficial effects and they are classified in two major groups: pseudo tannins and true tannins.

Pseudo tannin, gallic acid, has been shown to ameliorate elevated cholinesterase and BACE-1 activities, as well as oxidative stress induced by β-amyloid generation in Alzheimer's disease model of *Drosophila melanogaster*. In another study, gallic acid obtained from *Vitis vinifera* seed has shown a very good effect in inhibition of fibril formation by the amyloid-β peptide (Ogunsuyiet al., 2019; Liu et al., 2013).

Condensed tannins, proanthocyanidin, like catechin, epicatechin, and epicatechin gallate obtain from *Vitis vinifera* seeds has shown to be strong antioxidants there for significant enhancement in cognition and spatial memory ability has been shown during studies as a result of improvement in the pathology of APP and tau protein (Lian et al., 2016).

Gallotannins isolated from *Cornus officinalis* fruits have a protective role against Alzheimer's disease's progression and this is due to inhibition of Aβ peptides accumulation whereas gallotannin 1,2,3,6-tetra-O-galloyl-b-D-glucose has shown inhibition of BACE-1 (Hussain et al., 2019).

Ellagitannins, tellimagrandin II, isolated from *Geum japonicum* and *Syzygium aromaticum* exhibited inhibitory activity against cholinesterase (Hussain et al., 2019; Bhakta et al., 2017).

Tannic acid found in *Quercus infectoria*, *Rhus coriaria,* and *Rhus glabra* showed excellent inhibitory effects against AChE, BChE, α glycosidase, and α-amylase (Türkan et al., 2019).

Other phenolics

Convolvulus pluricaulis constituents like flavonol glycosides, anthocyanins, and triterpenoids have been effective for memory enhancing and nootropic attribution (Akram and Nawaz, 2017).

A study has shown that aqueous extract, ethyl acetate and also ethanolic extract of *Convolvulus pluricaulis* increased memory functions and learning abilities including increasing in acetylcholinesterase activity (Roy, 2018).

Lignans are low molecular weight polyphenols and may be promising compounds for treating Alzheimer's disease but further investigations have to be done.

A number of lignans present in *Cannabis sativa*, including lignanamides, cannabisin-M, cannabisin-N, and cannabisin-O have been investigated for their potential use in the treatment of Alzheimer's disease.

This study has shown that cannabisin-M exhibited a powerful radical-scavenging activity, while cannabisin-N exhibited weak acetylcholinesterase inhibitory activity.

So, this can be a promising candidate for multipurpose target drug (with both antioxidant and AChE inhibitory activities) in the treatment of Alzheimer's disease (Pollastro et al., 2018).

Seven lignans were isolated from the seeds of *Crataegus pinnatifida* arylnaphthalene-type lignan, (7′*S*, 8′*R*, 8*R*)-isolariciresinol, (7′*R*, 8′*S*, 8*S*)-isolariciresinol, (7′*S*, 8′*R*, 8*R*)-lyoniresinol, (7′*S*, 8′*R*, 8*R*)-isolariciresinol-9′-β-D-glucopyranoside, lyoniside, nudiposide and it is reported that these lignans may inhibit the accumulation of Aβ and reduced brain Aβ accumulation *in vivo* and glycosides chain may be related to the inhibition activity (Fig. 14). It is suggested that the absolute configurations which were (7′*S*, 8′*R*, 8*R*) of compounds may be important for inhibitory activity, and from those seven lignans (7′*S*, 8′*R*, 8*R*)-isolariciresinol-9′-β-D-glucopyranoside and lyoniside exhibited the strongest inhibition activity (Huang et al., 2017).

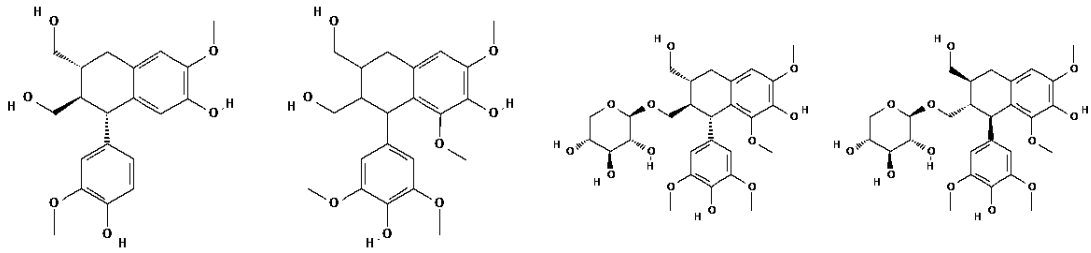
Two dibenzylbutyrolactone lignans, patrinians A and B, found in e 70% EtOH extract of *Patrinina villosa* showed significant antioxidant activity and also marked inhibitory effects on Alzheimer's disease (Bai et al., 2017).

Stilbenes are natural phenolic compounds and have been shown to have multiple pharmacological effects.

Stilbene has the common structure of a central ethene double bond with each carbon atom of the double bond substituted with phenyl rings, and compounds within the group differ from each other by phenyl ring R groups (Wang, 2017).

Resveratrol, found in plants like *Polygonum cuspidatum* and *Vitis vinifera*, is the most common natural stilbene, widely studied, and has shown to have multiply pharmacological effects in different diseases including neurodegenerative disease.

Studies have shown that administration of resveratrol decreased plaque deposits, especially in the medial cortex, striatum, and hypothalamus. Resveratrol has also exhibited neuroprotective effect by decreasing the amyloid burden and reducing tau hyperphosphorylation and amyloid-β-induced cell death, and also decreased oxidative stress resulting in protection against spatial memory impairment (Rioux et al., 2020; Wightman, 2017).



Isolariciresinol Lyoniresinol Lyoniside Nudiposide

Fig. 14. Phytochemicals isolated from *Crataegus pinnatifida*

Resveratrol and its glucoside derivative piceid that can be found in barks of *Picea sitchensis*, could also suppress Aβ aggregation (Phan et al., 2019).

Polygonum multiflorum, with the main active phytochemicals, tetrahydroxy stilbene glucoside, can help to improve learning and memory abilities at mice with Alzheimer's disease and has been shown to reduce the expression level of the amyloid precursor protein (Shi et al., 2016).

Free radical scavenging and antioxidant activity of *Hypericum perforatum* extract are mainly due to the presence of flavonoids such as quercetin and quercitrin and also from phytochemicals like anthraquinone derivative hypericin and hyperforin. In a study testing for learning and memory impairment, associated with changes in the brain caused by oxidative stress, resulting in improvement of passive avoidance memory in mice using shuttle boxes when *Hypericum* and its active ingredient, hyperforin, was frequently administered to rats by acute injection of scopolamine. (Natarajan et al., 2013).

Conclusion

There are many scientific studies demonstrating the beneficial effects of plants and the low level of side effects. The action of phenolic phytochemicals on several disease targets could lead to better results in the treatment of Alzheimer's. Phenolic acids and flavonoids are more widely studied and many phytochemicals has shown promising results whereas, stilbenes, tannins, and lignans have been studied sparingly, but based on the powerful radical-scavenging properties those plants have demonstrated, they should also be considered promising candidates for Alzheimer's disease.

Polyphenols have generally shown good antioxidant and anti-inflammatory properties, while fewer studies have examined AChE and BChE inhibition properties.

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Резиме

Фенолни фитосоединенија за третман на Алцхајмерова болест - преглед

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Клучни зборови: Алцхајмерова болест, фенолни фитохемикалии, невродегенеративно заболување, растенија, медицина

Прогресивната невродегенеративна болест, Алцхајмерова болест, влијае на секојдневниот живот поради сериозното губење на меморијата и намалената когнитивна функција.

Постојат неколку хипотези за настанувањето на Алцхајмеровата болест врз основа на кои, истражувачите континуирано работат на различни патолошки цели во насока на пронаоѓање на ефикасен лек или пак симптоматски третман.

Одамна е познато дека растенијата се ефикасни во лекувањето на деменција, амнезија и Алцхајмерова болест. Притоа, многу од претклиничките и клиничките студии за хербални лекови покажаа ветувачки резултати во лекувањето на оваа болест.

Во овој преглед, ќе се фокусираме на растенијата богати со фенолни фитосоединенија и придобивките од тие фитохемикалии во третманот на Алцхајмеровата болест.