OPEN ACCESS

Phytopharmacological Communications

DOI: doi.org/10.55627/ppc.002.001.0042

Review Article

Natural Inhibition of β-secretase in Alzheimer's Disease by Medicinal Plants

Aisha Altaf[1], Muhammad Akhlaq[2], Jalal Uddin[3], Ajmal Khan[4], Ahmed Al-Harrasi[4], Farman Ullah[5], Fawad Ali[5]

[1]Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan
[2]Faculty of Pharmacy, Gomal University, Dera Ismail Khan, Pakistan
[3]Department of Pharmaceutical Chemistry, College of Pharmacy, King Khalid University, Abha 62529, Kingdom of Saudi Arabia
[4]Natural and Medical Sciences Research Center, University of Nizwa, P.O Box 33, Postal Code 616, Birkat Al Mauz, Nizwa, Oman
[5]Department of Pharmacy, Kohat University of Science & Technology, Kohat, Pakistan
*Correspondence: ajmalkham@unizwa.edu.om

Abstract

Alzheimer's disease (AD) is the most common type of dementia, an irreversible neurodegenerative disease that worsens over time. It frequently affects the elderly population, and its prevalence is soaring in countries with a high proportion of the aging population. The incidence of AD is likely to increase further with increasing life expectancy throughout the world. Despite the significant expansion in our understanding of the disease at molecular, cellular, and system levels in the last 50 years, there is still no sight of therapies that could stop or slow the progression of AD. The only medications approved by the Food and Drug Administration (FDA) for the treatment of AD are acetylcholinesterase inhibitors (donepezil, galantamine, tacrine, and rivastigmine) and glutamate receptor antagonist (memantine) in addition to a monoclonal antibody. Apart from acetylcholinesterase inhibition, another important therapeutic target for treating AD is the Inhibition of β-site APP cleaving enzyme-1 (BACE1), which is involved in the proteolysis of the amyloid precursor protein (APP), leading to the formation of neurotoxic amyloid β (Aβ) protein. Extensive research following this approach has led to the rationally designed synthetic and potent BACE1 inhibitors, several of which are in clinical trials. However, the high failure rate of the BACE1 inhibitors in clinical trials necessitates finding a different source of BACE1 inhibitors. This review discusses the most promising phytocompounds and plant extracts showing potent BACE1 inhibitory activity. Future research directions are suggested, and recommendations are made to expand the use of medicinal plants and their formulations to prevent, mitigate, and treat AD.

Keywords: Amyloid β-peptide, tau protein, BACE1 inhibitors, Alzheimer's disease, Natural products, phytocompounds

Introduction

Alzheimer's disease (AD) is an advanced-level neurodegenerative disorder starting with mild cognitive impairment (MCI), which progressively leads to further cognitive decline, especially in the elderly population. In more advanced stages of the disease, significant neuronal atrophy is apparent in AD patients **(figure 1)**. Typically, the disease starts with a slight impairment in cognitive abilities, including short-term memory loss. With the advancement of the disease, other cognitive capabilities, for instance, the ability to calculate and use common objects and tools, are diminished (Yassin, El-Shenawy et al. 2013). Furthermore, this disease is characterized by irreversible brain damage with symptoms of confusion, impaired memory, loss of orientation, slurred speech, inability to correlate, and loss of judgment (Frydman-Marom, Levin et al. 2011). It is the major contributing factor to dementia all over the world and is ranked as the fourth biggest cause of death. Neurological diseases such as brain trauma, vascular brain disorder, and stroke are the major

factors associated with AD and may account for the morbidity and mortality accompanied by the disease (Maccioni, Rojo et al. 2009). AD is one of the biggest unresolved medical problems causing a significant financial and physical impact on patients, especially on the family and caregivers (Roberds, Anderson et al. 2001).

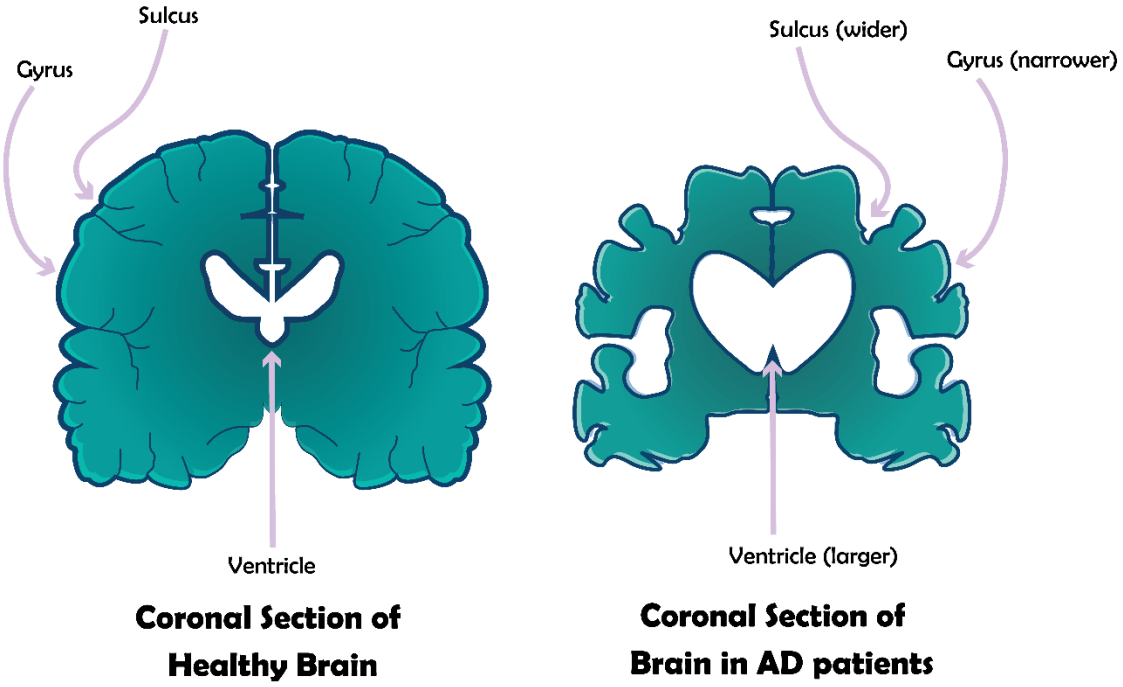


Figure 1: Difference between the brains of a healthy person and an Alzheimer's disease patient.

Epidemiology

AD is overwhelmingly the most important type of dementia. It typically affects about 12% of the elderly population (over the age of 65), with a rising incidence of 46% above the age of 80. Almost 36 million cases of AD were reported worldwide in 2010, which are expected to approximately double every 20 years, reaching 66 million in 2030, and 115 million in 2050 (Parthsarathy, McClean et al. 2013). The worldwide cost of dementia care is about 818 B $ annually (Wimo et al. 2017). In the United States, the population affected by AD is around 5 million, and around 100,000 of those die per year, which translates to an annual economic burden of over $100 billion (Maccioni, Rojo et al. 2009). Around 58-66% of the world's dementia population exists in developing countries. Hence, eradicating or even slowing this disease's progression would greatly benefit both socially and economically (Cole and Vassar 2007).

Pathophysiology

AD, a highly complex pathogenesis disorder, is a disorder of altered protein folding and aggregation (Smith and Perry 1998). Although several pathologies characterize this disease, amyloid plaques and neurofibrillary tangles are found to be the two major culprits (Smith and Perry 1998, Cole and Vassar 2007). Amyloid plaques (senile plaques or neuritic plaques) are spherical lesions formed from beta-amyloid protein (Aβ) aggregates. The disease cascade starts with the proteolytic cleavage of β-amyloid precursor protein (APP) via a pair of enzyme

proteases, β-secretase (BACE-1) and γ-secretase, which leads to the generation of Aβ, predominantly Aβ40, and Aβ42. Although both species have been found in senile plaques, Aβ42 seems to favor aggregation more as compared to Aβ40. An increase in levels of both Aβ40 and Aβ42 has been associated with the severity of dementia and Aβ levels in AD brains. These plaques are quite stable and are found to be neurotoxic, instigating neuronal death (Ghosh and Osswald 2014). Neurofibrillary tangles, another hallmark of AD, are generally composed of hyper-phosphorylated tau proteins **(figure 2)**. They are present in the perinuclear cytoplasm as an insoluble bundle of fibers. The appearance of neurofibrillary tangles in the AD brain is probably a neuronal response to the formation of Aβ plaques (Yassin, El-Shenawy et al. 2013, Ghosh and Osswald 2014). Therefore, considerable effort has been directed toward these disease-modifying targets and finding better, safer, and more potent acetylcholinesterase inhibitors. Apart from these bonafide targets, glutamate receptor antagonists, lipid-lowering drugs, antihypertensive drugs, stem cell therapy, transition metal chelators, selective phosphodiesterase inhibitors, and insulin resistance drugs are also being investigated in various preclinical phases with variable degrees of success.

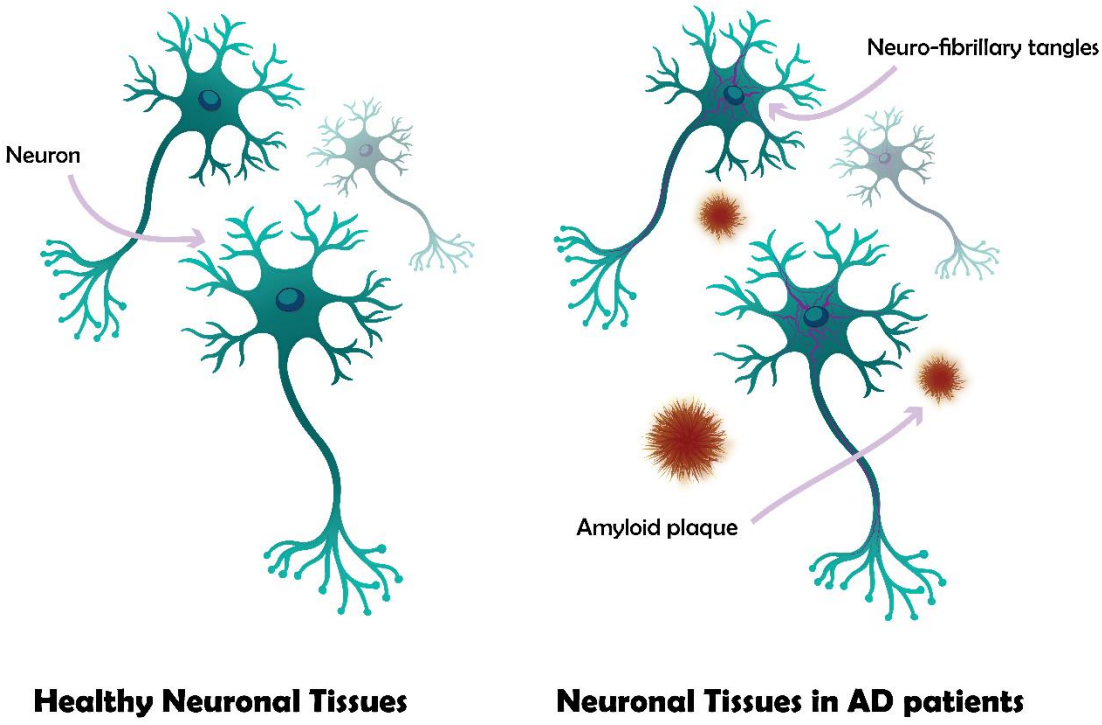
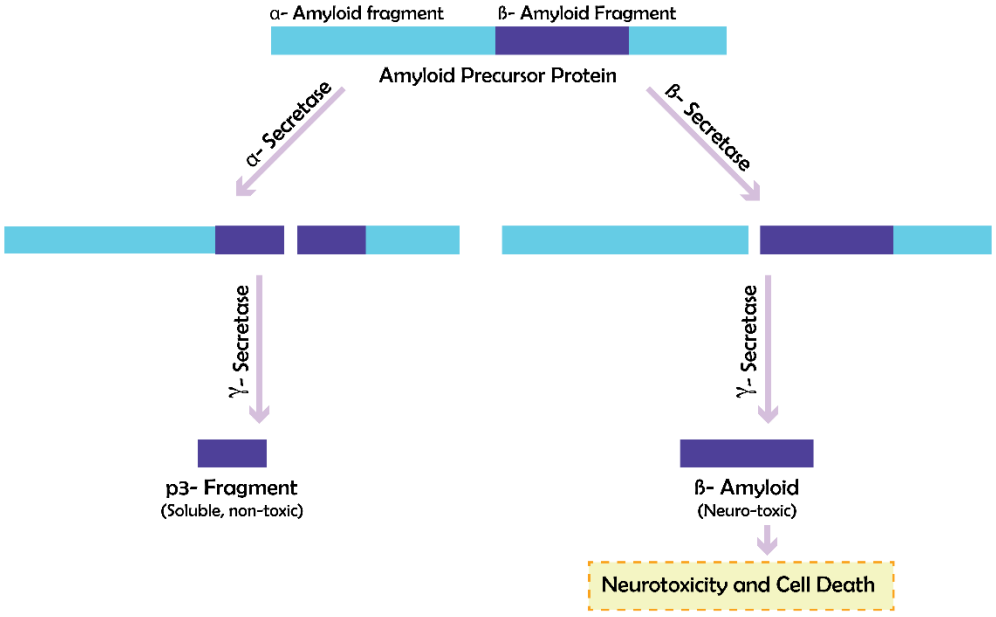


Figure 2: Neuronal tissues in healthy and Alzheimer's disease patients.

Inhibition of β-secretase

One validated target for potential AD treatment is the enzyme system responsible for forming Aβ. Three different enzymes act upon the APP- α-secretase, β-secretase (BACE1), and γ-secretase to produce Aβ **(figure 3)**. These enzymes play crucial roles in a systematic and ordered cleavage of APP and could, therefore, serve as an important drug target for the treatment of AD. Since the formation of 'senile plaques' by the aggregation of amyloid ß

peptide in the brains of AD patients is the result of sequential proteolysis of APP by BACE1 and γ-secretase, BACE1 is considered an excellent therapeutic target against AD and can be targeted by small molecule inhibitors for blocking the formation of amyloid ß peptide. Several promising phytocompounds with highly potent activity against BACE1, discussed in this review, have the potential to proceed to clinical trials. Here in this section, we review those BACE1 inhibitors from natural sources.

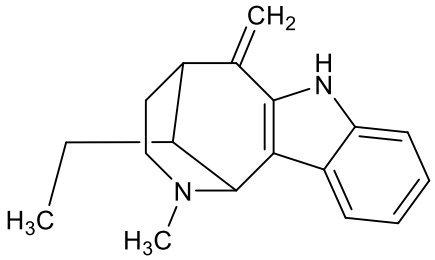


Pathophysiology of Alzheimer's Disease

Figure 3: Pathophysiology of Alzheimer's disease.

Apocynaceae

In an investigational study, Uleine (**1**) was isolated from *Himatanthus lancifolius* stem barks and was investigated for BACE1 Inhibition. Inhibitory activity against BACE1 was reported with an IC_{50} value of 180±22 nM. Self-aggregation of Aβ peptide was inhibited significantly. Uleine also exhibited Inhibition of AChE and BChE. Additionally, it was not found to be toxic for PC12 cells. Multiple target inhibition by uleine has the significant potential to be an effective therapy for AD (Seidl, Aimbire de Moraes Santos et al. 2017).

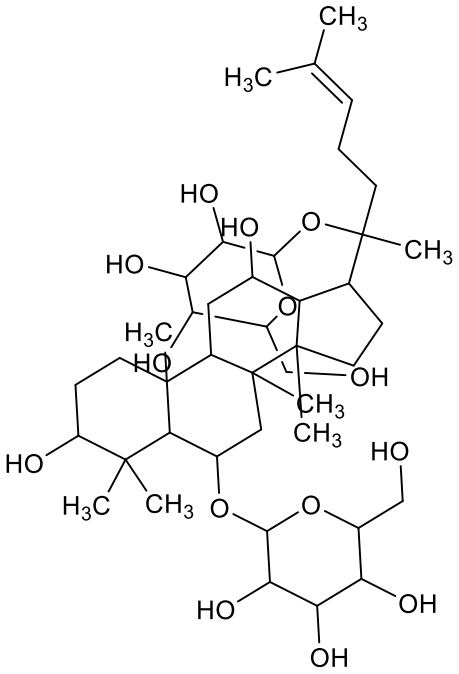


(1)

Araliaceae

Ginsenoside Rg1 (**2**) is a major active component isolated from *Panax notoginseng* (Araliaceae family commonly known as Asian ginseng) and subjected to various experiments to determine its BACE1 inhibitory potential. Results showed that

Ginsenoside Rg1 protected PC12 cells against Aβ-induced cytotoxicity and inhibited BACE1 in vitro, indicating its potential as an anti-AD agent (Wang and Du 2009).



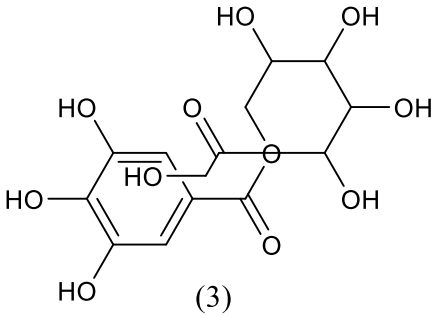
(2)

Betulaceae

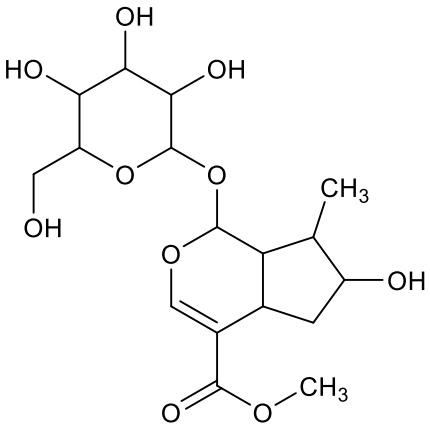
The Bark of *Betula platyphylla* was investigated for effects on memory impairment and amyloid β peptide-induced neurotoxicity. Inhibition of BACE1 activity was observed along with reduced amyloid β peptide levels in the brain. Brain-derived neurotrophic factor and cyclic adenosine monophosphate (cAMP) responsive element-binding protein expression was upregulated in the hippocampus of amyloid β peptide-injected mice after treatment with the extract (Cho, Lee et al. 2014). These activities suggest the potential of this plant to modify AD.

Cornaceae

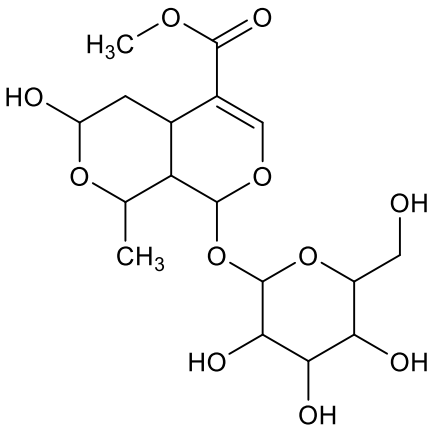
In an attempt to find BACE1 inhibitors from natural sources, several phytocompounds, including 7-O-galloyl-D-sedoheptulose **(3)**, loganin (**4**), and morroniside (**5**) were isolated from *Corni Fructus*. These were evaluated for BACE1 Inhibition and the Inhibition of AChE and BChE. Morroniside and 7-O-galloyl-D-sedoheptulos were found mixed inhibitors of BACE1 while Loganin showed inhibitory effects of the non-competitive type. Significant Inhibition of AChE and BChE was also reported which suggests the triple inhibitory effect of these compounds (Bhakta, Park et al. 2016).



(3)



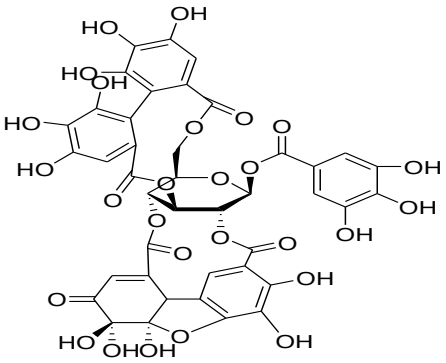
(4)



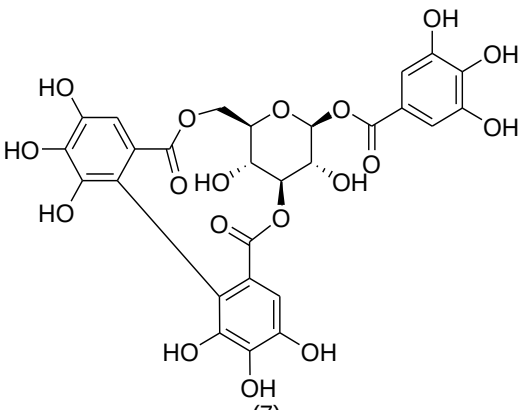
(5)

Geraniaceae

In a recent study, BACE1 inhibition was shown by the ethanolic soluble fraction of *Geranium thunbergii*. Two phytocompounds- geraniin (**6**) and corilagin **(7)** were isolated from this fraction and were further evaluated. IC_{50} values of 4.0 μM and 34 μM against BACE1 were shown by geraniin and corilagin, respectively. These compounds showed noncompetitive BACE1 Inhibition, as demonstrated by Dixon plot (Youn and Jun 2013).



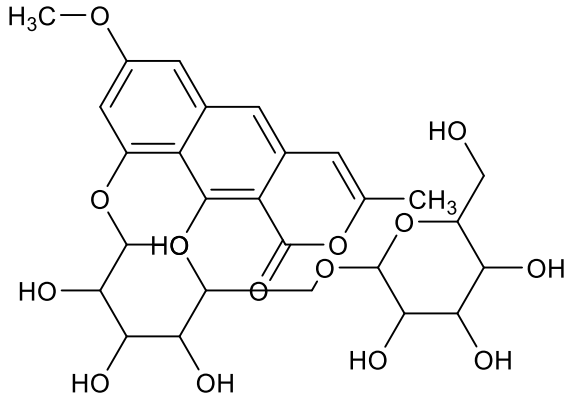
(6)



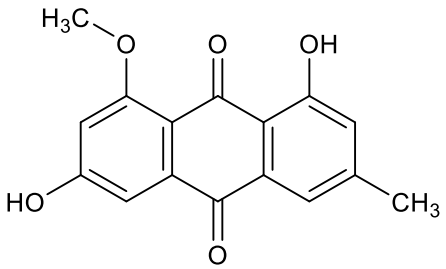
(7)

Leguminosae

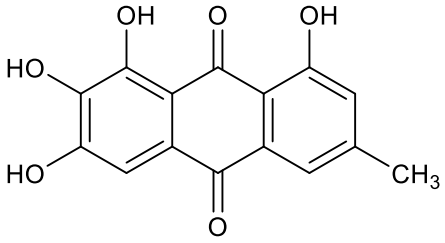
Seeds extract of *Cassiae obtusifolia* is previously reported to have memory-enhancing effects. In another study, compounds responsible for this activity were isolated and evaluated against different targets related to AD. All of the isolated compounds showed potent Inhibition of AChE and BACE1. Toralactone gentiobioside **(8)**, questin (**9**), and alaternin (**10**) showed significant Inhibition of BChE. Molecular docking stimulation experiments showed that the hydroxyl group of emodin and alaternin interacted tightly with BACE1 active site residue (Jung, Ali et al. 2016). In a separate study, prenylated flavonols isolated from *Sophora flavescens* were also found to inhibit BACE1. Activity-guided isolation from dichloromethane fraction resulted in the isolation of sophoflavescenol (**11**) as the most potent inhibitor. A Structural activity relationship study revealed that C-5 hydroxyl group of prenylated flavonoids is essential for BACE1 Inhibition (Jung, Jin et al. 2011). In another study, lavandulyl flavanones isolated from *Sophora flavescens* exhibited potent inhibitory effects on BACE1 (Hwang, Ryu et al. 2008).



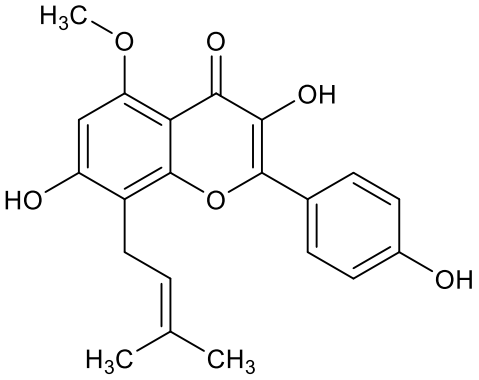
(8)



(9)



(10)



(11)

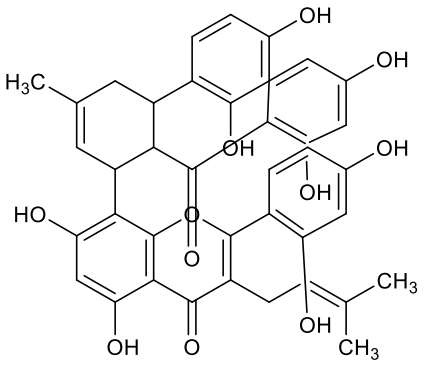
Magnoliaceae

Neuroprotective, anti-inflammatory, and anti-oxidative activities of *Magnolia officinalis* herb are well known. In an investigation, ethanol extract of M. officinalis was evaluated to determine its effect on memory dysfunction. The herb decreased the expression of BACE1 and also reduced the conversion of APP to amyloid β peptide by inhibiting BACE1 activity. These results suggest that ethanolic extract from *M. officinalis* can help prevent memory impairment by downregulating BACE1 expression and activity (Lee, Choi et al. 2012).

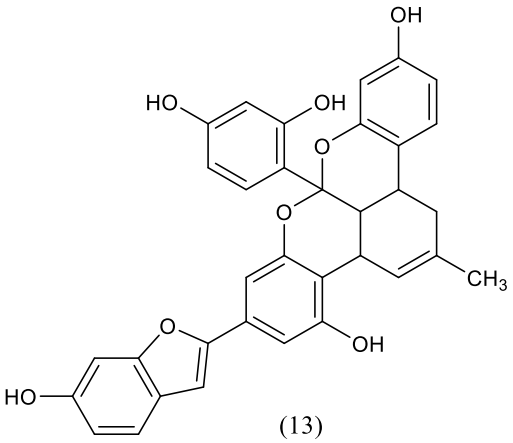
Moraceae

In an investigation to explore BACE1 inhibitors from natural sources, roots, bark, branches, fruits, and leaves of *Morus alba* L. were evaluated for their potential to inhibit BACE1 from converting APP into amyloid ß peptide. Root bark exhibited the highest Inhibition and was further processed for the isolation of compounds and their activity. Three compounds were isolated, kuwanon G (**12**), mulberrofuran G (**13**), and albanol B (**14**). All of these exhibited significant BACE1 inhibitory activity (Kuk, Jo et al. 2017).

In another study, screening of lead compounds of *Morus alba* was done along with molecular docking and molecular dynamic simulations to investigate the binding domains of its constituents. A compound named Morusin, a major phenolic antioxidant of the root bark was identified as a potential lead compound for BACE 1 based on computational analysis, which can serve as a pharmacophore skeleton for future drug design (Borah, Sharma et al. 2019).



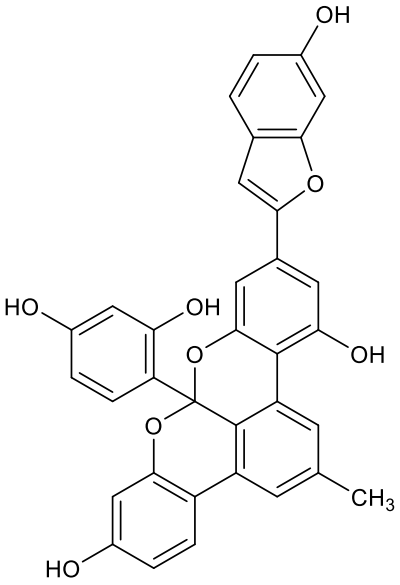
(12)



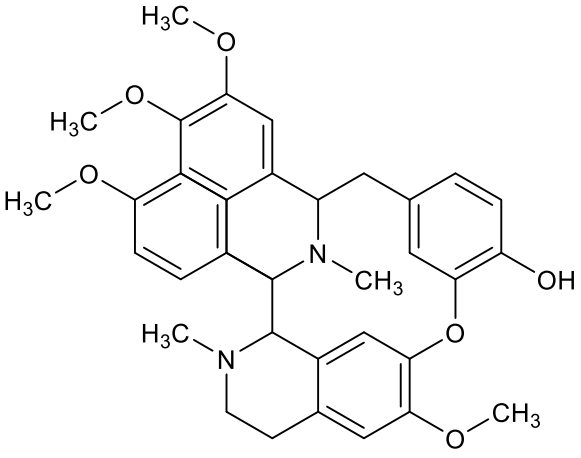
(13)

Nelumbonaceae

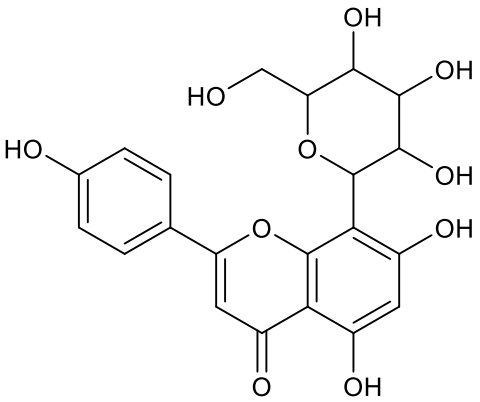
In a recent study, different parts of the *Nelumbo nucifera* were screened for inhibitory effects against BACE1. Extracts made from rhizomes, stamens, leaves, de-embryo seeds, and embryos showed significant inhibitory activity against BACE1. Detailed investigation of embryo extract revealed n-butanol, dichlomethane, and ethyl acetate fractions to have promising inhibitory activity against BACE1. Five compounds were isolated from these extracts by repeated column chromatography which was northalifoline, neferine (**15**), vitexin (**16**), liensinine (**17**), and quercetin 3-O-glucoside (**18**). Liensinine showed the most potent Inhibition of BACE1 with IC_{50} of 6.37 ± 0.13 μM. Neferine and vitexin also displayed significant inhibitory activity against BACE1 (Jung, Karki et al. 2015).



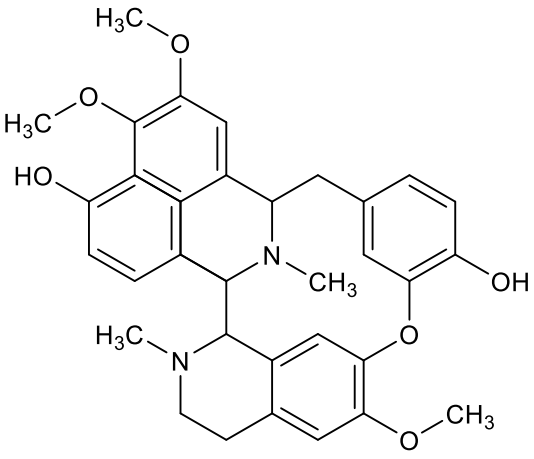
(14)



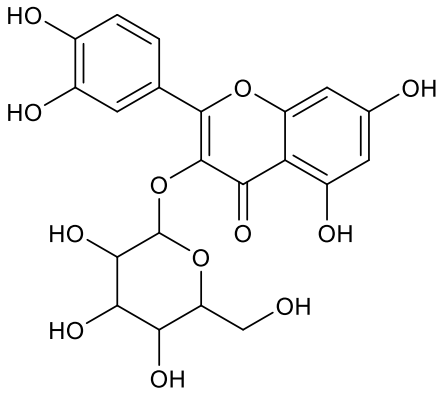
(15)



(16)



(17)



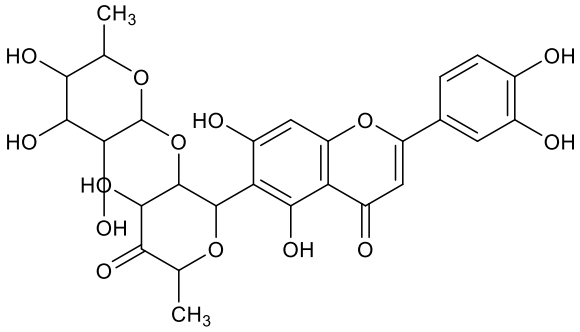
(18)

Poaceae

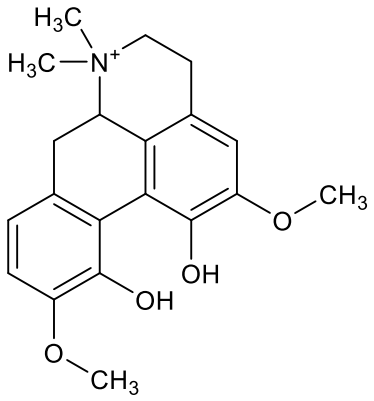
Ethyl acetate fraction of *Eremochloa ophiuroide* Hack., also known as centipede grass, was evaluated for its role in AD therapy. This fraction was found to contain phytocompound maysin (**19**) and its derivatives. Dose-dependent Inhibition of BACE1 was observed, and neurotoxicity induced by amyloid β peptides was also significantly reduced while cell viability was increased up to 82.5% (Song, Kim et al. 2015).

Ranunculaceae

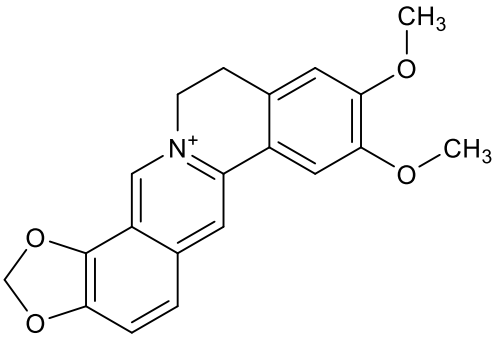
Coptidis Rhizoma is known to have neuroprotective and antioxidant effects. In a study to evaluate *C. rhizoma* use in AD, one aporphine alkaloid (magnoflorine (**20**) and six protoberberine alkaloids (berberine, coptisine, epiberberine, groenlandicine, palmatine, and jateorrhizine) were isolated and tested for Inhibition of BACE1. However, only epiberberine (**21**) and groenlandicine (**22**) showed inhibitory activity against BACE1 (Jung, Min et al. 2009).



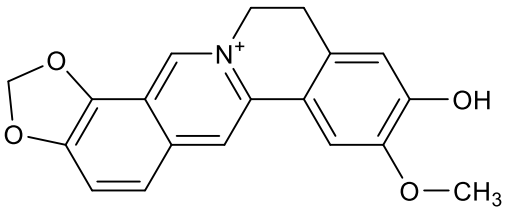
(19)



(20)



(21)



(22)

Rosaceae

In a study, Sanguisorbae Radix, the dried root of *Sanguisorba officinalis* L. was used for the isolation of different active compounds for potential BACE1 Inhibition. Two phytocompounds were isolated with the help of activity-guided purification from ethyl acetate soluble fraction-1,2,3-trigalloyl-4,6-hexahydroxydiphenoyl-β-D-glucopyranoside and 1,2,3,4,6-pentagalloyl-β-D-glucopyranoside. Both compounds were able to inhibit BACE1 non-competitively, and IC_{50} values

were found to be 3.10 μM and 3.76 μM, respectively (Lee, Seong et al. 2005).

Selaginellaceae

In a research study, *Selaginella doederleinii* was used for the isolation of triflavonoids which were evaluated for BACE1 Inhibition. A Total of eight triflavonoids were isolated. Structures were determined, and IC_{50} values were calculated for BACE1 Inhibition. The Strongest Inhibition was shown by Selagintriflavonoid A, with an IC50 value of 0.75 μM. All eight compounds showed BACE1 inhibitory activity (Zou, Xu et al. 2017).

Solanaceae

In a study, β-secretase and β-amyloid aggregation inhibitory potential of extracts from *Capsicum annuum* var. grossum (Bell Pepper) were evaluated. Methanol- 1N HCl (1:1 v/v) was used for the extraction from ripe and unripe fruits of bell pepper. HPLC was used to determine the phenolic composition of fruits. Dose-dependent BACE1 Inhibition by ripe fruits was higher in comparison to unripe fruit. Transmission electron microscopy and Thioflavin-T analysis exhibited that phenolic extracts from pepper fruits can also counteract the initial aggregation of amyloid β peptide, as well as prevent further aggregation of preformed fibrils (Ogunruku, Oboh et al. 2017).

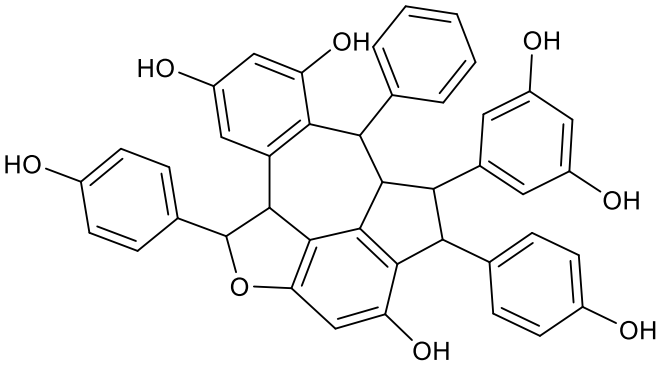
Withania somnifera, commonly known as Ashwagandha is the most commonly used plant in the Ayurvedic system of medicine. A computational study was performed to screen the lead compounds of this plant, and a medicinal component named Withanone and 27-Hydroxywithanolide B has the potential to serve as a promising lead according to docking and molecular dynamic simulation studies (Borah, Sharma et al. 2019).

Datura metel L, also a member of this family has shown inhibitory potential with its extracts and an isolated compound daturaolone with an IC_{50} value of 304.21±2.98 μg/mL and 260.70±1.87 μM against BACE 1 enzyme. This study proposes a new gateway toward novel compound isolations (Bawazeer, Rauf et al. 2020).

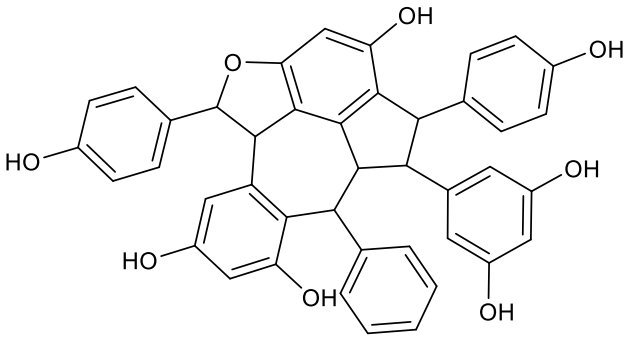
Vitaceae

Twelve polyphenols were isolated and evaluated from the leaf extracts of *Vitis thunbergii* var. taiwaniana for BACE1 Inhibition. Out of these, ampelopsin C (**23**), davidiol A (**24**), stenophyllol C (**25**), stenophyllol B (**26**) and vitisin A (**27**) significantly reduced amyloid β peptide levels in N2a695 cells. On further investigation, ampelopsin C and vitisin A were found to inhibit BACE1 while other polyphenols reduced Aβ generation through different mechanisms (Hu, Lin et al. 2016). In another study, miyabenol C isolated from leaves and stem of *Vitis thunbergii* var. taiwaniana, was found to inhibit BACE 1 *in vitro* as well as *in vivo* (Hu, Lin et al. 2015).

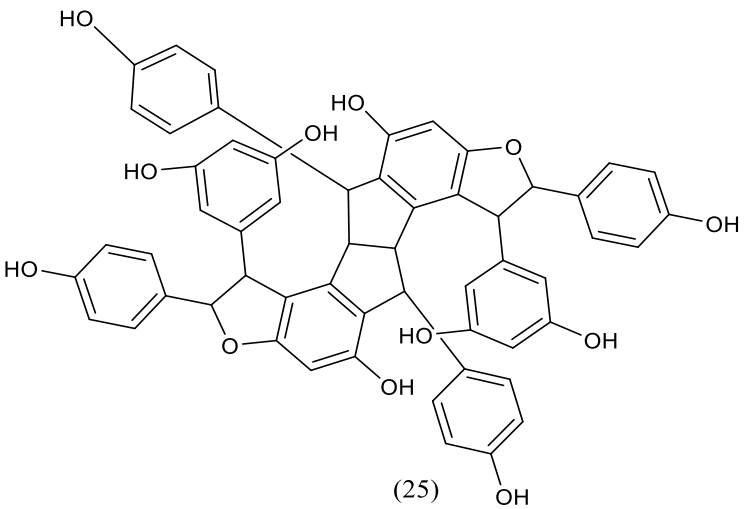
Leea indica (L.indica) was studied because of its traditional use in folk medicines and around 40 molecules have been isolated from this plant. Two of the most promising triterpene candidates that showed potent BACE 1 inhibitory potential after virtual screening were lupeol and ursolic acid. It was evident from studies that these compounds have interactions with Tyr 71 residues and form hydrophobic interactions. Lupeol was found to have BACE 1 inhibitory potential with an IC_{50} Value of 5.12 μM (Moussa-Pacha, Abdin et al. 2020).



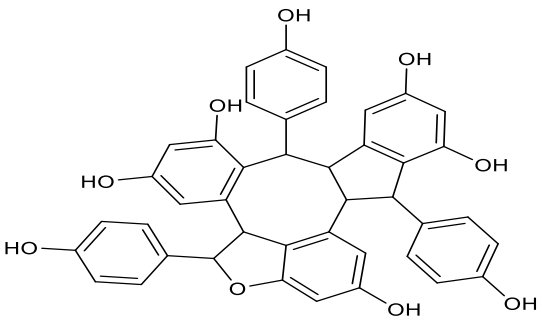
(23)


OH
O
OH
HO
OH
HO
OH
OH

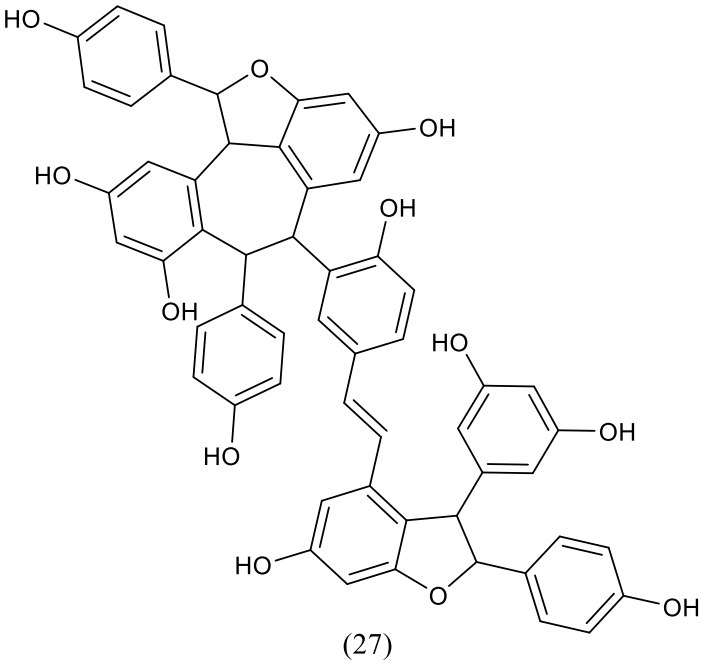
(24)


HO
HO
OH
HO
O
OH
HO
O
HO
OH
OH
OH

(25)


OH
OH
OH
HO
OH
HO
O
OH
OH

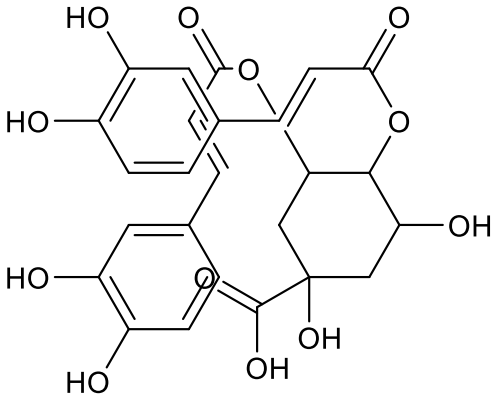
(26)


HO
O
OH
HO
OH
OH
HO
HO
OH
HO
O
OH

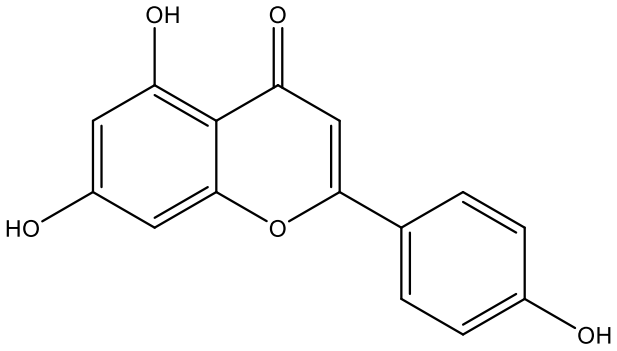
(27)

Acanthaceae

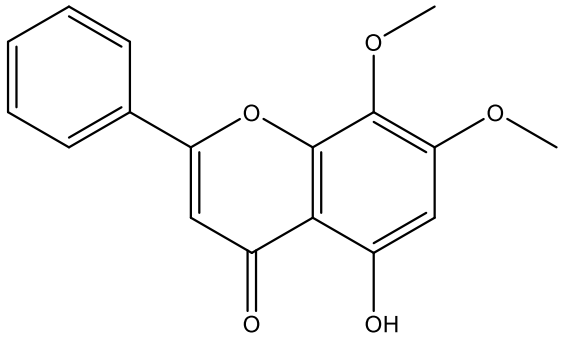
Out of 40 species, only a few are medicinally important, and among them is *Andrographis paniculate, a* famous species having neuroprotective effects. The major bioactive components of this species include flavonoids, polyphenols, and diterpenoids. In this study, phenolic compounds (3,4-di-o-caffeoylquinic acid **(28)**, apigenin (**29**), and 7-o-methylwogonin (**30**) were studied with molecular docking and dynamics to predict the binding affinities with BACE 1. According to docking analysis, the compound 3,4-di-o-caffeoylquinic acid showed the highest binding affinity with BACE 1 with -7.684kcal/mol and -7.108kcal/mol respectively, while apigenin showed binding modes with -7.422kcal/mol. The compound 7-o-methylwogonin showed moderate affinity towards BACE 1, which is around -4.879kcal/mol. In vitro enzyme assays were carried out, which correlated with predicted results of molecular docking, and showed them as potential multi-drug targets along with BACE 1 inhibition (Panche, Chandra et al. 2019).



(28)



(29)



(30)

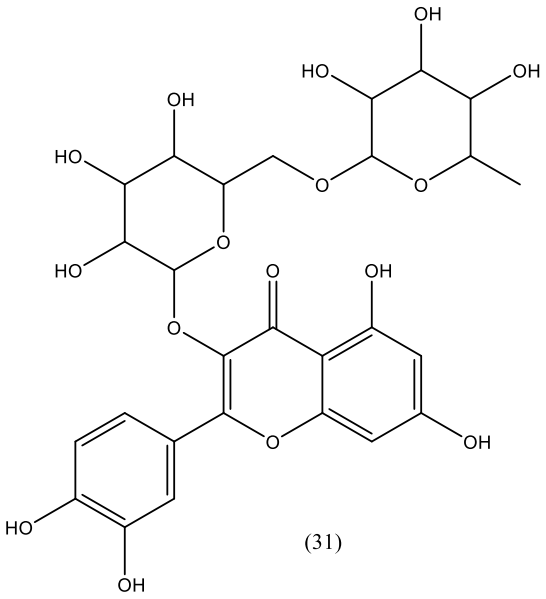
Polygonaceae

A bioflavonoid named rutin (**31**) obtained from the plant *Fagopyrum esculentum* Moench can act as a potent inhibitor of BACE 1. The inhibition mechanism adopted by this flavonoid has no effect on neuregulin during BACE-dependent beta-amyloid precursor protein nuclear signaling. This indicates a novel mechanism for BACE 1 inhibition that prevents toxicities associated with direct Inhibition of BACE 1 (Naushad, Durairajan et al. 2019).

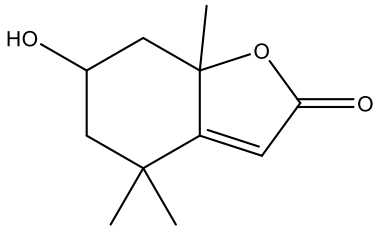
Scrophulariaceae

Bacopa monnieri is known traditionally to have a neuroprotective effect which was evaluated by cheminformatics studies for digging out the potential leads from the constituents of this plant. Almost 52 active compounds were computationally validated. The bioactive compounds, namely Asiatic acid (**32**) and loliolide (**33**) were identified to have therapeutic potential

to treat AD (Jeyasri, Muthuramalingam et al. 2020). In another study, *Bacopa monnieri* was found to be effective in treating colchicine-induced inflammation by targeting BACE 1 activity (Saini, Singh et al. 2019).



(31)



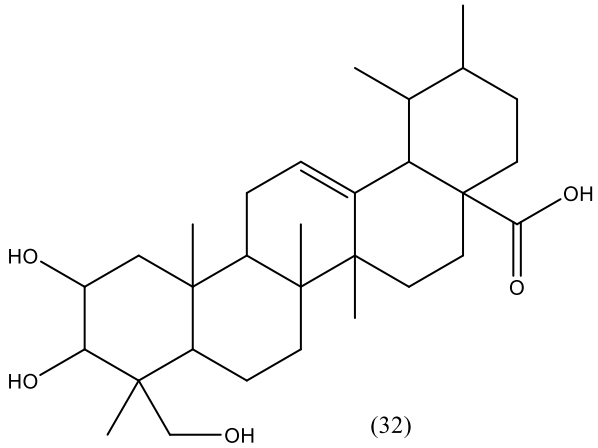
(33)

Cunoniaceae

Weinmannia racemose is a native plant of New Zealand, the bark of which has been shown to have a marked neuroprotective effect. Methanolic and ethyl acetate extracts have shown 59.69% ± 3.83 μg/mL and 38.85% ± 8.30 μg/mL inhibition against BACE 1 enzyme (Majid and Silva 2020).

Myrtaceae

The leaves of *Kunzea ericoides* are traditionally utilized by the people of New Zealand for the treatment of memory-related issues. To establish this fact, these plants' methanolic and ethyl acetate extracts have been investigated against multi-targets (AChE, BChE, and BACE 1). The methanolic extracts have shown remarkable inhibitory potential with 95.86% ± 3.29 μg/mL, while the ethyl acetate extracts have shown 90.59% ± 1.05 μg/mL inhibition against BACE 1 enzyme. The leaves of *Leptospermum scoparium* also showed an inhibitory potential of 27.67% ±1.39 μg/mL with a methanolic extract while 43.77% ± 1.96 μg/mL with an extract of ethyl acetate (Majid and Silva 2020).



(32)

Scrophulariae

Picrorhiza kurroa is a traditionally used medicinal herb with neuroprotective effects. This study investigated the effect of this herb on spatial learning and memory in knockout mouse models, which proved to be effective in decreasing beta-amyloid plaques by decreasing beta-secretase expression, suggesting a key impact on disease pathophysiology (Kim, Do et al. 2020).

Zingiberaceae

Kaempferia parviflora is commonly known as black ginger. The three major extracts, namely polymethoxyflavones, 5,7-dimethoxyflavone (DMF), 5,7,4′-trimethoxyflavone (TMF), and 3,5,7,3′,4′-pentamethoxyflavone (PMF) has a significant BACE 1 inhibitory impact. The inhibitory activity of DMF is (IC_{50} = 49.5 μM), while TMF has shown the most potent inhibitory potential with an IC_{50} of 36.9 μM and PMF has the least inhibitory potential with an IC_{50} of 59.8 μM (Moussa-Pacha, Abdin et al. 2020).

Conclusion & Future Directions

This review attempts to provide a comprehensive account of medicinal plants, their extracts, fractions, and phytocompounds that have the potential to treat AD by inhibiting BACE1. Translating the folkloric knowledge of medicinal plants about the prevention, mitigation, and treatment of AD is a formidable challenge. Experience-based claims supported by sound science must be transformed into medicine in the clinic. With the increasing role of pharmacogenetics in clinical medicine, the need for standardizing the treatment vs. individuating it must be carefully weighed. Widespread use of anti-AD therapies, and herbal medicine in general, as a safe, effective, and affordable form of healthcare would only be possible once we resolve these issues.

For the longest time, most of the neuroscience research community focused their energies and time on the amyloid hypothesis and worked tirelessly to find the cure for AD by targeting gamma secretases. However, the failure of such inhibitors in clinical trials has shifted the focus to BACE1 in recent years. Although none of the BACE1 inhibitors are in the clinic yet, this certainly has not dampened the spirit of the investigators, and several laboratories around the world are exploring the possibilities of bringing safe and potent BACE1 inhibitors to slow the progression of AD.

BACE1 is an attractive and important target for the treatment of AD. A large amount of research in this area has resulted in several promising lead compounds. Various drug discovery approaches led to the development of potent BACE1 inhibitors. Several of these small molecule inhibitors have advanced to late stages in clinical trials. Nonetheless, the high failure rate of lead drug candidates targeting BACE1 brought the need for finding new sources of BACE1 inhibitors to the forefront. Natural compounds would be a useful resource to explore. Several of the phytocompounds discussed in this review could end up in the market if pursued further in clinical trials.

One potential advantage of using the plant extracts and fractions would be the possible synergy among the various phytocompounds present in the plant. This could lead to enhanced efficacy and fewer adverse effects. The complex pathophysiology of AD may respond to a complex interplay among several phytocompounds, synergizing each other's therapeutic effects and neutralizing the untoward effects. With conventional AD therapies only offering symptomatic and/or partial relief, and the lower success rate of the synthetic BACE1 inhibitors in clinical trials, complementary and alternative sources of BACE1 inhibitors hold significant promise and should be further explored.

AD is a mysterious disease with its pathophysiology not fully understood. However, there is a continuous search for interventions to halt or slow down the progression of this neurodegenerative disease. There is still optimism in finding a cure for the pains and sufferings experienced by AD patients. Since the tremendous efforts put in to discover and develop BACE1 inhibitors have not served well so far, phytocompounds from natural sources might hold the solution to unpin this puzzle. With the advent of various multidimensional approaches to tackle multifactorial diseases in the 21st century, there is hope that a breakthrough drug to cure this complicated disease is not too far in the future.

Conflict of Interest

The authors declare that they have no competing interests.

Funding

This article received no external funding.

Consent Forms

Not applicable

Authors Contribution

AK and AAH conceptualized the study, AA,

and JD helped in the analysis and writing the first draft, FU and FA did the literature analysis, and AK supervised the whole project and wrote the final manuscript.

Acknowledgments

The authors are thankful to the University of Nizwa, Oman for the help extended during the project.

Reference

Abourashed, E. A., et al. (2015). "Potential of Horse Apple Isoflavones in Targeting Inflammation and Tau Protein Fibrillization." Natural product communications**10** (9):1577-1580.

Akaberi, M., et al. (2016). "Molecular signaling pathways behind the biological effects of Salvia species diterpenes in neuropharmacology and cardiology." Phytotherapy Research **30**(6): 878-893.

Ali, M. Y., et al. (2015). "Anti-diabetic and anti-Alzheimer's disease activities of Angelica decursiva." Archives of pharmacal research **38**(12): 2216-2227.

Bawazeer, S., et al. (2020). "Potent In Vitro α-Glucosidase and β-Secretase Inhibition of Amyrin-Type Triterpenoid Isolated from Datura metel Linnaeus (Angel's Trumpet) Fruits." BioMed research international **2020**.

Bhakta, H. K., et al. (2016). "Kinetics and molecular docking studies of loganin, morroniside and 7-O-galloyl-d-sedoheptulose derived from Corni fructus as cholinesterase and β-secretase 1 inhibitors." Archives of pharmacal research **39**(6): 794-805.

Bihaqi, S. W., et al. (2012). "Supplementation of Convolvulus pluricaulis attenuates scopolamine-induced increased tau and Amyloid precursor protein (AβPP) expression in rat brain." Indian journal of pharmacology **44**(5): 593.

Borah, K., et al. (2019). "Structural bioinformatics-based identification of putative plant-based lead compounds for Alzheimer Disease Therapy." Computational Biology and Chemistry **78**: 359-366.

Cao, Z., et al. (2017). "Hypericum perforatum extract attenuates behavioral, biochemical, and neurochemical abnormalities in aluminum chloride-induced Alzheimer's disease rats." Biomedicine & Pharmacotherapy **91**: 931-937.

Cassimeris, L. and C. Spittle (2001). Regulation of microtubule-associated proteins. International review of cytology, Elsevier. **210:** 163-226.

Chakrabarti, M., et al. (2016). "Molecular signaling mechanisms of natural and synthetic retinoids for inhibition of pathogenesis in Alzheimer's disease." Journal of Alzheimer's Disease **50**(2): 335-352.

Chauhan, N. B. (2006). "Effect of aged garlic extract on APP processing and tau phosphorylation in Alzheimer's transgenic model Tg2576." Journal of ethnopharmacology **108**(3): 385-394.

Chen, W., et al. (2015). "Lycopene attenuates Aβ 1–42 secretion and its toxicity in human cell and Caenorhabditis elegans models of Alzheimer disease." Neuroscience letters **608**: 28-33.

Cho, N., et al. (2014). "The effects of Betula platyphylla bark on amyloid beta-induced learning and memory impairment in mice." Food and chemical toxicology **74**: 156-163.

Choi, D.-Y., et al. (2012). "Obovatol attenuates LPS-induced memory impairments in mice via inhibition of NF-κB signaling pathway." Neurochemistry international **60**(1): 68-77.

Cole, S. L. and R. Vassar (2007). "The Alzheimer's disease β-secretase enzyme, BACE1." Molecular neurodegeneration **2**(1): 1-25.

Cornejo, A., et al. (2017). "Rosmarinic acid prevents fibrillization and diminishes vibrational modes associated to β sheet in tau

protein linked to Alzheimer's disease." Journal of enzyme inhibition and medicinal chemistry **32**(1): 945-953.

Cutillas, A. B., et al. (2017). "Salvia officinalis L. Essential Oil from Spain: Determination of Composition, Antioxidant Capacity, Antienzymatic and Antimicrobial Bioactivities." Chemistry & biodiversity.

Daccache, A., et al. (2011). "Oleuropein and derivatives from olives as Tau aggregation inhibitors." Neurochemistry international **58**(6): 700-707.

Farooqui, A. A., et al. (2004). "Retinoic acid-mediated phospholipase A2 signaling in the nucleus." Brain research reviews **45**(3): 179-195.

Frydman-Marom, A., et al. (2011). "Orally administrated cinnamon extract reduces β-amyloid oligomerization and corrects cognitive impairment in Alzheimer's disease animal models." PloS one **6**(1): e16564.

Garcia, M. L. and D. W. Cleveland (2001). "Going new places using an old MAP: tau, microtubules and human neurodegenerative disease." Current opinion in cell biology **13**(1): 41-48.

Ghosh, A. K. and H. L. Osswald (2014). "BACE1 (β-secretase) inhibitors for the treatment of Alzheimer's disease." Chemical Society Reviews **43**(19): 6765-6813.

Goedert, M. and R. Jakes (2005). "Mutations causing neurodegenerative tauopathies." Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease **1739**(2-3): 240-250.

Goncalves, M. B., et al. (2013). "Amyloid β inhibits retinoic acid synthesis exacerbating Alzheimer disease pathology which can be attenuated by an retinoic acid receptor α agonist." European Journal of Neuroscience **37**(7): 1182-1192.

Hancianu, M., et al. (2013). "Neuroprotective effects of inhaled lavender oil on scopolamine-induced dementia via anti-oxidative activities in rats." Phytomedicine **20**(5): 446-452.

Hatcher, H., et al. (2008). "Curcumin: from ancient medicine to current clinical trials." Cellular and Molecular Life Sciences **65**(11): 1631-1652.

Hu, J., et al. (2015). "The resveratrol trimer miyabenol C inhibits β-secretase activity and β-amyloid generation." PloS one **10**(1): e0115973.

Hu, J., et al. (2016). "Polyphenols isolated from leaves of Vitis thunbergii var. taiwaniana regulate APP related pathway." Bioorganic & medicinal chemistry letters **26**(2): 505-511.

Hwang, E. M., et al. (2008). "BACE1 inhibitory effects of lavandulyl flavanones from Sophora flavescens." Bioorganic & medicinal chemistry **16**(14): 6669-6674.

Jeyasri, R., et al. (2020). "Bacopa monnieri and Their Bioactive Compounds Inferred Multi-Target Treatment Strategy for Neurological Diseases: A Cheminformatics and System Pharmacology Approach." Biomolecules **10**(4): 536.

Ji, C., et al. (2008). "Gossypium herbaceam extracts inhibited NF-κB activation to attenuate spatial memory impairment and hippocampal neurodegeneration induced by amyloid-β in rats." Journal of Alzheimer's Disease **14**(3): 271-283.

Jung, H. A., et al. (2016). "Inhibitory activities of major anthraquinones and other constituents from Cassia obtusifolia against β-secretase and cholinesterases." Journal of ethnopharmacology **191**: 152-160.

Jung, H. A., et al. (2011). "Antidiabetic complications and anti-alzheimer activities of sophoflavescenol, a prenylated flavonol from Sophora flavescens, and its structure–activity relationship." Phytotherapy Research **25**(5): 709-715.

Jung, H. A., et al. (2015). "BACE1 and cholinesterase inhibitory activities of Nelumbo nucifera embryos." Archives of pharmacal research **38**(6): 1178-1187.

Jung, H. A., et al. (2009). "Anti-Alzheimer and antioxidant activities of Coptidis Rhizoma alkaloids." Biological and Pharmaceutical Bulletin **32**(8): 1433-1438.

Khan, Q. (2014). Dementia: An Emerging Field in Pakistan (P5. 225), AAN Enterprises.

Kiko, T., et al. (2012). "Amyloid β levels in human red blood cells." PloS one **7**(11): e49620.

Kiko, T., et al. (2012). "Significance of lutein in red blood cells of Alzheimer's disease patients." Journal of Alzheimer's Disease **28**(3): 593-600.

Kim, J. Y., et al. (2015). "Ilex latifolia prevents amyloid β protein (25–35)-induced memory impairment by inhibiting apoptosis and tau phosphorylation in mice." Journal of medicinal food **18**(12): 1317-1326.

Kim, J. Y., et al. (2009). "In vitro anti-inflammatory activity of lignans isolated from Magnolia fargesii." Bioorganic & medicinal chemistry letters **19**(3): 937-940.

Kim, N., et al. (2020). "Picrorhiza kurroa prevents memory deficits by inhibiting NLRP3 inflammasome activation and BACE1 expression in 5xFAD mice." Neurotherapeutics **17**(1): 189-199.

Kosaraju, J., et al. (2014). "Dipeptidyl peptidase-4 inhibition by Pterocarpus marsupium and Eugenia jambolana ameliorates streptozotocin induced Alzheimer's disease." Behavioural brain research **267**: 55-65.

Kuk, E. B., et al. (2017). "Anti-Alzheimer's disease activity of compounds from the root bark of Morus alba L." Archives of pharmacal research **40**(3): 338-349.

Lakey-Beitia, J., et al. (2017). "Anti-amyloid aggregation activity of novel carotenoids: implications for Alzheimer's drug discovery." Clinical interventions in aging **12**: 815.

Lee, E., et al. (2012). "Neuroprotective effect of undecylenic acid extracted from Ricinus communis L. through inhibition of μ-calpain." European Journal of Pharmaceutical Sciences **46**(1-2): 17-25.

Lee, H.-J., et al. (2005). "β-Secretase (BACE1) inhibitors from Sanguisorbae Radix." Archives of pharmacal research **28**(7): 799-803.

Lee, S., et al. (2017). "In vitro assessment of selected Korean plants for antioxidant and antiacetylcholinesterase activities." Pharmaceutical biology **55**(1): 2205-2210.

Lee, Y. J., et al. (2012). "Inhibitory effect of ethanol extract of Magnolia officinalis on memory impairment and amyloidogenesis in a transgenic mouse model of Alzheimer's disease via regulating β-secretase activity." Phytotherapy Research **26**(12): 1884-1892.

Li, H., et al. (2017). "Ginseng Protein Reverses Amyloid Beta Peptide and H2O2 Cytotoxicity in Neurons, and Ameliorates Cognitive Impairment in AD Rats Induced by a Combination of D-Galactose and AlCl3." Phytotherapy Research **31**(2): 284-295.

Li, L., et al. (2013). "Ginsenoside Rd attenuates beta-amyloid-induced tau phosphorylation by altering the functional balance of glycogen synthase kinase 3beta and protein phosphatase 2A." Neurobiology of disease **54**: 320-328.

Lim, H. J., et al. (2008). "Suppression of inducible nitric oxide synthase and cyclooxygenase-2 expression by tussilagone from Farfarae flos in BV-2 microglial cells." Archives of pharmacal research **31**(5): 645.

Liu, J., et al. (2010). "Beta-asarone attenuates neuronal apoptosis induced by Beta amyloid in rat hippocampus." Yakugaku Zasshi **130**(5): 737-746.

Maccioni, R. B., et al. (2009). "The role of neuroimmunomodulation in Alzheimer's disease." Annals of the New York Academy of Sciences **1153**(1): 240-246.

Majid, H. and F. V. Silva (2020). "Inhibition of enzymes important for Alzheimer's disease by antioxidant extracts prepared from 15 New Zealand medicinal trees and bushes."

Journal of the Royal Society of New Zealand: 1-14.

Miethbauer, S., et al. (2009). "Antimicrobial, antiproliferative, cytotoxic, and tau inhibitory activity of rubellins and caeruleoramularin produced by the phytopathogenic fungus ramularia collo-cygni." Planta medica **75**(14): 1523-1525.

Min, J.-y. and K.-b. Min (2014). "Serum lycopene, lutein and zeaxanthin, and the risk of Alzheimer's disease mortality in older adults." Dementia and geriatric cognitive disorders **37**(3-4): 246-256.

Molina, J., et al. (1999). "Serum levels of beta-carotene, alpha-carotene, and vitamin A in patients with amyotrophic lateral sclerosis." Acta neurologica scandinavica **99**(5): 315-317.

Moussa-Pacha, N. M., et al. (2020). "BACE1 inhibitors: Current status and future directions in treating Alzheimer's disease." Medicinal research reviews **40**(1): 339-384.

Mullan, K., et al. (2017). "Serum concentrations of vitamin E and carotenoids are altered in Alzheimer's disease: A case-control study." Alzheimer's & Dementia: Translational Research & Clinical Interventions **3**(3): 432-439.

Naushad, M., et al. (2019). "Natural Compounds with Anti-BACE1 Activity as Promising Therapeutic Drugs for Treating Alzheimer's Disease." Planta medica **85**(17): 1316-1325.

Newman, D. J. and G. M. Cragg (2012). "Natural products as sources of new drugs over the 30 years from 1981 to 2010." Journal of natural products **75**(3): 311-335.

Obulesu, M., et al. (2011). "Carotenoids and Alzheimer's disease: an insight into therapeutic role of retinoids in animal models." Neurochemistry international **59**(5): 535-541.

Ogunruku, O. O., et al. (2017). "Capsicum annuum var. grossum (Bell Pepper) Inhibits β-Secretase Activity and β-Amyloid1–40 Aggregation." Journal of medicinal food **20**(2): 124-130.

Ono, K. and M. Yamada (2012). "Vitamin A and Alzheimer's disease." Geriatrics & gerontology international **12**(2): 180-188.

Panche, A. N., et al. (2019). "Multi-target β-protease inhibitors from Andrographis paniculata: In silico and in vitro studies." Plants **8**(7): 231.

Park, W. H., et al. (2015). "Ethanol extract of Bupleurum falcatum and saikosaponins inhibit neuroinflammation via inhibition of NF-κB." Journal of ethnopharmacology **174**: 37-44.

Parthsarathy, V., et al. (2013). "A novel retro-inverso peptide inhibitor reduces amyloid deposition, oxidation and inflammation and stimulates neurogenesis in the APPswe/PS1ΔE9 mouse model of Alzheimer's disease." PloS one **8**(1): e54769.

Polydoro, M., et al. (2009). "Age-dependent impairment of cognitive and synaptic function in the htau mouse model of tau pathology." Journal of Neuroscience **29**(34): 10741-10749.

Prakash, A. and A. Kumar (2014). "Implicating the role of lycopene in restoration of mitochondrial enzymes and BDNF levels in β-amyloid induced Alzheimer' s disease." European journal of pharmacology **741**: 104-111.

R Carratu, M., et al. (2012). "Are retinoids a promise for Alzheimer's disease management?" Current medicinal chemistry **19**(36): 6119-6125.

Roberds, S. L., et al. (2001). "BACE knockout mice are healthy despite lacking the primary β-secretase activity in brain: implications for Alzheimer's disease therapeutics." Human molecular genetics **10**(12): 1317-1324.

Saini, N., et al. (2019). "Bacopa monnieri prevents colchicine-induced dementia by anti-inflammatory action." Metabolic brain disease **34**(2): 505-518.

Santacruz, K., et al. (2005). "Tau suppression in a neurodegenerative mouse model improves memory function." Science **309**(5733): 476-481.

Seidl, C., et al. (2017). "Uleine Disrupts Key Enzymatic and Non-Enzymatic Biomarkers that Leads to Alzheimer's Disease." Current Alzheimer Research **14**(3): 317-326.

Smith, M. A. and G. Perry (1998). "What are the facts and artifacts of the pathogenensis and etiology of Alzheimer disease?" Journal of chemical neuroanatomy **16**(1): 35-41.

Sodhi, R. K. and N. Singh (2014). "Retinoids as potential targets for Alzheimer's disease." Pharmacology Biochemistry and Behavior **120**: 117-123.

Song, J., et al. (2008). "JNK/p38 MAPK involves in ginsenoside Rb1 attenuating beta-amyloid peptide (25-35)-induced tau protein hyperphosphorylation in embryo rat cortical neurons." Yao xue xue bao= Acta pharmaceutica Sinica **43**(1): 29-34.

Song, Y., et al. (2015). "Protective effect of centipedegrass against A β oligomerization and A β-mediated cell death in PC12 cells." Pharmaceutical biology **53**(9): 1260-1266.

Spires-Jones, T. L., et al. (2008). "In vivo imaging reveals dissociation between caspase activation and acute neuronal death in tangle-bearing neurons." Journal of Neuroscience **28**(4): 862-867.

Van Marum, R. J. (2008). "Current and future therapy in Alzheimer's disease." Fundamental & clinical pharmacology **22**(3): 265-274.

Velagapudi, R., et al. (2016). "Pomegranate inhibits neuroinflammation and amyloidogenesis in IL-1β-stimulated SK-N-SH cells." European journal of nutrition **55**(4): 1653-1660.

Venkatesha, S. H. and K. D. Moudgil (2016). Celastrol and its role in controlling chronic diseases. Anti-inflammatory Nutraceuticals and Chronic Diseases, Springer**:** 267-289.

Wang, W., et al. (2008). "Nutritional biomarkers in Alzheimer's disease: the association between carotenoids, n-3 fatty acids, and dementia severity." Journal of Alzheimer's Disease **13**(1): 31-38.

Wang, Y.-H. and G.-H. Du (2009). "Ginsenoside Rg1 inhibits β-secretase activity in vitro and protects against Aβ-induced cytotoxicity in PC12 cells." Journal of Asian Natural Products Research **11**(7): 604-612.

Xie, Y., et al. (2007). "Ginsenoside Rb1 attenuates beta-amyloid peptide (25-35)-induced hyperphosphorylation of tau protein through CDK5 signal pathway." Yao xue xue bao= Acta pharmaceutica Sinica **42**(8): 828-832.

Yadav, R. S. and N. K. Tiwari (2014). "Lipid integration in neurodegeneration: an overview of Alzheimer's disease." Molecular neurobiology **50**(1): 168-176.

Yassin, N., et al. (2013). "Effect of Boswellia serrata on Alzheimer's disease induced in rats." J Arab Soc Med Res **8**: 1-11.

Yin, Y., et al. (2010). "Anti-apoptosis effect of Astragaloside IV on Alzheimer's disease rat model via enhancing the expression of Bcl-2 and Bcl-xl." Scandinavian Journal of Laboratory Animal Science **37**(2): 75-82.

Youn, K. and M. Jun (2013). "In vitro BACE1 inhibitory activity of geraniin and corilagin from Geranium thunbergii." Planta Med **79**(12): 1038-1042.

Zhang, H., et al. (2012). "Inhibition of Aβ25–35-induced cell apoptosis by Low-power-laser-irradiation (LPLI) through promoting Akt-dependent YAP cytoplasmic translocation." Cellular signalling **24**(1): 224-232.

Zhang, L., et al. (2014). "The effect of electroacupuncture on neuronal apoptosis and related functions in rats with acute spinal cord injury." Chinese Medicine **5**(04): 199.

Zhang, X., et al. (2014). "Ginsenoside Rd attenuates Tau protein phosphorylation via the PI3K/AKT/GSK-3β pathway after transient forebrain ischemia." Neurochemical research **39**(7): 1363-1373.

Zou, Z., et al. (2017). "Selagintriflavonoids with BACE1 inhibitory activity from the fern

Selaginella doederleinii." Phytochemistry **134**: 114-121.