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Review Article

# Inhibition of Tau by Phytocompounds and Extracts from Medicinal Plants

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## 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. Apart from an antibody recently approved, 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 acetylcholinesterase inhibition, another important therapeutic target for treating AD is the inhibition of hyperphosphorylation of tau proteins leading to the formation of neurofibrillary tangles. Extensive research following this approach has led to rationally designed synthetic and potent tau inhibitors, several of which are in clinical trials. However, a high failure rate of the tau inhibitors in clinical trials necessitates finding a different source of tau inhibitors. This review discusses the most promising phytocompounds and plant extracts showing potent tau inhibitory activities. 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**: Alzheimer's disease, tau protein, hyperphosphorylation, 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. 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, such as the ability to calculate, and use common objects and tools, are diminished (Yassin et al. 2013). This disease is characterized by irreversible brain damage, which shows up with the symptoms of confusion, impaired memory, loss of orientation, slurred speech, inability to correlate, and loss of judgment (Frydman-Marom 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 et al. 2009). AD is one of the biggest unresolved medical problems causing a significant financial and physical burden on patients, especially on the family and caregivers (Roberds et al. 2001).

**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 et al. 2013) (figure 1). 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 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 is a neurodegenerative disorder characterized by progressive deterioration of neurons of the hippocampus and cortex which relates to cognitive ability and memory, which is why there is short-term memory loss as a first clinical feature of the disease. With the progression of the disease, other cognitive capabilities are impaired, which includes the ability to use common objects or do calculations (Yassin et al. 2013). AD is presented with complex pathophysiology involving various processes and neurotransmitter systems (figure 2). The major pathological hallmarks at the molecular level are β-amyloid plaques (Aβ) and neurofibrillary tangles (Morrison and Lyketsos 2005).

Amyloid plaques play a key role in the pathophysiology of AD. They are presented as clusters of amyloid precursor protein (APP), formed after its abnormal cleavage by a set of various secretases (α,β,ϒ) (Morrison and Lyketsos 2005). The amyloid cascade begins with the enzymatic cleavage APP through a pair of secretase enzymes, i.e., β-secretase and γ-secretase. These enzymes lead to the formation of Aβ plaques, predominantly Aβ40 and Aβ42. The greater the levels of these peptides, especially of Aβ42, the more severe dementia will be. These plaques formed are stable and neurotoxic, leading to the death of neurons (Ghosh and Osswald 2014).

Besides the amyloid cascade, the second player is neurofibrillary tangles (NFTs). The formation of NFTs is associated with the destruction of microtubules in the neurons because there is a modification of tau proteins that support them (Morrison and Lyketsos 2005). In an adult brain, the presence of tau protein associated with microtubules is ubiquitous, which normally functions to maintain the stability and assembly of microtubules (Williams 2006). Microtubules are the fundamental structural component of neuronal cells (Morrison and Lyketsos 2005). The normal tau protein binds to microtubules in axons (Williams 2006) (figure 3). Microtubules are involved in neuronal transmission and transport of nutrients towards the neuron axon. In the pathogenesis of AD, the tau protein is hyperphosphorylated, which leads to the bond disruption between the microtubule and tau protein, leading to the loss of the microtubule's structural integrity. The neuronal communication and transport system is halted, leading to neuronal death (Morrison and Lyketsos 2005).

Several kinases are responsible for the hyperphosphorylation of tau protein. The most important among them is glycogen synthase kinase 3 (GSK 3) and cyclin-dependent kinase 5(cdk 5), which maintains neuronal plasticity. There is an interesting connection between the APP metabolism and tau protein

hyperphosphorylation, which is explained by the fact that APP increases the activities of GSK3 and cdk5, thus stimulating not only the tau protein hyperphosphorylation but also increasing the expression and metabolism of APP (Sotiropoulos et al. 2008).

## Current Pharmacological Therapeutics for Alzheimer's disease

Most of the current pharmacological therapies for treating AD do not aim toward curing the disease but towards managing symptoms of the disease. Two of the most commonly used classes of drugs indicated for the treatment of AD include NMDA receptor antagonists and acetylcholinesterase inhibitors.

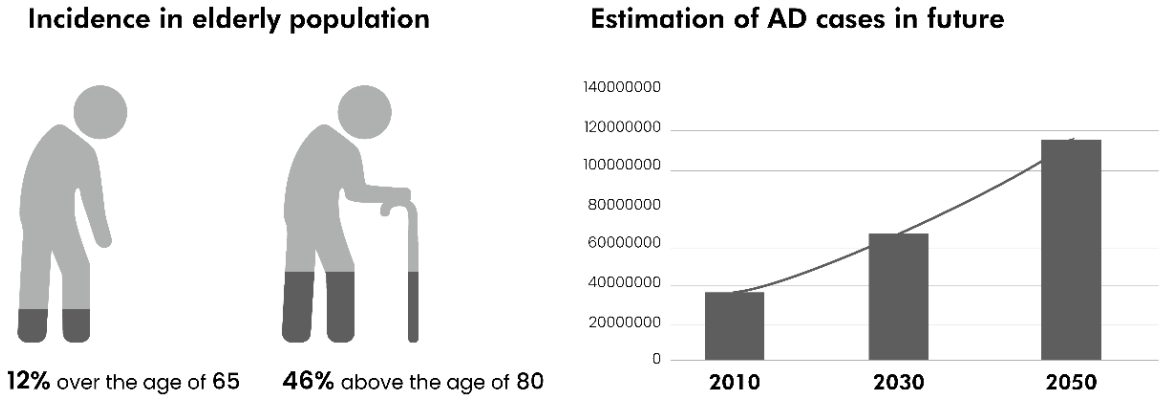



**Figure 1 Epidemiology of Alzheimer's disease.**

### NMDA Receptor Antagonist

It has been observed that overstimulation of glutamate receptors in the central nervous system may cause neuronal apoptosis by increasing the influx of $Ca^{2+}$ into the cells, thus contributing to the neurodegenerative effects of the disease. Memantine, an NMDA-type glutamate receptor antagonist, prevents the activation of the glutamate receptors and thus alleviate the signs and symptoms of AD (Whalen 2018).

#### Acetylcholinesterase Inhibitors (AChEI)

One of the major features of AD is the loss of cholinergic neurons in the cerebral cortex, which leads to dementia, loss of cognitive function, and motor control (Whalen 2018). To minimize the effects, one major approach is to increase the concentration of ACh at the synaptic cleft. This is achieved by blocking the enzyme responsible for the metabolism of ACh called Acetylcholinesterase (AChE) (Golan, Tashjian, and Armstrong 2011). Three drugs are currently approved for the treatment of AD: Rivastigmine, Donepezil, and Galantamine. Galantamine has shown activity at both nicotinic and muscarinic ACh receptors, whereas Rivastigmine is the only AChEI approved for treating Parkinson's disease (Whalen 2018, Golan, Tashjian, and Armstrong 2011).

### Challenges with the Existing Drugs

Despite significant development in AD therapy, a cure for this progressive neurodegenerative disease is still elusive. Current drugs, AChEI, Memantine, and the drugs that are currently in clinical trials are intended to improve the quality of life, alleviate symptoms or slow down the progression of the disease (table 1). Some drugs are no

longer in use due to their adverse effects such as Tacrine has been discontinued as it was hepatotoxic (Golan, Tashjian, and Armstrong 2011). The common adverse effects of the drugs currently used for AD include nausea and vomiting. diarrhea, and anorexia (Whalen 2018). Parasympathomimetic effects are also seen, such as bradycardia and urinary incontinence. Moreover, myalgia and tremors are also observed (Whalen 2018, Golan, Tashjian, and Armstrong 2011). Furthermore, CNS defects are associated with some agents, such as Memantine which has the potential to cause confusion, agitation, and restlessness. Even though AD is a separate condition on its own, neurodegenerative disorders are usually quite complex, where multiple diseases tend to transpire simultaneously. However, the drugs indicated for one condition may be contraindicated in the other. For instance, AChEIs are used to treat AD but cannot be used in Parkinson's disease except for Rivastigmine (Whalen 2018) (Behrens et al. 2018). Until and unless a therapeutic agent or strategy that simultaneously tackles multiple ailments exists, permanent treatment of neurodegenerative disorders cannot be achieved. Despite the factors mentioned above, the cost of the aforementioned drugs is also a problem in the developing world. Due to their usefulness as no more than a symptomatic therapy, these drugs have to be taken for life. As a result, a huge financial burden falls on the patient and the family. Without addressing these concerns, AD will remain a debilitating disorder that will continue to affect millions of people throughout the globe.

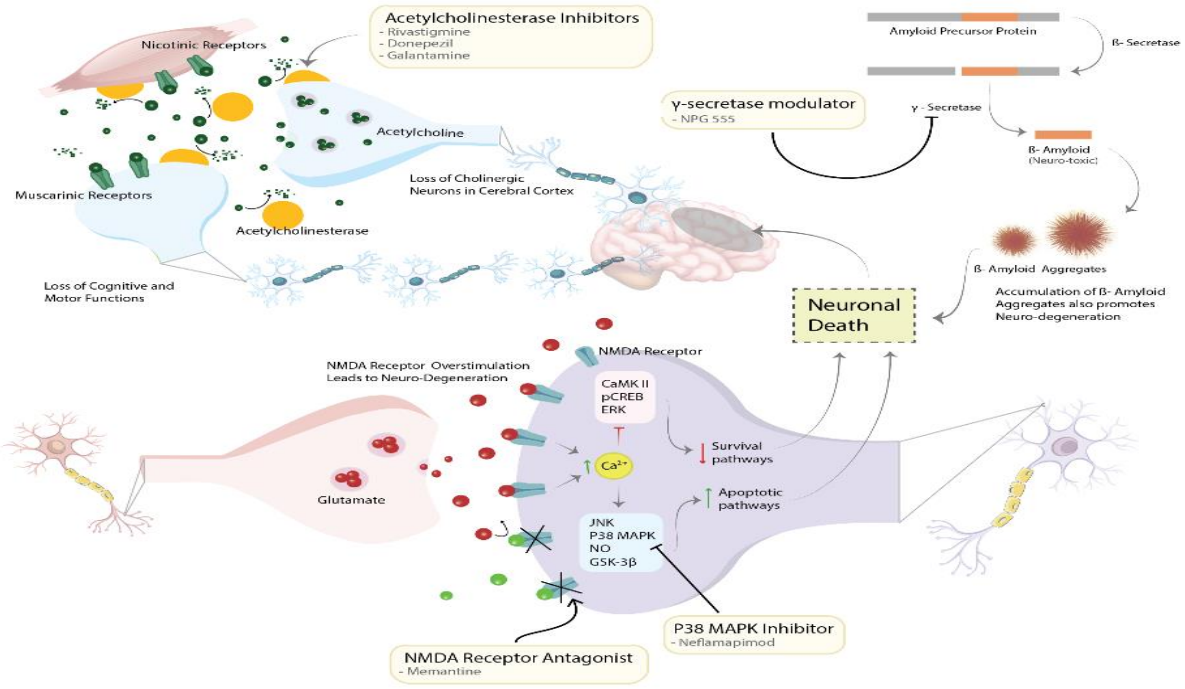



**Figure 2 Different pharmacological targets against Alzheimer's disease.**

**Table 1 FDA Approved Drugs against AD**

| Drugs (Generic/Brand) | Mode of Action | Indicated for | Adverse effects | Ref |
|---|---|---|---|---|
| Donepezil Aricept® | Cholinesterase inhibitor | Cognitive symptoms | Nausea, vomiting, loss ofappetite, cramps, increasedmovements | (Whalen 2018) |
| Galantamine Razadyne® | Cholinesteraseinhibitor | Mild to Moderate AD | Nausea, vomiting, loss of appetite, Increased frequency of bowel movements | (Whalen 2018) |
| Rivastigmine Exelon® | Cholinesteraseinhibitor | Mild to Moderate AD | Nausea, vomiting, loss ofappetite, Increased frequency of bowel movements | (Whalen 2018) |
| Memantine Namenda® | Glutamate regulators | Moderate to Severe AD | Headache, constipation, confusion, dizziness | (Whalen 2018) |
| Memantine + Donepezil Namzaric® | Cholinesterase inhibitor, glutamate regulator | Moderate to Severe AD | Nausea, vomiting, loss ofappetite, increased frequency ofbowel movements, headache, constipation, confusion, anddizziness | (Whalen 2018) |
| Aducanumab Aduhelm™ | Targets Aβ42 | Mild AD | ARIA (Amyloid-related imaging abnormalities),Headache, fall | (Whalen 2018) |
| Suvorexant Belsomra® | Orexin receptor antagonist | Insomnia in AD patients | Impaired alertness, coordination, depression, suicidal thinking, sleepparalysis, compromised respiration | (Whalen 2018) |

**Table 2: Small Molecule Drugs against AD in Clinical Trials**

| Molecules | Trial Phase | Category | Developer | NCT | Ref |
|---|---|---|---|---|---|
| NGP 555 | Phase 1 | Reduces Aβ42 | NeuroGenetic Pharmaceuti-cals | NCT0 25344 0 | (Prins et al. 2021) |
| Neflamapi-mod | Phase 2 | Selective p38 MAPK$\alpha$ Inhibi-tor | EIP Pharma Inc. | NCT0 34026 59 | (LLC 2019, Kounnas et al. 2017) |

**Anti-AD Drugs in Clinical Trials**

Two promising drugs are currently undergoing clinical trials to treat AD, summarized in Table 2 (LLC 2019, Kounnas et al. 2017) (Prins et al. 2021). These drug candidates, namely NGP 555 and Neflamapimod are being developed by Neurogenetic Pharmaceuticals Inc and EIP Pharmaceuticals Inc, respectively. It has been observed in Phase 2, a double-blind, randomized, placebo-controlled clinical trial, that a 24-week treatment with 40 mg Neflamapimod twice daily did not improve episodic memory in patients with mild AD. However, Neflamapimod treatment lowered CSF biomarkers of synaptic dysfunction. Combined with PK–PD findings, the results indicate that a longer duration study of Neflamapimod at a higher dose level to assess effects on AD progression is warranted (Kounnas et al. 2017, LLC 2019) (Prins et al. 2021). NPG 555 which is a γ-secretase modulator with a selective mechanism to reduce Aβ42 while raising shorter Aβ forms such as Aβ 37 and 38, is being tested in a Phase 1 clinical trial (Kounnas et al. 2017). It has shown promising results in shifting the ratio of amyloid biomarkers in human cerebrospinal fluid at safe doses (Kounnas et al. 2019).

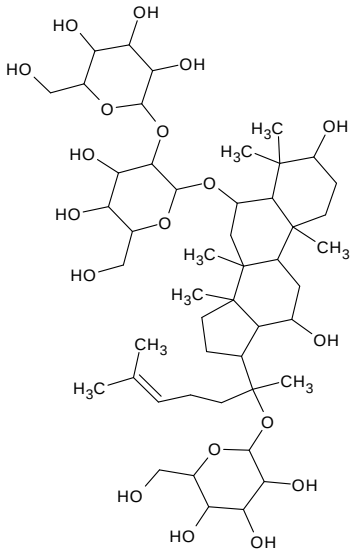
**Promise of Medicinal Plants**

As mentioned previously, frequent and severe adverse effects accompany conventional AD therapy. Moreover, these drugs provide symptomatic relief only without addressing the root cause and hence are not able to reverse the progression of the disease. Since AD is overwhelmingly a disease of the elderly, treatment response to conventional drugs is notoriously poor in this age group (Cho et al. 2019). Because of the potential of several investigated plant extracts and phytocompounds as antioxidants and inhibitors of protein misfolding, and iron accumulation, considerable effort and money are being directed at further exploring them for potential clinical use (Engelbrecht, Petzer, and Petzer 2019). Plant-based phytocompounds usually act through multiple pathways and are likely to be helpful in treating AD, a multifactorial disease. Success with vincristine and vinblastine in the treatment of cancer serves as an excellent example of this approach, where the above-stated benefits make phytocompounds an important source of new therapeutic agents for unmet medical needs (Elufioye et al. 2017).

**Araliaceae**

Ginseng protein (GP) from ginseng (*Panax ginseng* C.A. Meyer) displayed significant neuroprotective effects in animal and cellular models of AD, primarily by reducing the levels of phosphorylated tau (Li et al. 2013). Ginsenoside Rd (1) (table 3) from the same source also inhibited the phosphorylation of tau proteins induced by β amyloid. This anti-tau effect was shown to be mediated by GSK 3β and PP2A (Li et al. 2017). Further studies showed that Ginsenoside Rd

retains this anti-tau property after transient forebrain ischemia (Zhang et al. 2014). Similarly, ginsenoside Rb1 (2) markedly decreased tau protein hyperphosphorylation in embryonic rat cortical neurons, acting through JNK/p38 MAPK signaling pathway (Song et al. 2008), while the same effect in hippocampal neurons was mediated through cyclin-dependent kinase (CDK) 5 signal pathway (Xie et al. 2007).



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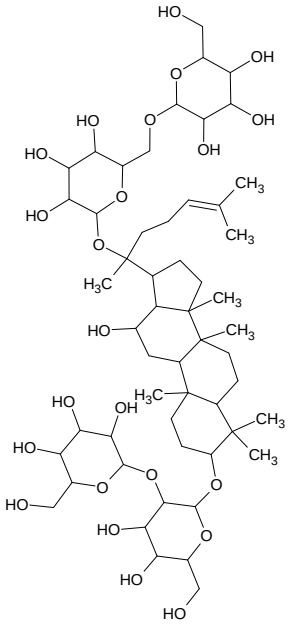

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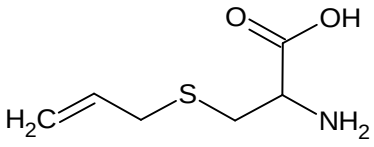
**Amaryllidaceae**

*Allium sativum* (garlic) and its various preparations are known to have pleiotropic effects. Therefore, Aged garlic extract (2%), its prominent constituents, i.e. S-allyl-cysteine (3) (20 mg/kg) and di-allyl-disulfide (4) were explored in relation to AD pathology and were reported to possess potent anti-tau properties (Chauhan 2006). These two compounds are relatively easier to synthesize and are promising candidates for clinical investigations.



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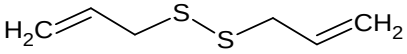

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**Apiaceae**

The traditional use of herbs for treating diseases is undoubtedly a rich source of natural medicine. The extracts of *Angelica sinensis* (AS) found to be effective in treating the neurotoxicity in a culture of cortical neurons while targeting tauopathy by phosphorylation which is attributed to glycogen synthase kinase-3β (GSK-3β) activation (Zhang et al. 2011). Within this family, the furocoumarins from *Notopterygium incisum* were explored for their effect on various pathologies that leads to AD. The results exhibited that this plant has the potential to be a promising drug candidate

because of its attenuation of tau phosphorylation pathway, neuroinflammation and Aβ cascade both in vitro and in vivo (Jiang et al. 2020).

**Aquifoliaceae**

*Ilex latifolia* Thunb. (Aquifoliaceae), a Chinese bitter tea called "kudingcha," locally exhibited

anti-inflammatory and neuroprotective properties in cultured cells and animal models of AD. The authors described inhibition of tau phosphorylation and anti-apoptotic effects as the underlying mechanism targeted by the plant extract (Kim et al. 2015).

**Table 3: Phytocompounds with great potential as anti-tau agents.**

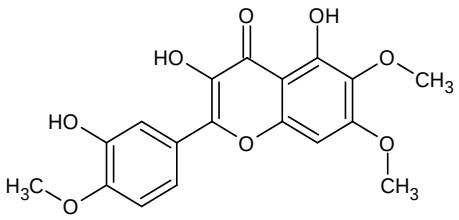
| Plant | Family | Fraction/ compound | Ref. |
|---|---|---|---|
| *Panax ginseng* | Araliaceae | ginsenoside Rb1 | (Li et al. 2013) |
| *Allium sativum* | Amaryllidaceae | S-allyl-cysteine, | (Chauhan 2006) |
| *Notopterygium incisum* | Apiaceae | Furocoumarins | (Jiang et al. 2020) |
| *Artemisia annua* | Asteraceae | Eupatin | (Chou et al. 2020) |
| *Acori Tatarinowii Rhizoma* | Araceae | ß-caryophyllene | (Zhang et al. 2020) |
| *Ricinus communis* | Euphorbiaceae | Undecylenic acid | (Lee et al. 2012) |
| *Ginkgo biloba* | Ginkgoaceae | Ginkgolide A | (Qin et al. 2018) |
| *Crocus sativus L.* | Iridaceae | Crocin | ( Chalatsa et al. 2019) |
| *Rosmarinus officinalis* | Lamiaceae | Rosmarinic acid | (Cornejo et al. 2017) |
| *Olea europaea* | Oleaceae | Oleuropein | (Daccache et al. 2011) |
| *Gastrodia elata* | Orchidaceae | Gastrodin | (Wang et al. 2021) |
| *Pinus pinaster* | Pinaceae | Catechin | (Kim et al. 2006) |
| *Uncaria rhynchophylla* | Rubiaceae | Isorhynchophylline | (Xian et al. 2014) (Zeng et al. 2021) |
| *Litchi chinensis* | Sapindaceae | Catechin, procyanidin A1 | (Xiong et al. 2020) |

**Asteraceae**

*Artemisia annua* is an important plant of the Asteraceae family. It possesses several useful phytocompounds. In a study to investigate Eupatin (5), a polymethoxyflavonoid isolated from *Artemisia annua*, it was found to have the inhibitory potential for tau phosphorylation and neuroinflammation (Chou et al. 2020). The data suggest that Eupatin has the potential to mitigate AD progression.

**Araceae**

From the rich pool of traditional Chinese medicine, *Acori Tatarinowii Rhizoma*, a herb from the family Araceae was investigated for its neuroprotective effects during AD by utilizing an approach of network pharmacology. Two active constituents ß-asarone and ß-caryophyllene were studied and ß-caryophyllene (6) was found to reduce the mRNA expression of tau protein, amyloid precursor protein along with other pathways (Zhang et al. 2020).

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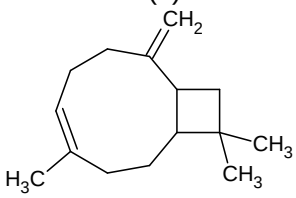


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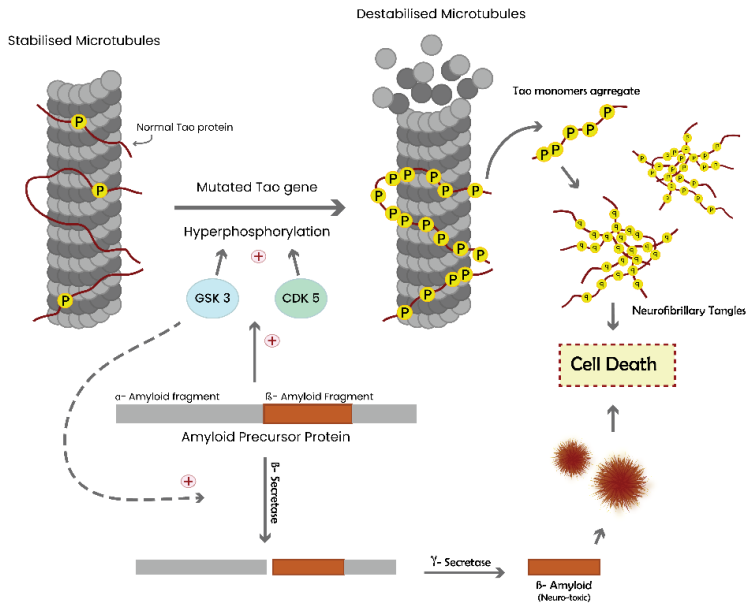



**Figure 3 Tau as a target to treat Alzheimer's disease.**

**Cucurbitaceae**

*Momordica charantia*, a member of the Cucurbitaceae family, was found to possess a neuroprotective effect when given for the treatment of AD. Both in vitro and in vivo data suggest that it targets tau hyperphosphorylation. These neuroprotective effects were further enhanced when the extract of the plant was given in combination with LiCl, which also counteracted some of the adverse effects of LiCl (Huang et al. 2018).

**Convolvulaceae**

A study on the aqueous extract of *Convolvulus pluricaulis* (CP), a herb from the family Convolvulaceae, known for its use in chronic cough, anxiety, and hallucinations (Mahaman et al. 2018) was conducted for its neuroprotective effect in male Wistar rats. This result showed that CP attenuated neurotoxic effects and reduced the increase in tau proteins induced by scopolamine in a rat model of AD (Bihaqi, Singh, and Tiwari 2012).

**Cannabacea**

The effects of *Humulus japonicus* Siebold & Zucc. (HJ) from the family, Cannabacea was investigated to treat AD. The study was conducted using methanolic extracts in a mouse model. The results exhibited strong anti-tau and anti-amyloidogenic potential (Park et al. 2017).

**Table 4 Plant extracts showing significant promise as inhibitors of tau.**

| Plant | Family | Fraction/ compound | Ref. |
|---|---|---|---|
| *Angelica sinensis* | Apiaceae | Extract | (Zhang et al. 2011) |
| *Ilex latifolia* | Aquifoli-aceae | Extract | (Kim et al. 2015) |
| *Convolvulus pluricaulis* | Convolvu-laceae | Aqueous extract | (Mahaman et al. 2018) (Bi-haqi, Singh, and Tiwari 2012) |
| *Momordica charantia* | Cucurbita-ceae | Extract | (Huang et al. 2018) |
| *Humulus japonicus* | Cannabacea | Methanolic extracts | (Park et al. 2017) |
| *Pterocarpus marsupium* | Fabaceae | Extract | (Kosaraju et al. 2014) |
| *Trigonella foenum-graecum* | Fabaceae | Extract | (Prema et al. 2017) |
| *Eugenia jambolana* | Myrtaceae | Extract | (Kosaraju et al. 2014) |
| *Moringa Oleifera* | Moringaceae | Extract | (Mahaman et al. 2018) |
| *Piper sarmentosum* | Piperaceae | Extract | (Yeo et al. 2018) |
| *Bergenia ciliata* | Saxifraga-ceae | Methanolic extracts | (Barai et al. 2018) |
| *Tamarix gallica* | Tamarica-ceae | Methanolic extracts | (Salissou et al. 2018) |
| *Alpinae Oxyphyllae* | Zingibera-ceae | Extract | (Wang et al. 2018) |

**Euphorbiaceae**

Undecylenic acid (7) extracted from *Ricinus communis L.* belonging to the family Euphorbiaceae showed neuroprotective effects by reversing Aβ-induced neuronal cell death. The major underlying mechanism was inhibition of tau phosphorylation in addition to amyloid β oligomerization and amyloid β fibrillation (Lee et al. 2012). These data indicate the potential of this plant in ameliorating AD pathology in clinical settings.

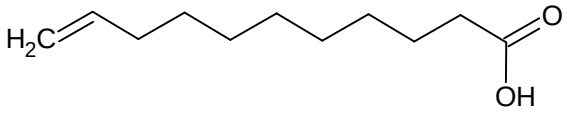
**Fabaceae**

*Pterocarpus marsupium* extracts from the family Fabaceae reported neuroprotection in the streptazocin-induced AD model showing a dose-dependent attenuation of tau phosphorylation (Kosaraju et al. 2014). Another plant from this family-Fenugreek (*Trigonella foenum*-graecum) is well-known for multiple uses such as

hypoglycaemic, galactagogue, hypocholesterolemic, and traditionally used for various neurological disorders. An investigation focusing on the effect of fenugreek seed as a neuroprotective agent in the $AlCl_3$-induced animal model of AD shows that it plays a substantial role in targeting various pathologies of AD, such as amyloid aggregations and tau hyperphosphorylation. These results suggest that the plant possesses constituents responsible for improving AD symptoms and may alter the course of the disease (Prema et al. 2017).

**Ginkgoaceae**

Ginkgo biloba is an important plant from this family. A recent study focuses on the effects caused by Ginkgo biloba extracts as well as its constituents (ginkgolide A, B, or C, bilobalide, and flavonoids) on the hyperphosphorylation of tau protein in cultured neurons and tau transgenic mice. This study showed that the long-term treatment of Ginkgo biloba extracts helps in relieving AD pathogenesis by decreasing cerebral tau protein phosphorylation levels. Among the components ginkgolide A (8), bilobalide (9), and flavonoids were involved in the dilapidation of tau proteins (Qin et al. 2018).

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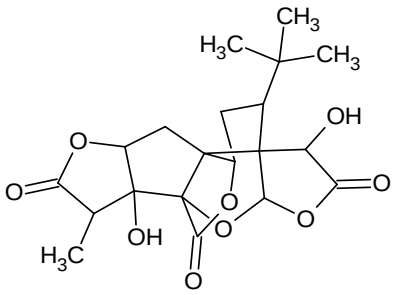


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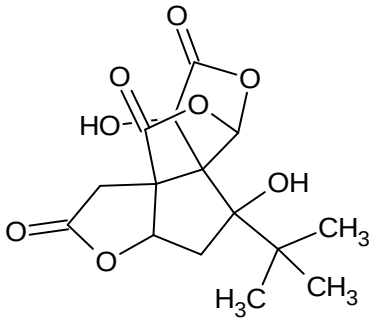


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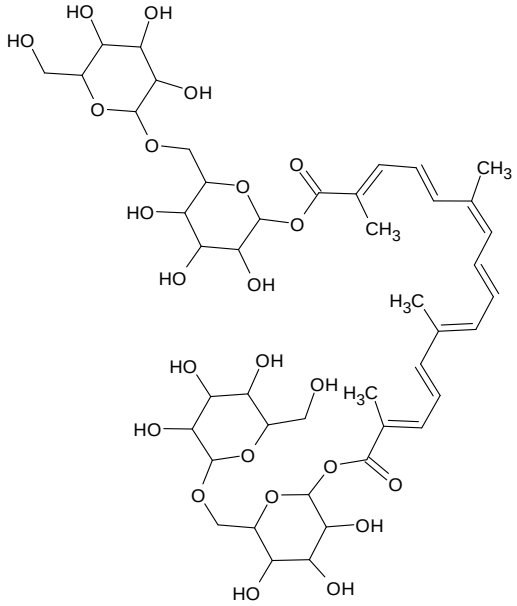
**Iridaceae**

*Crocus sativus L.* is a well know medicinal plant from Iridaceae family. It is known for its use in traditional herbal medicine for diseases such as dementia and depression. Crocin (10), isolated from this plant, is a glycosylated form of crocetin. It is found to have an inhibitory potential for tau aggregates formation, as shown by *in vitro* studies. This suggests its anti-tau properties target the nucleation phase, which promotes tau formation (Karakani et al. 2015). A significant role of trans-crocin 4 and trans-crocetin in preventing AD pathology by decreasing tau phosphorylation and total tau pool was observed. These observations were supported by the studies of these two compounds on PC12 cell lines (Chalatsa et al. 2019).

**Lamiaceae**

Phenolic diterpenoids and Rosmarinic acid (11) isolated from the family Lamiaceae were reported to prevent tau fibrillization. This effect was found useful in reducing vibrational modes associated with β-sheets in tau protein and consequently effective in AD (Cornejo et al. 2017). The structure-activity relationship of Rosmarinic acid derivatives suggests that the phenolic hydroxyl group on one side of the molecule is essential for the activity as well as for lipophilicity (Taguchi et al. 2017).



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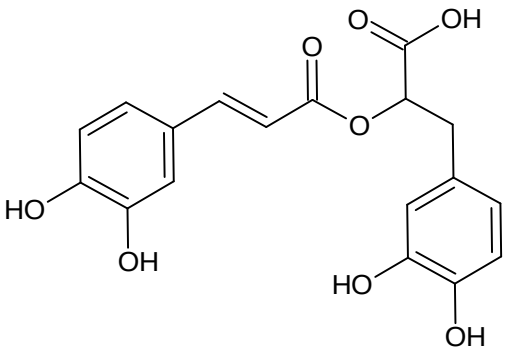

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**Myrtaceae**

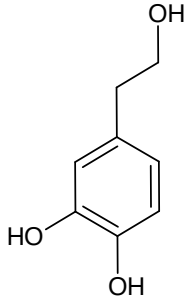
*Eugenia jambolana* extracts from the Myrtaceae family were reported to have neuroprotective potential. A study was designed to investigate the effects of this extract in the streptozocin-induced AD model. The result showed that the plant extract attenuates phosphorylation in a dose-dependent manner (Kosaraju et al. 2014). These findings indicate the promise of *Eugenia jambolana* for finding the treatment of AD.

**Moringaceae**

A famous member of this plant family *Moringa Oleifera* (MO), with a well-established neuroprotective, antioxidant, and anti-inflammatory potential, was studied on a homocysteine-induced rat model of AD. This study concluded that MO significantly decreased the tau protein hyperphosphorylation at various sites, including S-199, T-231, S-396, and S-404, and also reduced beta-amyloid protein production via downregulation of BACE1, which makes it a promising candidate for AD treatment (Mahaman et al. 2018).

**Oleaceae**

Three natural phenolic derivatives obtained from olives (olea europaea from the family Oleaceae) and derived food products, namely hydroxytyrosol (12), oleuropein (13), and oleuropein aglycone (14) showed strong anti-tau properties. Specifically, oleuropein aglycone was very potent, more than the standard used, in inhibiting the fibrillization of tau proteins (Daccache et al. 2011).



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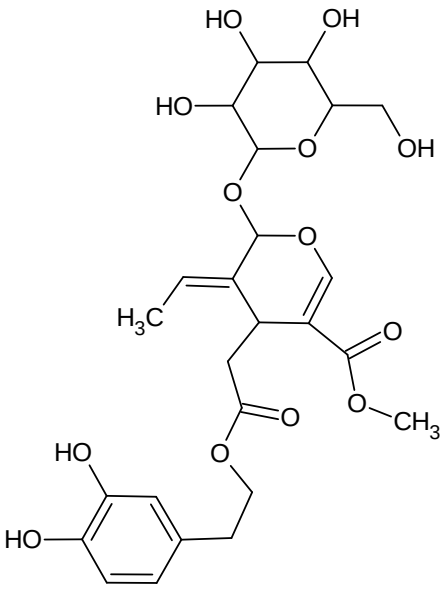

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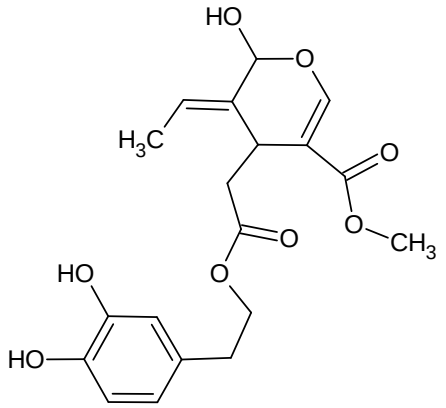

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**Orchidaceae**

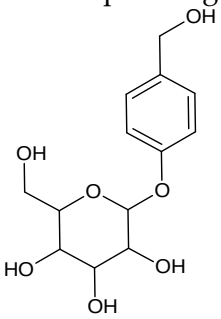
Gastrodin (15) a glycosidic chemical constituent of *Gastrodia elata* from the family Orchidaceae, was investigated for its potential neuroprotective and anti-inflammatory effects in postoperative cognitive dysfunction in aged mice. The pathways that lead to cognitive dysfunction included phosphorylation of tau in aged mice with GSK-3β overexpression. All the neurodeleterious effects were prevented by gastrodin, suggesting that it may prevent neuroinflammation and GSK-3β-induced tau phosphorylation (Wang et al. 2021). In a related study, the potential role of gastrodin in suppressing the deposition of phosphorylated tau protein in the hippocampus of rats was investigated. Their results suggest that it could become a promising candidate for treating Alzheimer's pathology (Shi et al. 2020).

**Piperaceae**

A member of the Piperaceae family, *Piper sarmentosum Roxb* is a medicinal plant that is used to enhance memory and treat headaches. A study on the SH-SY5Y cells found that this plant has significantly reduced the hyperphosphorylation of tau protein through its anti-inflammatory effect. These findings illustrate its neuroprotective role in treating Alzheimer's pathology (Yeo et al. 2018).

**Pinaceae**

In the quest to find natural compounds for treating neurodegenerative disorders, polyphenolic compounds obtained from the genus Pinus of the family Pinaceae are gaining attention owing to their antioxidant, anti-inflammatory, and anti-tumor properties. These phytocompounds are also used traditionally in the treatment of degenerative disorders. The polyphenolic extract from pine bark called Oligopin, which is composed of low molecular weight proanthocyanidins oligomers (LMW-PAOs), such as catechin (16) (C) and epicatechin (EC) including flavan-3-ol units, has been investigated for its neuroprotective role against AD. It was found that Oligopin inhibits the oligomer formation of amyloid protein and tau protein in vitro (Ono et al. 2020). These results indicate that Oligopin would be effective in treating AD and related pathologies.



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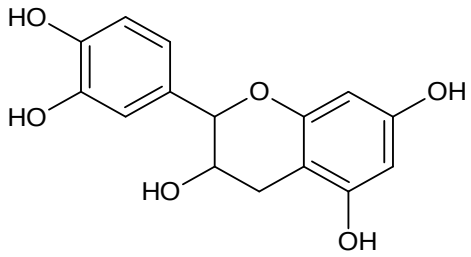
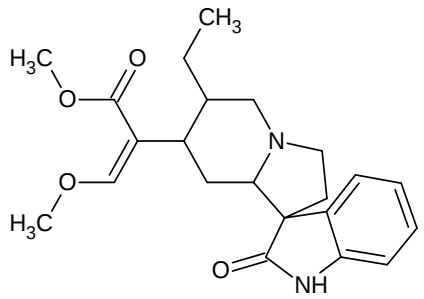



(16)

**Rubiaceae**

The neuroprotective potential of isorhynchophylline (17) (IRN), a chemical constituent obtained from *Uncaria rhynchophylla* was investigated recently. Experiments in Aβ25-35-treated rats' hippocampus established the fact that IRN treatment significantly improved cognitive impairment by reducing the hyperphosphorylation of tau proteins at the Ser396, Ser404, and Thr205 sites, which indicated that IRN is a promising therapeutic candidate for tauopathies (Xian et al. 2014). In another related study, alkaloids obtained from Uncaria rhynchophylla also supported the fact that IRN treatment improves cognitive function by targeting tau protein hyperphosphorylation and apoptosis of neurons (Zeng et al. 2021).

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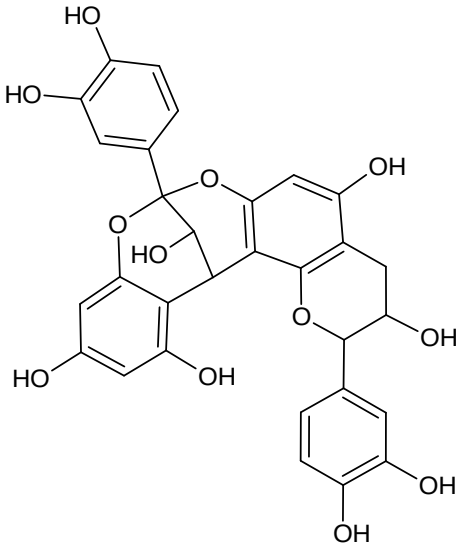


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**Sapindaceae**

*Litchi chinensis* Sonn, a sole member of genus Litchi (from the family Sapindaceae), famous for its Lychee seeds which are commonly used in Chinese traditional medicine to treat hyperglycaemia, hyperlipidaemia and has antioxidant effects. Three important polyphenols catechin (15), procyanidin A1 and A2 (18) were extracted from Lychee seeds. These phytocompounds inhibited the hyperphosphorylated tau protein by the down-regulation of GSK-3β and up-regulation of IRS-1/PI3K/Akt (Xiong et al. 2020).

**Saxifragaceae**

*Bergenia ciliata* (Haw) Sternb from the family Saxifragaceae was explored for its neuroprotective effect in AD. The methanolic extract of this plant was investigated to have any effects on tau aggregation. The outcome of this investigation revealed that it is beneficial against multiple targets of AD, especially attenuating the tau protein (Barai et al. 2018).

**Tamaricaceae**

A naturally occurring plant *Tamarix gallica* (TG) from the family Tamaricaceae, known for its ant-amyloidogenic, antioxidant, and anti-inflammatory properties, was investigated in the form of its methanolic extract against homocysteine-induced AD model (table 4). Results suggest that these extracts reduced the hyperphosphorylation of tau protein at various sites via attenuating some kinases and

upregulating phosphatase activity (Salissou et al. 2018).

**Zingiberaceae**

*Alpinae Oxyphyllae* Fructus, from the family Zingiberaceae, a medicinal plant known for its use in traditional medicine, was explored for its neuroprotective effect in the lipopolysaccharide-induced AD rat model. Their results indicate that the plant was neuroprotective attenuating AD pathology via inhibition of tau protein, beta-amyloid protein, and neuroinflammation (Wang et al. 2018).

**Conclusion & Future Directions**

Translating the traditional knowledge of medicinal plants for the treatment, prevention, and diagnosis of AD is a formidable challenge. This translation is possible by critically evaluating the claims made in traditional medicine by validating them through sound science. In this report, we have compiled studies conducted on medicinal plants, their extracts, fractions, and phytocompounds showing promising and interesting results, and that have the potential to treat AD by inhibiting the formation of neurofibrillary tangles consisting of hyper-phosphorylated tau proteins. Roles of genomics and other factors affecting 'precision medicine' should also be considered. This would address the need to 'individualize' the treatment vs. 'standardizing' it. If we address these issues, it is possible that there will soon be safe, affordable, and effective phytocompounds available for treating AD.

For the longest time, most of the neuroscience research community focused their energies and time on the amyloid hypothesis and worked tirelessly to find out the cure for AD by targeting gamma secretases. However, the failure of such inhibitors in clinical trials has shifted the focus to preventing neurofibrillary tangles, which consist of hyperphosphorylated tau proteins, in recent years. Although none of the tau 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 tau inhibitors to slow the progression of AD.

Prevention of neurofibrillary tangles formation 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 tau 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 tau proteins brought the need for finding new sources of tau inhibitors to the forefront. Natural compounds would be a useful resource to explore. Several phyto-compounds 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 phyto-compounds, 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 synthetic tau inhibitors in clinical trials, complementary and alternative sources of tau 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 tau 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.

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**Consent Forms**

Not applicable

**Authors Contribution**

MHB Conceptualized the study, AA, MKZ, AH, AL and FSS wrote the initial manuscript, AA, MKZ helped in the analysis and writing the first draft, did the literature search, and MHB supervised the whole project and wrote the final manuscript.

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