Potential of medicinal plant compounds to targeting Tau protein in the therapy of Alzheimer's disease– A review

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ABSTRACT

Alzheimer's disease (AD) is a devastative neurodegenerative disorder with complex etiology. AD is characterized by blood-brain barrier disruption, oxidative stress, mitochondrial impairment, neuro-inflammation, hypo-metabolism; it decreases in acetylcholine levels and a reduction of cerebral blood flow. It is also not solely the end-product of aberrantly processed, misfolded, and aggregated oligomeric amyloid-beta peptides but hyper phosphorylated Tau (tubulin binding protein) which formed senile plaque and intracellular neurofibrillary tangles respectively. However, despite the long-term and worldwide effort for a more effective therapy, the only available treatment is a symptomatic use of acetylcholinesterase inhibitors and memantine. Then, many researchers focused their attention to modulate amyloid-beta peptides. These therapeutic approaches as well as those based on cholinergic or amyloid theory have not brought the desired benefits yet. Thus, the main features related with the Tau pathology found in AD are Tau phosphorylation and aggregation. Based on the biochemically diverse range of pathological Tau protein, a number of approaches have been proposed to develop new potential therapeutics like inhibition of Tau phosphorylation, proteolysis and aggregation; promotion of intra- and extracellular Tau clearance and stabilization of microtubules (MTs). Medicinal plants have been used in different systems of medicine and exhibited their powerful roles in the management and cure of memory disorders. This review paper discusses the potential of medicinal plant molecules to targeting Tau protein in Alzheimer's disease therapy.

Keywords: Alzheimer's disease; medicinal plants; Tau protein; hyper phosphorylation; aggregation therapy; natural compound.

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disorder that leads to progressive disturbance of cognition function including memory, decision making, orientation to physical surrounding and language (1). 47 million people live with dementia worldwide. This number is projected to increase to more than 131 million by 2050, as population age. It is the most common form of neurodegenerative diseases and represents a major public health problem and then, the most common cause of progressive dementia in the aging population globally (2). AD is a progressive neurodegenerative disease characterized by senile plaques, neurofibrillary tangles (NFTs); and loss of neurons and synapses in the brain. NFTs are intra-neuronal aggregations mainly composed of abnormally phosphorylated Tau protein. However, Tau phosphorylation is regulated by a balance between Tau kinase and phosphatase activities. Disruption of this equilibrium was suggested to be at the origin of abnormal Tau

phosphorylation and thereby contributes to Tau aggregation (1).

For instance, natural polyphenols, flavonoids and others compounds have reported anti-aggregating capacity to prevent amyloid formation, and a standardized plant extract reduced both amyloid-β and phosphorylated Tau levels in a many transgenic models (3). Tau expression, stabilizing Tau conformations, or clearing hyper phosphorylated Tau aggregates represent challenges for the therapeutic that targeting Tau toxicity in AD. Another approach is to re-stabilize microtubules for preserving neuronal health and axonal transport (4). Pharmacologically, these polyphenols and their derivatives exhibit potential for preventive and therapeutic purposes against protein aggregation during neurodegeneration. Although compounds act on various biochemical pathways, their role in stabilizing the protein degradation machinery at different stages may be an attractive therapeutical strategy to halt the accumulation of misfolded proteins (5).

However, some studies have shown that medicinal plants with potential sources of molecules (natural polyphenols, flavonoids and alkaloids) have neuroprotective effects (5) and can be helpful for the development of the news drugs for Alzheimer's disease.

Now, the current treatments of Alzheimer's disease are symptomatic and do not affect the underlying course of the disease, and clinical trials with research derived molecules have proven inconclusive. Therefore, it is imperative to find new and alternative treatments like phytotherapy which is a science-based approach to the use of natural products with medicinal purposes. It is now widely accepted that Tau is an important therapeutic target in neurodegenerative disease (6). These therapeutic include; (a) reduction of Tau hyper phosphorylation using kinase inhibitors and phosphatase activators, (b) activation of proteasome degradation pathways of Tau, (c) Tau clearance by immunotherapy, (d) inhibition of Tau aggregation using small molecules and stabilizing microtubules (MTs; 7). In this paper, we review current ideas regarding the use of medicinal plant compounds as a potential source for development of cure of Alzheimer's disease targeting specifically Tau protein.

Alzheimer disease overview

Alzheimer's disease (AD) is the most common form of dementia. Ageing is the primary risk for AD. Most common forms of AD are sporadic which start at age 65 around and progressing slowly over. Less than 1% of all cases are early onset familial AD, which is inherited in an autosomal dominant manner and develops similar symptoms as sporadic AD prior to age 65. AD symptoms are associated with progressive loss of neurons and synapses in multiple brain regions, especially in the frontal cortex and hippocampus (8) (Fig. 1A). Literature reports changes in Tau protein and amyloid β oligomers as the most important factors responsible for neuronal dysfunction in the pathogenesis of AD. NFTs observed initially in the entorhinal cortex and hippocampus subsequently extend to the amygdala and cortical areas (temporal, frontal, and parietal) (Fig. 1B; 9).

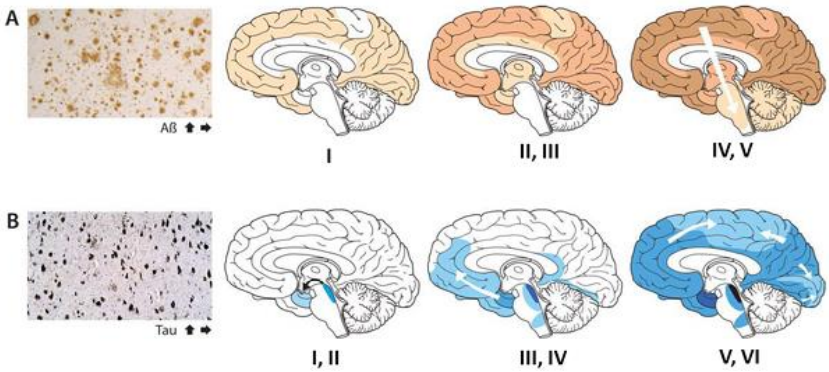


Fig. 1: Spacio-temporal evolution of the lesions in AD. A: Amyloid deposits progression; B: NFTs progression. I, II; III, IV; V, VI: different regions of brain (10).

AD is a progressive neurodegenerative disease that is characterized by the increased abundance of amyloid beta (Aβ) plaques, and neurofibrillary tangles composed of hyperphosphorylated Tau. Normally, Tau is phosphorylated by kinases like cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase 3 beta (GSK-3β). When Tau becomes hyperphosphorylated at phosphorylation sites, it can no longer bind to the MTs. This phosphorylation has been reported to be abnormal in AD. Tau has phosphorylation sites (Threonine or Serine) located in the proline-rich region (P-region) (residues 172–251) and the C-terminal tail region (C-region) (residues 368-441). It is reported that these sites of phosphorylation of Tau are Ser396, Ser262, Ser 202/Thr205 (11).

Alzheimer and TAU protein

Tau is a member of the microtubule-associated protein (MAPs) family. It is a protein that is highly enriched in neurons and was originally defined by its ability to bind and stabilize MTs. Tau plays a role in mediating axonal transport, neurite outgrowth, synaptic structure and function, and neuronal signaling pathways. Physiologically, Tau involves in neurodegenerative diseases, and most prominently in the pathogenesis of AD. The soluble hyper phosphorylated Tau is, however, clearly distinct from aggregated fibrillary Tau in NFTs, despite both being implicated in Tau toxicity (12).

Tau is a highly soluble and natively unfolded protein that binds and promotes the assembly of MTs. Tau protein contains a tandem repeat of 31 or 32 amino acids in the C-terminal half. The repeat region was shown to have a microtubule binding function, and Tau promotes assembly of tubulin and stabilizes MTs (12; Fig. 2).

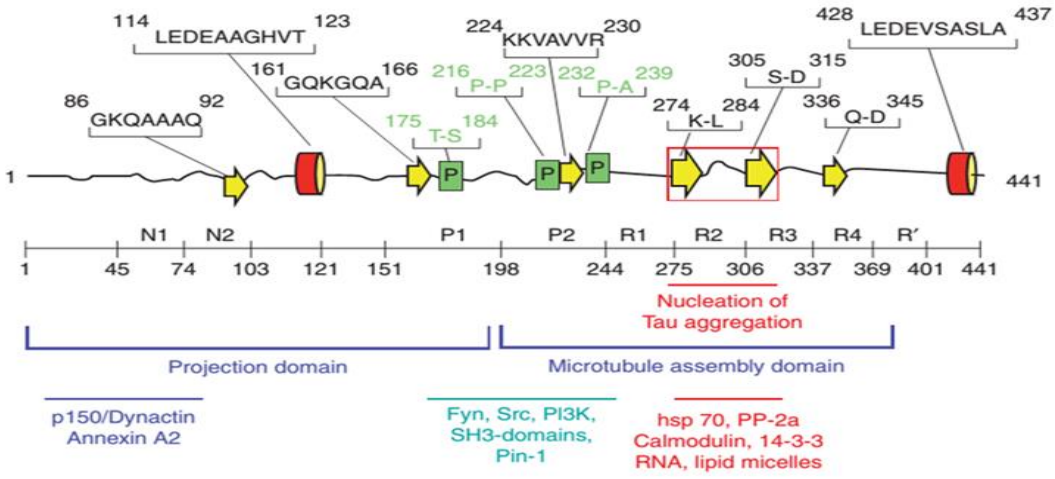


Fig. 2. Domains and structural elements in Tau. Top: Representation of Tau deduced from NMR. Bottom: Approximate location of interaction sites with other proteins (13).

Tau is encoded by a single gene located on chromosome 17 (17q21), possessing 16 exons in its primary transcript. Six different isoforms are expressed by post transcriptional modifications generated by splicing from the primary transcript (6). Mature protein length is about 352 up to 441 amino acid residues, and a molecular- weights of 45–65 k Da depending on the Tau isoforms. The C-terminal region has a domain containing the microtubule binding repeats, which is critical for microtubule assembly, whereas the affinity of Tau for MTs is finely regulated by an orchestrated set of phosphorylation (14; Fig. 3).

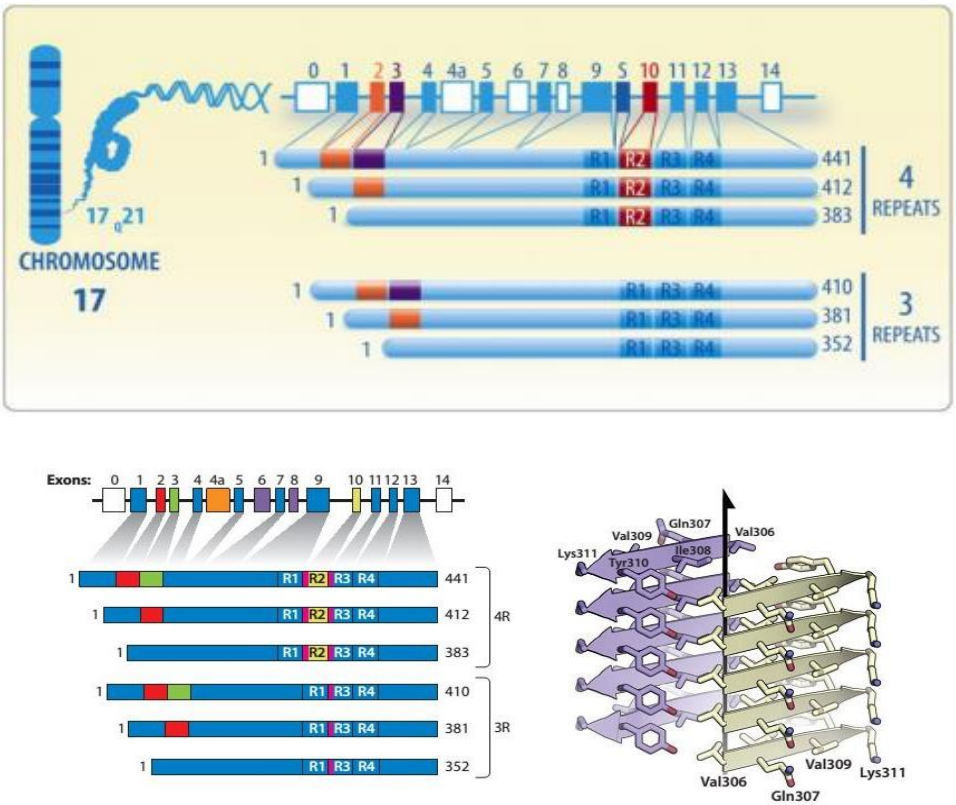


Fig. 3. Domains and alternative splicing of Tau protein. The MAPT (microtubule-associated Protein Tau) gene is situated on the long arm of chromosome 17 at band site 17q21 and encodes to six Tau proteins as product of alternative splicing in the adult human brain. These isoforms are splicing variants of exons 2, 3 and 10 (14).

In tauopathies, Tau accumulates in NFTs that are visualized within dystrophic neurites and cell bodies. The amount of Tau pathology correlates with progressive neuronal dysfunction, synaptic loss, and functional decline in humans. These tangles are bundles of paired helical filaments composed of hyper phosphorylated Tau. Tau promotes tubulin assembly into MTs and stabilizes them. However, the ability of Tau to stabilize MTs is inversely related to the level of Tau hyper phosphorylation. Moreover, Tau may have other post-translational modifications, including glycosylation, ubiquitination, truncations, and nitration (4).

Disruption of this equilibrium of balance between Tau kinase and phosphatase activities was suggested to be at the origin of abnormal tau phosphorylation and thereby might contribute to Tau aggregation. Both kinases and phosphatases have been implicated in the appearance of abnormally phosphorylated Tau (15).

1. Kinases of TAU

It is well-known that some kinases which are involved in the induction of synaptic plasticity modulate Tau phosphorylation (16). Kinases belong to the enzyme group termed "transferases" because they transfer phosphate group from high-energy donor molecules (ATP or GTP) to specific substrates. Tau is a substrate of various protein kinases. Tau kinases include proline-directed Ser/Thr kinases (SP/TP kinases) such as CDK5, GSK3β, and MAPK, as well as non-SP/TP kinases including microtubule affinity-regulating kinase (MARK)/Par-1, AMPK, protein kinases A, C (PKA, PKC), CK (17).

So, Tau protein kinases are grouped into proline-directed protein kinases (PDPK), protein kinases non-PDPK and tyrosine protein kinases. Among these kinases, GSK-3β is the major Tau kinase involved in most of the hyper phosphorylated serine/threonine sites in Tau. However, GSK-3β is a target of the phosphatidylinositol-3-kinase (PI3K)/serine/threonine PKB (Akt) signaling pathway (18).

2. Phosphatases of TAU

Tau function and subcellular localization are tightly regulated by the orchestrated interplay between phosphorylation and de-phosphorylation events (19). Phosphatases are generally classified into three groups according to their amino acids sequences, the structure of their catalytic site and their sensitivity to inhibitors: phosphoprotein phosphatase (PPP), the metal-dependent protein phosphatase and the protein tyrosine phosphatase (PTP). Tau phosphatases belong to PPP group: PP1, PP2A, PP2B and PP5; and PTP group: phosphatase and tensin homolog (PTEN) (1). Of particular relevance, the phosphatase battlefront is largely led by a distinct pool of protein phosphatase enzymes that are responsible for the bulk of neuronal Tau dephosphorylation particularly protein phosphatase 2A (PP2A) which is the most study. PP2A dysfunction has been linked to Tau hyper phosphorylation and synaptic deficits. Deregulation of PP2A enzymes also affects the activity of many protein kinases implicated in AD (20).

3. Microtubules

Tau contains a number of lysine residues, of which positive charges are critical for binding to negatively charged microtubules. Tau protein with an abnormal high degree of phosphorylation is hindered from binding to microtubules increasing free Tau protein concentration and is missorted to the somatodendritic compartment (21). When appropriate physiological Tau phosphorylation is maintained, Tau maintains also affinity to MTs and structure of MTs, axon integrity and cellular function are preserved. When Tau is hyper phosphorylated, it is thought to lose affinity from MTs, form insoluble aggregates, leading to impaired axonal transport, neuronal damage and cell death (22; Fig. 4).

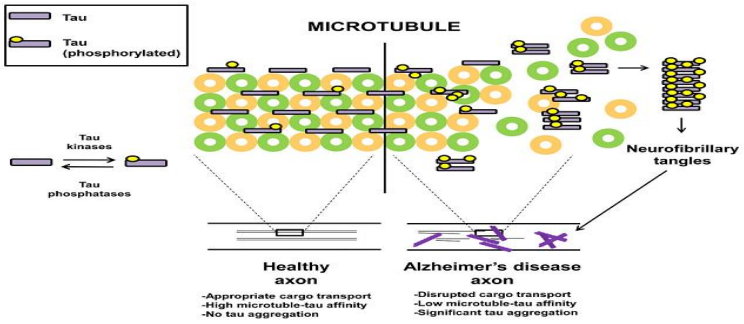


Fig. 4. Tau metabolic pathway (22).

4. Compound as inhibitors of TAU protein

Efforts to develop effective disease-modifying treatments for AD have mostly targeted the amyloid β protein; however, there has recently been increased interest in other targets including phosphorylated Tau and other forms of Tau. Aggregated Tau appears to spread in a characteristic pattern throughout the brain (23). The complexity of Tau biology provides many potential therapeutic targets to prevent Tau production, aggregation, or spread at the level of transcription, phosphorylation, de-polymerization, and transport (4, 23-25).

Now, some literature shows that 14-3-3 proteins interact with Tau and regulate Tau phosphorylation by bridging Tau with various protein kinases (11). 14-3-3 proteins are a family of proteins highly conserved and are mainly expressed in the brain especially in central nervous system. These proteins impact many aspects of brain function like neural signaling, neuronal development and neuroprotection.

a. Immunotherapy

Recently, Tau has become one of the most actively pursued therapeutic targets for AD (26). One strategy used for targeting Tau protein is the immunotherapy. This approach is based in on immunization of subjects against the misfolded Tau protein with the result that hyperphosphorylation and aggregation of Tau are prevented with direct link and strong association between Tau pathology and loss of cognition (27).

b. Therapeutic targeting of Tau hyper-phosphorylation

Another strategy may be the prevention of Tau hyper-phosphorylation by the inhibition of Tau kinases. Tau hyper-phosphorylation is widely known to be induced by increased phosphokinase activity and/or decreased phosphatase activity (28). Therefore, treatment with chemical inhibitors may reduce the rates of NFTs in AD. However, most attention has been paid to the role of GSK-3β because high levels of GSK-3β activity lead to alterations in amyloid beta precursor protein (AβPP) processing and increased neuronal death. Some compound isolated from plants showed strongly inhibition of GSK-3β the enzyme mainly responsible for this process (29).

c. Therapeutic targeting Tau aggregation

Post-translational modifications and loss of microtubule binding lead to elevated levels of cytosolic Tau, thereby increasing the potential for Tau–Tau interactions and polymerization. In humans, Tau aggregation and the presence of NFTs correlate more closely with symptom severity and neuron loss. Large fibrils might contribute to cell dysfunction via molecular crowding and effects on cell metabolism validity of targeting extracellular Tau in the later stages of the disease. Compounds that could facilitate the proteolytic degradation of tau aggregates and prevent propagation of NFTs are very important. Therefore, there are some natural compounds that are able to inhibit Tau aggregation and possibly, make an impact in neurodegenerative diseases especially AD (26) (Fig. 5).

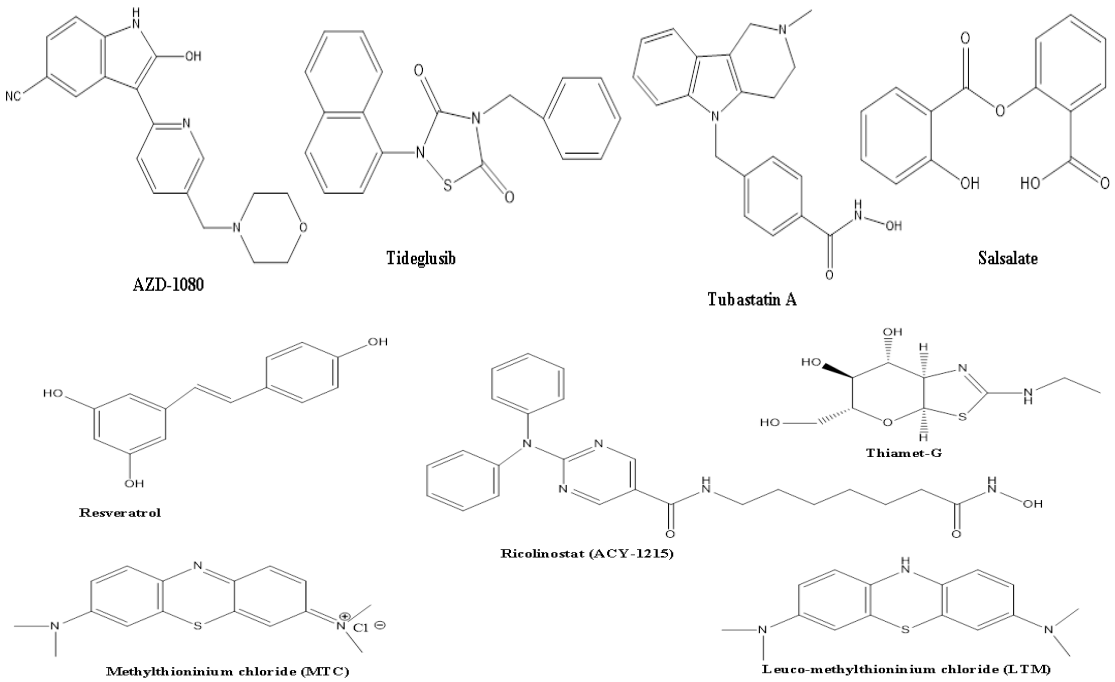


Fig. 5. Some drugs targeting tau pathology, some of them in clinical trials (26).

3.4. Therapeutic targeting microtubule stabilization

In physiological conditions, Tau is normally bound to MTs in axons, modulating tubulin assembly and MT stability. However, hyper phosphorylation of Tau reduces the tubulin binding affinity of the protein and detaches normal Tau from MTs, leading to MTs destabilization and impaired axonal transport. Thus, MT-stabilizing agents that can compensate for the loss of Tau function and restore axonal transport have therapeutic potential in AD and other tauopathies (30; Fig. 6).

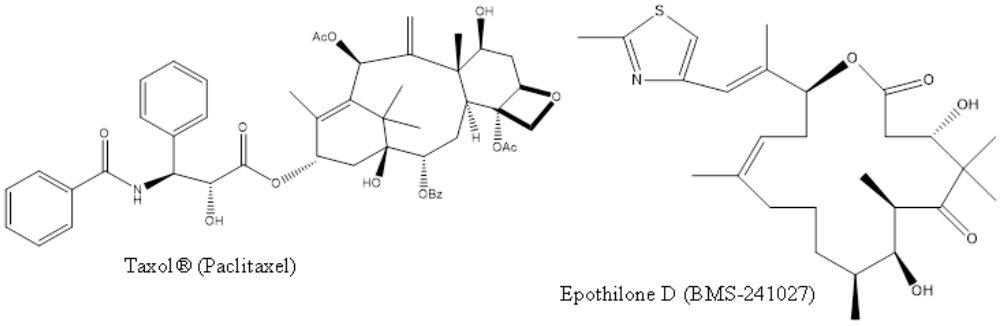
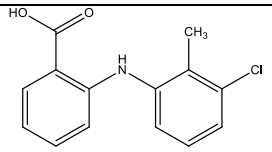
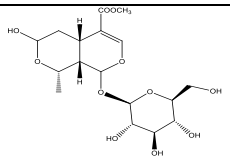
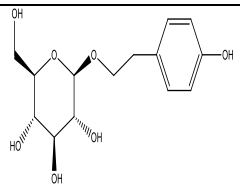
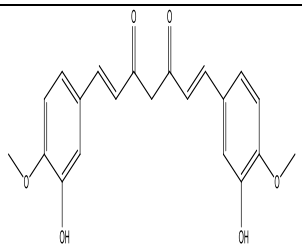


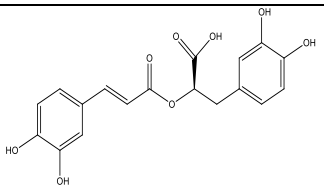
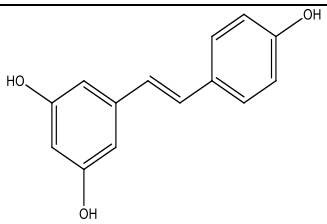
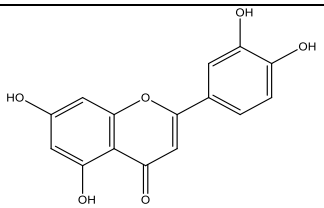
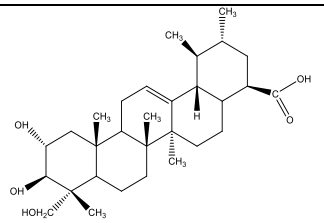
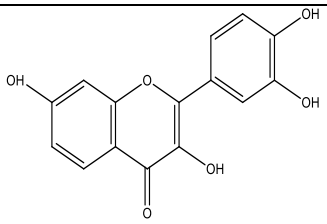
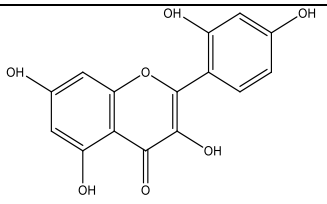
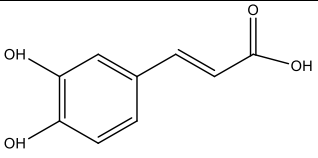
Fig. 6. Structure of MT-stabilizing natural products, paclitaxel and epothilone D (30).

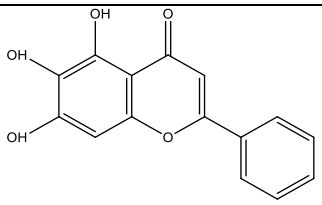
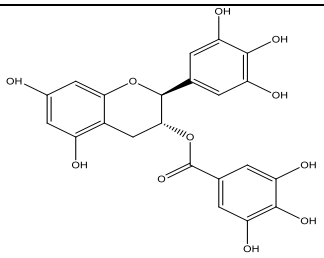
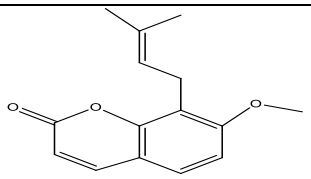
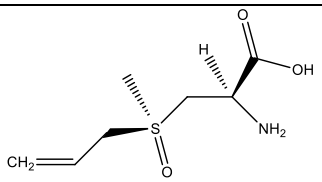
4. Natural Compound of Medicinal Plants as Inhibitors of Tau protein hyper phosphorylation and Aggregation

In recent decades, great interest has been raised due to the potential of polyphenols to prevent many diseases like neurodegenerative diseases (31). Phosphorylation of Tau takes place on serine/threonine residues principally located in the basic proline-rich domains of the protein. However, these domains are potent targets able to fix polyphenols and that polyphenols could inhibit Tau aggregation. Some polyphenols and others compound from plant were also shown to inhibit phosphorylation and aggregation of Tau. Moreover, polyphenols induce disaggregation of aggregated Tau and modify ultrastructure of paired helical filaments isolated from AD brains, decreasing enlargement of filaments (32) (Table 1).

Table1: Natural products for the treatment of Alzheimer's disease targeting Tau protein

Compound	Structure	Plant	Activities	Ref
Tolfenamic acid			Reduces total Tau as well as in site specific hyperphosphorylation of Tau and lowers tau mRNA and protein, as well as the levels of its phosphorylated form and CDK5.	(33)
Morroniside		*Cornus officinalis*	Inhibits Tau hyperphosphorylation in SK-N-SH cells induced by okadaic acid, a PP2A inhibitor.	(34)
Salidroside		*Rhodiola rosea* L	Up regulates the level of p-GSK-3β and downregulated p-Tau in Tau transgenic Drosophila and inhibiting neuronal loss	(35)
Curcumin		*Curcuma longa*	Up-regulates an anti-Tau co-chaperone BCL2-Associated Athanogene2 (BAG2) and thus, suggest probable benefit of curcumin against AD-associated tauopathy.	(7)

Rosmarinic acid		*Rosmarinus offcinalis* L.	Acts as Tau inhibitors by avoiding fibril formation *in vitro* and subsequent β sheet formation and is able to stop aggregation of Tau	(3)
Resveratrol		Red wine, grapes, berries, peanuts	Protects against hyperphosphorylation and/or mediates dephosphorylation of the Tau protein; Inhibits Tau phosphorylation mediated by activation of PP2A and AMPK-induced activation of PI3K/Akt signaling pathway by inhibition of GS3K.	(37, 38)
Luteolin			Reduces the zinc-induced hyperphosphorylation of the Tau protein, the mechanism of which may be explained by its antioxidant activity and ability to regulate the Tau phosphatase/kinase system;	(37)
Asiatic acid		*Centella asiatica*	Reduces phoshoTau by activating Akt/GSK3β pathway.	(39)
Fisetin		*Rhus succedaneae L.*	Promotes the *in vitro* degradation of phosphorylated Tau and reduced the *in vivo* Tau hyperphosphorylation	(40)
Morin		*Maclura pomifera*	Reduces Tau hyperphosphorylation	(41)
Caffeic acid			Reduces Tau phosphorylation	(25)

Baicalein		*Scutellaria baicalensis*	Prevents Tau phosphorylation in AD model and improve cognitive function	(42)
Epigallocatechin gallate			Inhibits the *in vitro* Tau aggregation and increases the *in vivo* clearance of phosphorylated Tau	(42)
Osthole		*Cnidium monnieri* (L.)	Decreases the phosphorylated Tau levels	(43)
Garlic		*Allium sativum* L.	Inhibits Tau hyperphosphorylation	(42)

CONCLUSION

Medicinal plants have been implicated in health benefits relevant to a number of disease conditions. Much of the evidence has focused on the polyphenol, flavonoid components. These main compounds have been shown to have effects against AD. Therefore, it is important to value medicinal plant, exploring new active compounds against AD.

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