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Medicinal Plants for Treatment Tauopathy- Recent Advances in Targeting Tau Phosphorylation

Mohammad Soheil Maveddat[1], Banafshe Salehi[2], Bahareh Salehi[3], Behdokht Jamali[4], Koorosh Shahpasand[5]*

[1]Department of Biotechnology, Faculty of Advance Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
[2]Department of Biotechnology, Faculty of Advance Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
[3]Department of Cellular Molecular Biology, Faculty of Advance Sciences and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.
[4]Department of microbiology, Kherad Institute of Higher Education, Bushehr, Iran.
[5]Department of Brain and Cognitive Sciences, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology (ACECR), Tehran, Iran.
*Corresponding Addresses: Department of Brain and Cognitive Sciences, Cell Science Research Center, PO Box 16635- 148, Tehran, Iran. *E-mail*: shahpasand@royaninstitute.org

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Abstract

The prevalence of neurodegenerative diseases such as Alzheimer's disease (AD) has increased in recent years and put additional strain on the health systems of most countries. Although great progress has been made in the treatment of these diseases, so far no effective treatment has been found that can block the progression of these diseases. In recent years, there have been reports of inhibition of hyperphosphorylation of Tau protein by extracts or natural compounds derived from medicinal plants. In this review article, we tried to review some of the medicinal plants that have shown these effects in electronic databases. Some medicinal plants including Curcuma longa, Rosmarinus officinalis, Vitis vinifera, Apocynum Venetum, Centella Asiatica, Rhus succedanea, Maclura pomifera Allium sativum and Ginkgo biloba have been found to show anti-Tau hyperphosphorylation effects and therefore can be considered as adjuvant therapy in Alzheimer disease (AD). The essential oils or natural products of some medicinal plants inhibited the Tau hyperphosphorylation in studies. The results showed suitable options for treatments of neurodegenerative diseases including AD.

Keywords: Alzheimer's disease, Hyperphosphorylation, Medicinal plant, Tau, Tauopathy.

1. Introduction

Alzheimer's disease (AD) is the most common and well-known type of dementia, which is caused by neuronal destruction and atrophy of the cerebral cortex. These changes are followed by a progressive decline in recent memory, disturbances of consciousness, and mood change (1). AD is the fifth leading cause of death in the elderly and is found in 6% of people over 65 and 22.2% of people over 80 (2). Approximately 40 million people worldwide suffer from AD, and that number will reach 100 million by 2040 (3). AD has two neuropathological features. One is the accumulation of amyloid-β (Aβ) peptide plaques on the outside of neurons produced by the breakdown of amyloid precursor protein (APP), and the other is the formation of neurofibrillary tangles (NFTs) inside neurons caused by aggregates of hyperphosphorylated of the Tau protein, accumulating in the hippocampus and other areas of the cortex (4, 5).

TNFs are characteristic of AD and other diseases of the central nervous system called tauopathy (6). The number of TNFs is a factor in determining the severity of the disease and decreases in synaptic transmission and the number of neurons due to the destruction of microtubules occurs as a result of the formation of TNFs (7). Increasing the rate of phosphorylation of Tau complexes in cerebrospinal fluid (CSF) had a significant positive correlation with decreasing scores in cognitive tests (8). Therefore, the accumulation of phosphorylated Tau protein in CSF has been suggested as a suitable biomarker for predicting AD (9).

Current treatments for AD include the use of acetylcholinesterase inhibitors (ChEIs) such as Rivastigmine and Neostigmine, adrenoceptor agonists, β-secretase (BACE1) inhibitors such as rosiglitazone, and N-methyl-D-aspartic acid receptor antagonist (NMDA) including dextromethorphan (10). These drugs have less therapeutic effect with many side effects, and this has led researchers to focus on medicinal plant-derived drugs to reduce Tua protein aggregation and Aβ accumulation. In this review article, an attempt was made to list and present medicinal plants with the characteristic of reducing Tao protein aggregation in diseases related to the central nervous system including AD.

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2. Tau protein

Tau is a microtubule-associated protein (MAP) found mainly in central nervous system neurons, especially in axons, and to a lesser extent in cell bodies and dendrites (11). Tau is also expressed in very small amounts in astrocytes and oligodendrocytes (12). This protein contains 352 to 441 amino acids and is encoded by the mapt gene (13). This protein consists of an amino-terminal region, two proline-rich regions, and a carboxyl region that contains microtubule-binding repeats (14). Several mutations in the Tau gene have been identified that lead to Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) (15). The Tau is primarily involved in regulating microtubule stability as well as axonal and synaptic transmission (16).

Tau-related toxicity in AD is due to its high phosphorylation (17, 18). Hyperphosphorylated Tau protein by Glycogen synthase kinase-3 beta G(SK3β) and Cyclin-dependent kinase 5 (CDK5) plays an important role in its insolubility and in neurodegenerative diseases such as Alzheimer disease (AD) (19). This leads to the formation of Paired Helical Filaments (PHF) and the formation of NFTs (20).

These enzymes are activated by soluble Aβ (21). Hence, there is an interaction between Amyloid beta (Aβ) and Tau in the pathology of AD (22, 23). NFTs are better associated with the pathogenesis and clinical progression of AD (24). Hyperphosphorylated Tau protein prevents its binding to the microtubule, leading to depolymerization and destruction (25). It has been suggested that Tau phosphorylation may be mediated by APP (26).

Tau is said to mediate NMDA receptor-induced excitatory toxicity through Fyn kinase (a member of the Src tyrosine kinase family) in a phosphorylation-dependent manner (27).

Interestingly, Fyn itself is activated by the binding of Aβ oligomers to prion proteins (28). Tau phosphorylation causes it to interact with Fyn, and the Tau in the dendrites places Fyn as the dendrites and postsynaptic site, thereby phosphorylating the NMDA receptor GluN2B subunit, increasing its function (29). Thus, improper placement of the Tau, phosphorylation, and its interaction with Fyn in dendrites all contribute to AD.

3. Tau Hyperphosphorylation mechanisms

The important mechanisms responsible for Tau hyperphosphorylation have not been fully elucidated. However, this most likely is due to the imbalance between the kinases and phosphatases that regulate Tau phosphorylation (30). Based on the apparent similarity of Niemann picks disease type-C (NPC) with AD, it has been hypothesized that defects in the autophagy-endolysosomal system may be the basis for the abnormal activity of enzymes controlling Tau phosphorylation (31). Since there is no mutation in the Tau in either Alzheimer's disease or NPC, it seems that lysosome destruction in these diseases is the result of a lack of regulation of Tau kinases and phosphatases. Many of these enzymes are involved in cellular signal transduction cascades, and endosomal membranes serve as important regulatory functions. Thus, defects in the endosomal-autophagic system may be responsible for at least part of the abnormal activity of enzymes controlling Tau phosphorylation (32).

Abnormal functioning of endolysosomal-autophagic systems also causes their accumulation due to impaired clearance of toxic Tau species (33). In addition, in AD mouse models, intracellular accumulation of Aβ oligomers caused a defect in the endosomal-autophagic system, which coincided with an initial increase in abnormally phosphorylated Tau (33). Hypotheses stated that Aβ formation precedes NFTs formation. However, neurodegeneration, synapse loss, and cognitive symptoms in AD patients are more associated with NFTs formation than amyloid plaque deposition (34). Therefore, the imbalance between the kinases and phosphatases that regulate Tau phosphorylation is the main pathology mechanism of Tau hyperphosphorylation.

4. Amyloid-beta and Tau interaction

Since there is an interaction between the two molecules Aβ and Tau, these two molecules do not act independently of each other. Transgenic mice with mutations in the APP, presenilin-1, and Tau genes induced Aβ deposition before the pathogenic effects of NFTs appeared (35). Researchers have also shown that lowering amyloid levels by immunotherapy prevents Tau pathogenesis (36) and eliminates spatial memory problems (37, 38). Therefore, it can be concluded that the formation of Aβ is a prelude to the pathogenic effects of the Tau and the prevention of the formation of Aβ can reduce the formation of the Tau. Although the Tau protein is located downstream of Aβ, there is also evidence to suggest that the Tau molecule is involved in inducing the Aβ-induced signaling cascade (39).

In addition to changes in synaptic plasticity and neuronal integrity, AD is associated with changes in neurogenesis in areas with the ability to produce new neurons (40). The neuronal degradation process is associated with increased CDK5, P35 and P25 activities. CDK5 kinase plays an important role in synaptic plasticity and neuronal development, and its upregulation in the neural progenitor cell is associated with the pathogenicity of neurodegenerative diseases (41).

5. Medicinal plants for treatment tauopathy

5.1. Curcuma longa

Curcuma longa belongs to the Zingiberaceae family and is one of the most popular spices in the world (42). Its most important secondary metabolite is curcumin, which has shown a broad pharmacological profile (43). This compound prevented Tau protein aggregation and insolubility in R406W tau-expressing worms and its mechanism of action was attributed to the stabilizing of microtubules and preventing its polymerization (44). This compound has the ability to bind to Aβ (45), α-synuclein (46), scrapie (47), and Tau proteins (48), preventing their aggregations. Curcumin is able to identify Tau aggregation and TNFs in AD and progressive supranuclear palsy (PSP) (48). Inhibition of Tau protein aggregation is a therapeutic goal for tauopathy and curcumin appears to be a promising treatment option. Recently, it has been shown that this compound not only inhibited the deposition of Aβ in AD but also the accumulation of Tau protein in the mouse tauopathy model (49). Therefore, Curcuma longa has the potential to be used in the treatment of AD.

5.2. Rosmarinus officinalis

Rosemary (Rosmarinus officinalis) from the Lamiaceae family has been shown to have antioxidant, anti-inflammatory, and antimicrobial properties (50, 51). The most important constituent of the essential oils of this plant is rosmarinic acid (RA), to which the pharmacological properties of Rosemary are attributed (52). In recent years, the anti-Tau protein accumulation properties of RA have attracted the attention of researchers. This compound has the ability to inhibit the fibrillization of the Tau protein and prevent the assembly of the secondary structure of that protein (53). Thus, Rosemary can be used to prevent AD development.

5.3. Vitis vinifera L

Grape from the Vitaceae family is one of the most important and popular fruits in the world and polyphenols such as stilbenoids are the most important components of this fruit and responsible for

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pharmacological properties such as antioxidant, anti-inflammatory, analgesic, and antipyretic activities (54). Among them, Resveratrol (RV) has attracted the attention of researchers in the treatment of diseases because of its extensive pharmacological activity (55, 56). Recently, the effects of RV on the mice model of tauopathy were studied and the results indicated its inhibitory effects on Tau integration, and Tau-induced toxicity (57). Preventing Tau aggregation by RV was attributed to reduced phosphorylation, and it also significantly reduced neuroinflammation and synapse losses (57). Therefore, RV results from grapevine can be considered a promising option in preventing AD. Another study showed a decrease in hyperphosphorylated Tau levels and an increase in solubility of Tau protein by administration of RV to transgenic mice (58). This compound appears to have the potential to disrupt the final stages of Tau aggregation. The enzyme responsible for the dephosphorylation of Tau is protein phosphatase 2A (PP2A), and increasing the activity of this enzyme can prevent the hyperphosphorylation of Tau protein. Increased activity of this enzyme and decrease of hyperphosphorylated protein as a result of treatment of primary cortical neurons with RVS were reported (59). Therefore, Grapefruit by having RV has the potential of being used for targeting Tau hyperphosphorylation.

5.4. Apocynum venetum

This plant belongs to the Apocynaceae family and has shown a wide range of pharmacological activities such as antihypertensive, heart and liver protection, antioxidant, antidepressant and anti-anxiety effects (60). The essential oils of Apocynum Venetum contain the active ingredient Quercetin (Que) and have recently been shown in studies of its anti-Tauopathy effects (61). This flavonoid compound prevented Tau hyperphosphorylation in okadaic acid-treated HT22 cells by inhibiting CDK5 enzyme activity (61). Increased Que release with nanobiocatalysts has recently been reported and it has been suggested that this compound may reduce tau aggregation (62). However, the bioavailability of Que is limited due to the blood-brain barrier (BBB), so researchers have tried to formulate this compound to overcome this limitation. Recently, quercetin-loaded exosomes were produced and studied on TNFs generated by hyperphosphorylated Tau protein. The results of their study suggested that the formulation was able to cross the BBB and increase Que bioavailability in mice brains. Also, quercetin-loaded exosomes were shown to improve cognitive function inhibit the production of TNFs, and reduce Tau phosphorylation (63). Endoplasmic reticulum stress has been shown to play an important role in Tau hyperphosphorylation. The results of a study showed that Que has the ability to reduce ER stress and this leads to a decrease in Tau phosphorylation (64). Therefore, it seems that Que could be a good treatment option to prevent tauopathy in neurodegenerative diseases.

5.5 Centella asiatica

Centella Asiatica belongs to the Apiaceae family and has strong antioxidant and anti-inflammatory properties. The effects of neuroprotection and cognitive function improvement have been demonstrated in the AD model (65). The extract of this plant has recently been shown to be able to reduce the phosphorylated Tau protein in the AD model hippocampus (66). The most important compound in this plant is Asiatic acid (AA), which belongs to the group of triterpenes and its high antioxidant properties have been reported (67).

This compound has been shown to have therapeutic effects in tauopathy leading to Parkinson's disease (68). The mechanism of its therapeutic effects was attributed to the transfer blocking of α-syn into the mitochondria (68). AA obtained from Centella Asiatica can cross the BBB and exert its pharmacological effects. This compound shows the ability to reduce phosphorylated Tau in the AD model of rats and it seems that its neuroprotective effects are related to the Akt/GSK3β pathway (69). AA was effective against Aβ25-35-induced neurotoxicity in PC12 cells, reduced apoptosis, prevented IκBα degradation, and reduced Tau protein hyperphosphorylation (70). This effect was attributed to the activation of the PI3K / Akt / GSK-3β signaling pathway (70). Thus, Centella Asiatica can be used to prevent AD development.

5.6. Rhus succedanea L

This plant has been considered in the treatment of tauopathy due to fisetin. This compound has been shown to reduce hyperphosphorylated Tu levels in primary neurons (71). Fisetin has the ability to activate autophagy and transcription factor EB (TFEB), reducing Tau phosphorylation (71). Inhibition of β-strand formation and Tau protein aggregation by fisetin extracted from Rhus succedanea L. has recently been reported (72). This polyphenolic compound has the ability to interact directly with the Tao protein by forming hydrogen bonds and van der Waals forces, preventing the formation of secondary Tau protein structures (72). These results suggest that fisetin can be considered a promising treatment option for tauopathy.

5.7 Maclura pomifera

This plant has antioxidant, anti-inflammatory, and neuroprotective properties and its methanolic extract prevents the fibrillization of Tao protein (73). It also inhibited iNOS and NF-κB at IC50 concentrations of 6-13 μg/ml (73). Its components that have been shown to have anti-tauopathic effects include Morin (58), osajin (OSA), and pomiferin (POM) (73). Morin extracted from this plant has been shown to be able to prevent Tau hyperphosphorylation and its accumulation in TNFs and exerts this effect by reducing the activity of glycogen synthase kinase 3β (GSK3β) (74). These results suggest that Maclura pomifera can be considered a promising treatment option for tauopathy.

5.8 Allium sativum L

Dietary aged garlic extract (AGE) has shown extensive pharmacological properties such as antioxidant, anti-inflammatory, and anti-TNFs formation effects in studies (75-77). Its effects on tauopathy were studied and the results showed a decrease in phosphorylated Tau in mice. These effects were attributed to reduced GSK-3β activity in the brains of AGE-receiving mice (77). Recently, Luo et al. (2021) investigated the mechanisms of protective effects of garlic extract in cognitive impairment and AD (78). They attributed the most important neuroprotective mechanism of garlic extract in AD to reduced cerebral Aβ levels. However, in future studies, it is suggested that the effect of the extract of this healing plant be investigated on Tau phosphorylation. Therefore, it seems that Allium sativum could be a good treatment option to prevent tauopathy in neurodegenerative diseases.

5.9 Ginkgo biloba

This plant belongs to the Ginkgoaceae family and its extract has shown extensive pharmacological properties. The extract of this plant has shown neuroprotective effects in AD conditions. Recently, the effects of EGb761 extract on AD rat model induced by Aβ in Tau phosphorylation and the activity of GSK-3β and PP2A were studied and the results showed that this extract reduces Tau phosphorylation (79). It also improved spatial memory and reduced the expressions of GSK-1B and PP2A (79). Reduced Tau phosphorylation by the

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EGb761 extract appears to be associated with decreased activity of GSK-3β and PP2A. In another study, EGb761 extract decreased Zn-induced Tau phosphorylation at Ser262 by reducing GSK-3β activity. The extract also reduced ROS and reduced nerve cell death (80). In human P301S tau mutant-transgenic mice treated with EGb761 extract for 5 months, inhibition of p38-MAPK and GSK-3β activities was seen, resulting in decreased tau phosphorylation (81). Activation of PI3K/Akt pathway by Ginkgolide A isolated from Ginkgo biloba also reduced Tau phosphorylation (82). In Table 1 some plants with their components that showed inhibition of Tau phosphorylation are listed.

Table 1. Some medicinal plant and their natural products inhibited Tau protein.

Plant	Secondary metabolite	Authors	Study type	Activities	Action Mechanism	Ref
Curcuma longa	Curcumin	Miyasaka et al. (2008)	In vivo Mutant tau-expressing worms	Curcumin reduced the expression of Unc and Tao protein and reduced neuritic disorders.	Prevent insolubilization of Tao aggergates and stabilized microtubules	(44)
		Mohorko et al. (2009)	Pilot- brain sections	Curcumin bind to hyperphosphorylated Tau proteins and TNFs in brain sections of AD and PSP patients and detected them.	Inhibition of Tau aggregation and polymerization	(48)
		Yanagisawa et al (2018)	In vivo- male rTg4510 mice	Cognitive defects and Tau protein aggregation were inhibited.	Inhibition of Tau aggregation	(49)
Rosmarinus officinalis	Rosmarinic acid	Cornejo et al (2017)	In vitro	Tau fibrillization and β-sheet assembly was inhibited.	Binding to steric zipper and occupied amyloid pharmacofore	(53)
Vitis vinifera	Resveratrol (RVS)	Sun et al (2019)	Mouse Model of Tauopathy	RVS significantly reduced cognitive deficits and hyperphosphorylated Tau protein. Neuroinflammation and synapse losses decreased as results of RVS administration.	Inhibiting Tau aggregation by preventing uptake of extracellular tau oligomers	(57)
		Yu et al (2018)	In vivo- Transgenic Mice	Tau aggregation was reduced by increasing the solubilizable tau.	RVS can interfere with late stage of Tau aggregation.	(58)
		Schweiger et al (2017)	In vitro- primary cortical neurons	Hyperphosphorylated Tau protein was reduced significantly in primary cortical neurons as results of RVS treatment.	Increasing the activity of protein phosphatase 2A (PP2A) enzyme responsible for dephosphorylating of Tau protein.	(59)
Apocynum venetum	Quercetin (Que)	Shen et al (2018)	In vitro- HT22 cells	Que significantly reduced Tau aggregation in okadaic acid-treated HT22 cells	Inhibit the CDK5 enzyme activity responsible for hyperphosphorylation of Tau protein.	(61)
		Kumar et al (2019)	In vitro	Que inhibit strongly tau aggregation via nanobiocatalysts	Change in conformational structure of Tau protein via hydrophobic interactions	(62)
		Qi et al (2020)	In vivo- AD mice	Exosomes loaded with Que rocked up cognitive function and inhibited TNFs.	CDK5 inhibition and Tau hyperphosphorylation reduced significantly.	(63)
		Chen et al (2016)	In vitro- SH-SY5Y cells	Que results in inhibition of Tau phosphorylation by reducing ER stress induced by okadaic acid	Enhamcement of AMPK activity and inhibition IREα and pERK phosphorylation	(64)
Centella asiatica	Asiatic acid (AA)	Chiroma et al (2019)	In vivo- rats	Improved cognitive function and decreased Ache, MDA, phosphorylated Tau and oxidative stress	Downregulation of CDK-5 expression by Akt/GSK3β pathway	(66)
		Ahmad Rather et al (2019)	In vivo- rats	AA reduced phosphorylated Tau, oxidative stress and apoptosis		(69)
		Cheng et al (2018)	In vitro-PC12 cell line	Tau hyperphosphorylation was reduced by treatment of PC12 cell line with AA.	PI3K/Akt/GSK-3β pathway was activated by AA and Tau phosphorylation reduced.	(70)
Maclura pomifera	Morin, osajin (OSA) and pomiferin (POM)	Abourashed et al (2015)	In vitro- HL-60 cells	OSA and POM overexpressed NSAID activated gene (NAG-1) gene and reduced the expressions of iNOS and NF- κB proteins. Tau fibrillization reduced by both compounds.		(73)
		Gong et al (2011)	In vitro- human neuroblastoma cells	Morin strongly reduced tau phosphorylation.	Reduced the activity of glycogen synthase kinase 3β (GSK3β)	(74)
Allium sativum L		Chauhan (2006)	In vivo- transgenic mice	aged garlic extract (AGE) reduced Tau protein phosphorylation	By reducing GSK-3β activity	(77)
Ginkgo biloba	Ginkgolide A	Zeng et al (2018)	In vivo- Rats	EGb761 extract reduced hyperphosphorylation of Tau protein.	By reducing GSK-3β and PP2A activity	(79)
		Kwon et al (2015)	In vivo- Rats	EGb761 extract reduced hyperphosphorylation of Tau protein. It also increased nerve cell viability and reduced ROS production.	By reducing GSK-3β	(80)
		Qin et al (2018)	In vivo- Human P301S tau mutant-transgenic mice	EGb761 extract inhibited Tau hyperphosphorylation, increased cognitive function and showed anti-inflammation properties.	By reducing p38-MAPK and GSK-3β activity.	(81)
		Chen et al (2012)	In vitro- N2a cell line	Ginkgolide A increased cell viability and reduced hyperphosphorylation of Tau protein at Awe	PI3K/Akt pathway activation by Ginkgolide A	(82)
	Plant extract	Maveddat et al. (2022)	In vitro- SH-SY5Y cell line	Plant extract reduced tau phosphorylation and increased cell viability	-	(83)

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4. Conclusion

The herbs listed in the current review have shown great potential in reducing tauopathy in neurodegenerative diseases. In these diseases, hyperphosphorylation of Tau leads to the insolubility of Tau and its deposition in TNFs, which has shown a significant positive correlation with the exacerbation of clinical symptoms, especially in AD. Therefore, herbs or natural compounds derived from them that prevent Tau phosphorylation can be considered useful treatment options in the treatment of tauopathy. Most researchers studied the effect of extracts of these plants or their natural compounds done in vitro or on animal models. It seems that clinical studies are necessary to study their effects and if their therapeutic effects are confirmed, they can be suitable options for the development of drugs with low side effects and high effectiveness.

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Conflict of Interest Statement

There is no conflict of interest among authors.

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