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NATURE-BASED TAU PROTEIN AGGREGATION INHIBITORS AS VALUABLE THERAPEUTIC COMPONENTS FOR TREATING ALZHEIMER'S DISEASES

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ABSTRACT

Background: Alzheimer's disease is progressive degenerative disorders of the brain that begins with memory impairment and eventually progresses to dementia, physical impairment, and death. Tau protein belongs to the family of microtubule association protein. They are mainly present in neurons, where they do important work; they assemble tubulin monomers into the microtubule networks. Molecular analysis depicted that abnormal phosphorylation might be an important event in the pathogenesis where tau is the remarkable marker of the neurodegenerative process.

Methodology: This review article was written after collecting a huge amount of latest literature on Tau protein inhibitors from varied pharmaceutical databases like ScienceDirect, PubMed, Google Scholar, etc. by using specific keywords. The collected data was appropriately classified and justified.

Results: The article moreover focuses on various natural products [Plant-derived (paclitaxel, curcumin, oleocanthal, diallyl disulfide, emodin, S-allyl cysteine, cinnamaldehyde, tanshinone-IIA,myricanone, and rosmarinic acid); Microbes-derived (adriamycin, daunorubicin, geldanamycin, rubellin-B, rubellin-D, rubellin-E, minocycline, epithilone-D, and fulvic acid); and Marine macroorganism-derived (peloruside-A, manzamine-A, palinurin, and hymenialdisine)] that acts as tau-protein aggregation inhibitors.

Conclusion: This fascinating literature concluded that the low molecular-weight natural inhibitors will positively provide research information or serve as a futuristic lead to enthusiastic medicinal chemists and curious pharmacologists in managing Alzheimer's disease by opening application avenues via pharmacotherapeutic approach.

Keywords: Alzheimer's disease, Tau protein, Inhibitors, Natural, Microbes, Marines

GRAPHICAL ABSTRACT

Nature-Based Tau Protein Aggregation Inhibitors as Valuable Therapeutic Components for Treating Alzheimer's Disease

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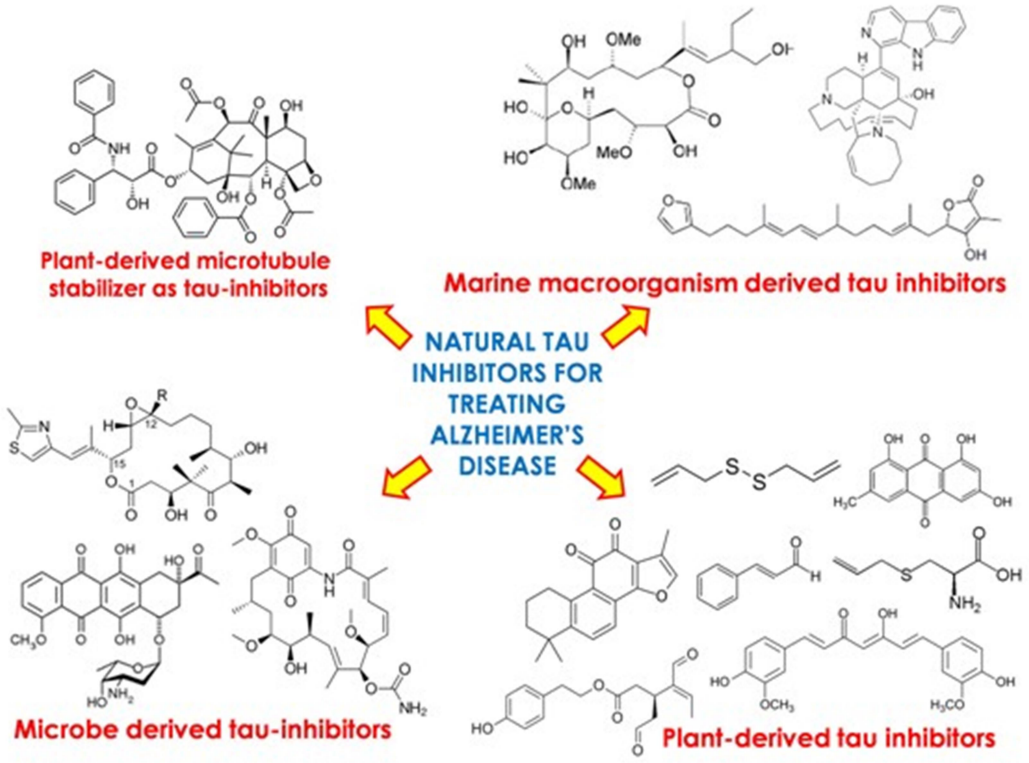


INTRODUCTION

Alzheimer's disease is a progressive degenerative disorder of the brain that begins with memory impairment and eventually progresses to dementia, physical impairment, and death.[1] The most common cause of dementia among older people is Alzheimer's Disease.[2] The daily life of people gets affected due to loss of cognitive functions and behavioral abilities.AD is certainly not the result of a single operative mechanism, but more likely comprise one or more possess that lead to intrinsic neuronal destruction.[3]

History

In 1907, Dr. Alois Alzheimer described the symptoms of his 51 years old patient Auguste Deter at the state asylum in Frankfurt Germany.[4] Dr. Alzheimer had examined her brain by application of new silver staining histological technique microscopically upon her death. When he studied her autopsy he observed that there is a presence of neuritic plaques, neurofibrillary tangles, and amyloid angiopathywhich are the hallmark of this disease.[5]

Causes of Alzheimer Disease

There are various factors which leads the healthy brain to AD brain:

Neurofibrillary tangles

Tau protein phosphorylates and aggregates within neuronal cytoplasm which ultimately forms neurofibrillary tangles.[6]when tau phosphorylates it detaches from the microtubule, thus it dissociates, and the cytoskeleton structure gets dispersed. A small number of neurofibrillary tangles are universal consequences of aging.[7]An increase in the population of tangles is theprime and possibly the main mechanism of neuronal death in AD.[8] Neurofibrillary tangles mostly occurs in the areas of the hippocampus which are involved in the storage of permanent memories, and hence memory is impaired in the early stages of AD.[9, 10]

Senile Plaques

Senile plaques are formed from the β-amyloid peptide. It is a peptide of 39-43 amino acid residues produced by proteolytic cleavage of a large precursor known as the amyloid precursor protein (APP), which is encoded by a gene located at chromosome 21 in humans.[11] Enzyme secretase (secretase and γ-secretase) is responsible for proteolysis of APP at position 597 and 637-639 and the release of β-amyloidfragments.[12] Aβ is a major protein constituent of the senile plaques found in the brain of AD patients.[13]

Role of Gene

Genes are involved in the development of AD as some mutations increase the production of short forms β-amyloid while the others favorthe formation of long-form β-amyloid which aggregates more readily. Mutation in other genes coding for the novel proteins presenilin-1 and presenilin-2 are reported to account for the majority of early-onset, familial dominant inherited AD.[14]

Role of Environmental Factors

Metals such as aluminum and lead are linked with a number of neurodegenerative disease including AD and causes toxicity to a number of organs in the human body.[15,16,17]Copper and arsenic disrupt the homeostasis of amyloid-β-protein.[18,19]Chronic exposure to pesticides like organophosphates leads to cognitive and psychomotor impairment.[20,21] Metals like aluminum copper, iron, lead, cobalt, cadmium, manganese, mercury, arsenic, selenium, and zinc directly or indirectly affect the healthy brain and may increase the chances of neurodegeneration. Insecticides or pesticides such as organochlorides and organophosphates may increase the risk of dementia in AD.[22]Industrial and commercial pollutants such as brominated flames retardants show impaired learning and memory and simultaneously decrease hippocampus cholinergic receptors.[23]Air pollutants involve nickel like toxic particulate matter.[22] In the nickel nanoparticles model of air pollution, there is an increased report in the levels of Aβ-40 and Aβ-42 levels in mice brain.[24]

Stages of Alzheimer's disease

The stages of AD follow the pattern in order to affect the cell types, cellular layers, and brain regions.[7] In stage-I, the first nerve cell in the brain develop neurofibrillary lesions located in layer pre-alpha of the trans-entorhinal region. Severe as well as mild involvement of the pre-alpha layer of the entorhinal cortex occurs in stage-II. People with this type of pathology are cognitively impaired that is why these stages; stage I and stage-II are clinically designated as silent stages of AD. Stage-III and stage-IV involves mild impairment of cognitive function.There are various neurofibrillary lesions that occur in stage-III. In the same stage, the first extracellular tangles also appear. In the later stage;*i.e.* stage-IV, the deep pre-alpha layer develops extensive neurofibrillary lesion in isocortical association areas. The symptoms of stage-V and stage-VI are found in extremely demented patients at the time of death.[25]

Structure of Paired Helical Filaments (PHF)

Most of the neurological disease involves the formation of dense fibrous aggregates. These

aggregates are morphologically different from the normal components of the neuronal cytoskeleton. There are two types of filaments; PHF (paired helical filament) and SF (straight filament) where the former constitutes the principal component that is neurofibrillary tangles in AD.[26, 27]

PHFs are the double-helical stock of morphological units, each with a C-shaped cross-section displaying three domains.[28,29] When seen under an electron microscope, PHFs have a fuzzy-coat that can be stripped off by pronase to leave a pronase-resistant core.[30-31] The earlier immunological studies showed that tau is associated with PHF as well as with some anti-tau antibodies which decorate fuzzy PHF's but not stripped PHF's.[31]The second minor class filaments found in the AD brain are straight filaments, having 15 nm wide dimension when seen in an electron microscope.[26] Isolated filaments from AD brain and antibody labeling of sectioned material shows SF's share epitope with PHF's.[27]

TAU PROTEIN

Tau protein belongs to the family of microtubule association protein.[32] They are mainly present in neurons, where they assemble tubulin monomers into the microtubule networks that keep the cell shape and it acts as axonal transport. The human adult brain consists of six different isoforms which are regulated by an alternative splicing mechanism. Tau proteins are major components of intraneuronal and glial fibrillar lesions. Molecular analysis depicted that abnormal phosphorylation might be an important event in the pathogenesis where tau is the remarkable marker of the neurodegenerative process.[33]

Gene Organization

The human tau gene is one of the unique and spotted over a hundred kb on the long arm of chromosome-17, denoting the position at 17q21 which contains 16 exons.[34-36]

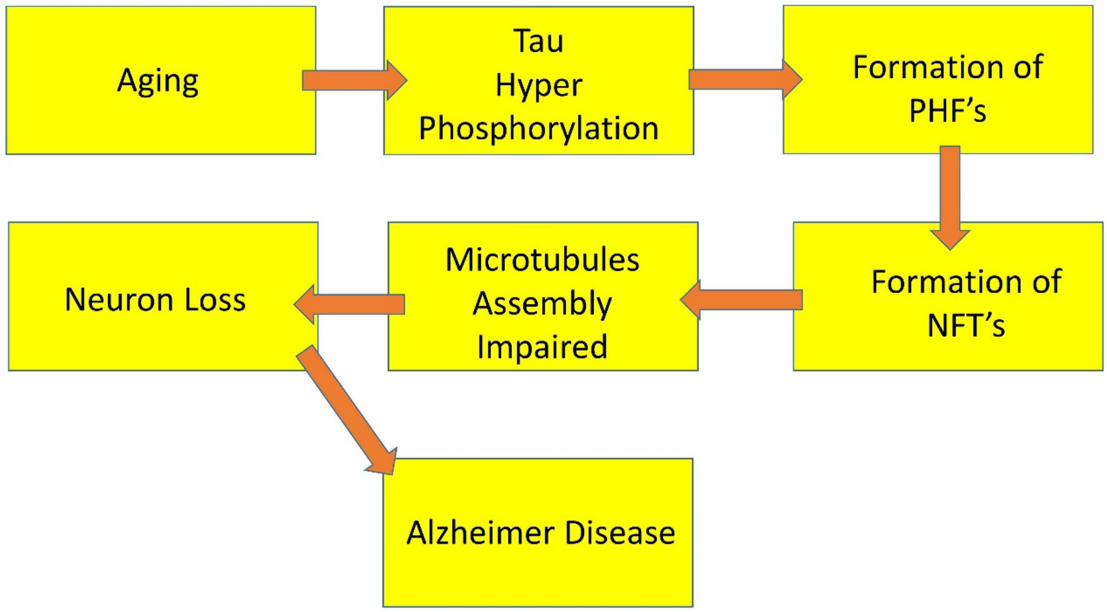
Splicing

Primary tau transcript contains 16 exons but three of them; exons 4A, 6, 8 are not present in any mRNA in the human brain.[37,38] Exon-1 is a part of the promoter and is transcribed but not translated. Exon-14 is usually identified in mRNA. Some of the consecutive exons are 1, 4, 5, 7, 9, 11, 12, 13 [36-41] and 2,3,10 are brain-specific of adult.[36] Alternative splicing of these three exons allows for six combination viz. (2-3-10-) , (2+3-10-) , (2+3+10-) , (2-3-10+) , (2+3-10+) , (2+3+10+).[39,40,41]Primary tau transcript gives rise to six mRNA.[39,40,42]

Structure and Role of Tau Protein

Tau isoforms are produced from a single gene through alternative mRNA splicing.[25] In

the adult brain, tau protein consistsof a family of six isoforms which range from 352 to442 amino acidwith amolecular weight range from 45 KDato 65KDa.[39, 40] There are two terminals present in tau; one is the carboxy-terminal (C-terminal) and the other is amino-terminal **(Figure 1)**. Tau isoforms differ from each other by the presence of either 3 or 4 repeat regions in the C-terminal and the absence or presence of one or two inserts in the amino-terminal part (N-terminal).[43,44]Tau isoforms are differentially determined during growth so that they have specific physiological roles independently.[45] Tau isoforms may be dispersed in the neuronal subpopulation.[33] N-terminal called as projection domain because it projects from the microtubule surface where it interacts with other cytoskeleton elements as well as the plasma membrane[46,47]whereas C-terminal is called the microtubule-binding domain because it binds on microtubules and stabilizes it.[33]



PHF's: Paired helical filaments **NFT's: Neurofibrillary tangles**

Figure 1: Tau hypothesis of Alzheimer's disease progression

Tau Aggregation Inhibitors

Several natural products are assessed for their effectiveness in the treatment of AD.[45,46] Recent clinical trialsput forward that tau-based therapies might be more efficacious than anti-Aβ treatments for patients already shows AD symptoms.[8,4,20] Few dietary sources including extract as well as preparation of ethnobotanical plant

components are operational in neurodegenerative disorders.[47,48]

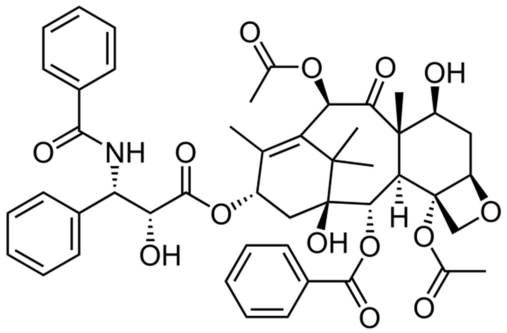
Natural products-derived Tau-protein aggregation inhibitors[49, 50]

Many anti-tau natural products made originated from plants such as curcumin, a linear diarylheptanoide present in 66.8% concentration of an optimized turmeric (*Curcuma longa*) extract which acts as an anti-oxidant and found to reduce tau levels **(Figure 2)**.

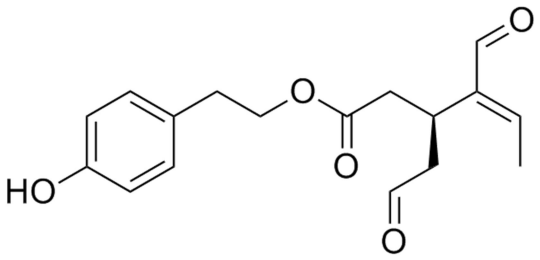
Myricanone has been identified as a potent macrocyclicdiarylheptanoid from bayberry root bark (*Myrica cerifera*) that reduces tau levels*ex-vivo* in a cell culture model of tauopathy.

Epicatechin 3-gallate derived from green tea (*Camellia sinensis*) has shown tau production inhibition with an IC_{50} valueof 1.8 µM.

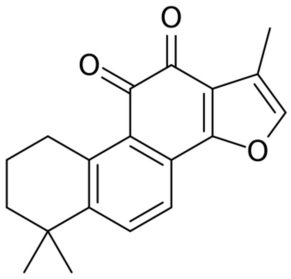
Cinnamaldehyde extracted from cinnamon (*Cinnamomum zeylanicum*) has been perceived to inhibit the aggregation of human tau *in vitro* and as well as procyanidin oligomers of catechins / epicatechins which displayed similar inhibitory activity.



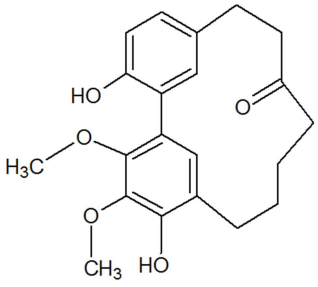
Paclitaxel



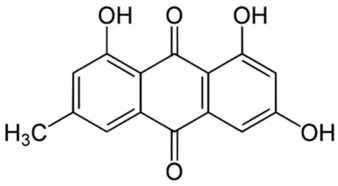
Oleocanthal



Tanshinone



Myricanone



Emodin

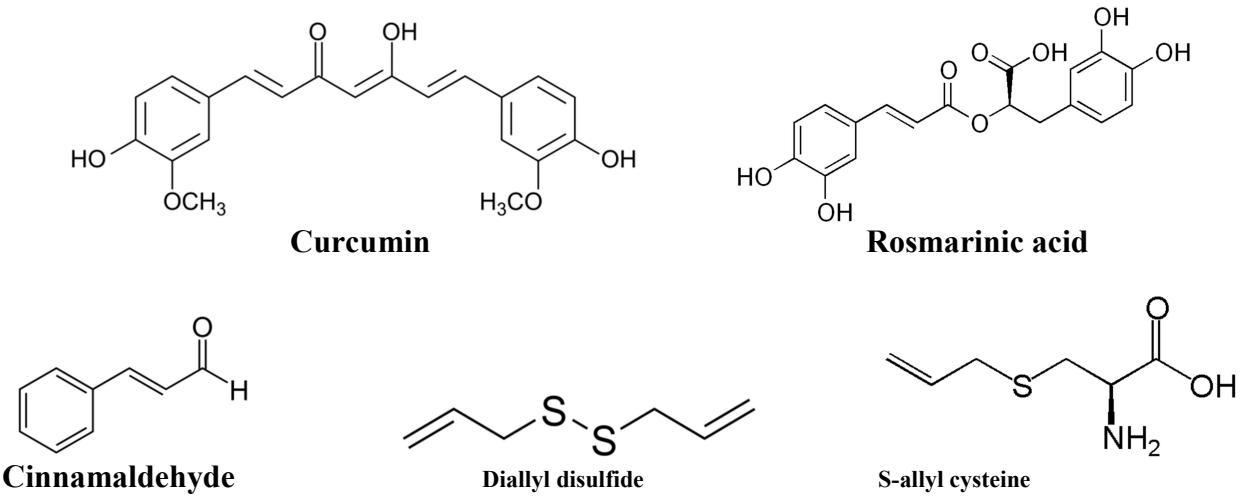


Figure 2: Plant-derived tau-aggregation inhibitors

Rosmarinic acid is the polyphenol and the main active ingredient of *Salvia officinalis* and is used for improving cognition and memoryby reducing tau hyper-phosphorylation. It also blocks several AD pathways such as reactive oxygen species formation, lipid percolation, DNA fragmentation, caspase-3 activation, and Aβ accumulation.

Tanshinone IIA, a norditerpine from red sage (*Salvia miltiorrhiza*) has been an active candidate against neurotoxicity and tau hyperphosphorylation.

Isoflavine from the water-soluble extract of Chinese Yew (*Taxusyunnanensis*) has a stimulatory effect on GSK-3B at 10μm concentration. It preferentially phosphorylates serine reduction rather than threonine reduction on recombinant human tau protein.

Paclitaxel derived from *Taxusbrevifolia* is a microtubule stabilizer drug that shows positive results against neurodegenerative tau properly.[44]

Oleocanthal from olive oil (*Oleaeuropaea*) has shown inhibition of filament formation of the longest tau T40.

Emodin is anthraquinone isolated from root and rhizome of rhubarb (*Rheumpalmatum*) whicheffectively inhibits PHF's.

Steroid glycoside ginsenoside from Asian ginseng, *Panax ginseng* showed *in vivo* and *in vitro* reduction of neurotoxicity and tau hyperphosphorylation by enhancing the activities of PP-2A.

Garlic (*Allium sativum*) extract has sulfur-containing constituents S-allyl-cysteine which is water-soluble component of garlic and diallyl-disulfide which is lipid-soluble compound.These components have

been found to possess anti-amyloidogenic, anti-inflammatory, and anti-tangle effects.

Microbes-derived Tau-protein aggregation inhibitors[51, 52]

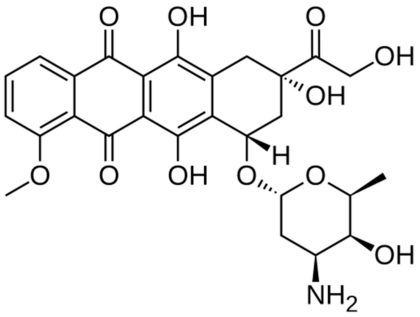
Anti-tau activities are not limited to plant sources, the bacterial-derived and fungal-derived compounds also show tau reducing activity. Daunorubicin and adriamycin, are the anthraquinones isolated from the bacterium *Streptomyces peucetius* have displayed tau aggregation inhibitor activity.

From the fungal kingdom, Rubellin-B, Rubellin-D, and Rubellin-E were isolated from the phytogenic fungus *Ramularia-collocygni* which were found to inhibit the formation of tau aggregates with IC_{50} values of 1.2 µM, 0.9 µM, and 0.9 µM, respectively.

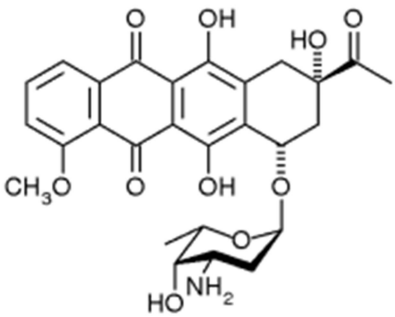
Minocycline **(Figure 3)** is a synthetic derivative of tetracycline that shows neuroprotection and reduces tau hyperphosphorylation. It is currently being tested in phase-II clinical trials in AD.[8, 4, 20]

Experiments were conducted on transgenic mice having forebrain tau pathology where macrocyclic-polyketideepothilone-D was found to inhibit the production of tau. However, tau tangles are still present in the optic nerve, which is expected.

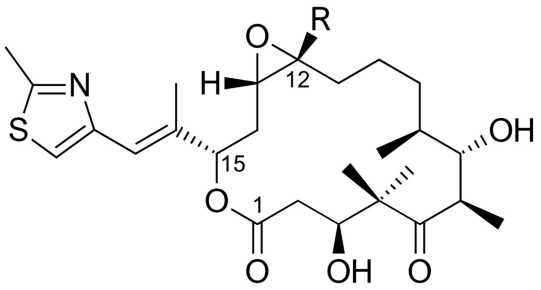
The higher-order polyphenolic, known as fulvic acid has been found to inhibit the aggregation of tau fibrils *in vitro* with an IC_{50} value of 37 µM and promote disassembly of tau fibrils with a DC_{50} value of 95 µM.



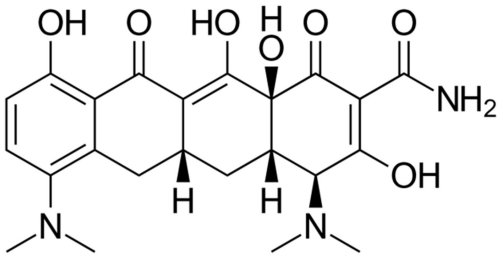
Adriamycin



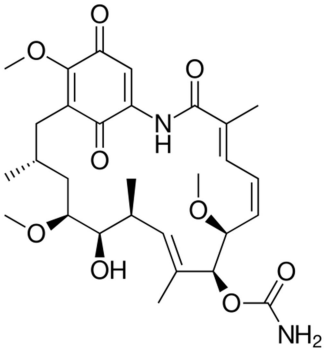
Daunorubicin



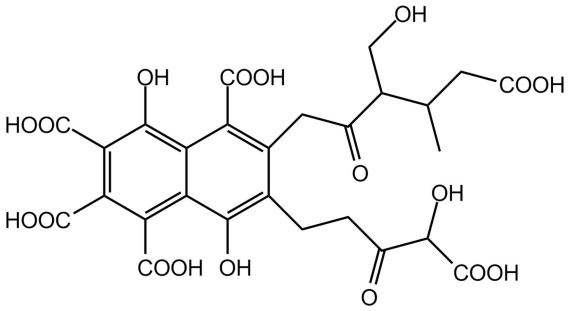
Epithilone-D



Minocycline



Geldanamycin



Fulvic acid

Figure 3: Microbes-derived tau-aggregation inhibitors

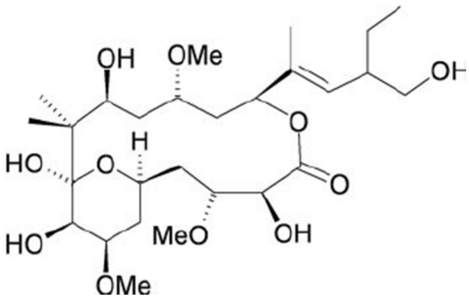
Marine microorganism-derived Tau-protein aggregation inhibitors[53, 54]

The marine organism also produces tau inhibiting compounds such as sponges and sea snails **(Figure 4)**. Peloruside A, isolated from marine sponge *Mycale hentscheli*, displayed the same mode of action as paclitaxel.

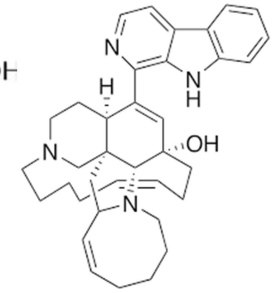
Palinurin is a linear furanosesterterpene from sponges of the genus *Ircinia* which emerged as a non-ATP competitive inhibitor of GSK-3B with an IC_{50} value of 4.5 µm, thereby resulting in the reduction of tau hyperphosphorylation.

Manzamine A and Haliclona A were isolated from two sponges; *Axinellaverrucosa* and *Acanthellaaurantiaca*. The compounds inhibited cyclin-dependent kinases and displayed IC_{50} values of 10 µm and 35 µm toward GSK-3β, respectively.

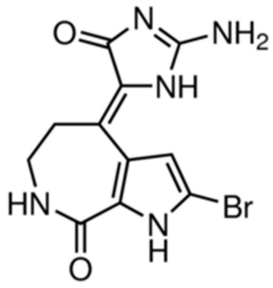
Bis-indole alkaloidindirubins such as 6-bromoinduribins were isolated from the Mediterranean mollurks *Hexaplextrunculus* and its synthetic derivatives 6-bromoinduribins shows selectivity towards an inhibitor of GSK-3B with IC_{50} values of 45 µm and 5 µm, respectively. This impressive result showed that brominatedbis-indoles may prove to be good candidates to develop for their ability to reduce tau.



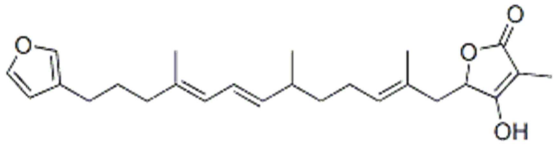
Peloruside-A



Manzamine-A



Hymenialdisine



Palinurin

Figure 4: Marine microorganism-derived tau-aggregation inhibitors

Tau Aggregation Inhibitors in Clinical Trials[55, 56]

Mainly, amyloid plaques and neurofibrillary tangles are responsible for the AD with associate damage synapses and neurons leads to dementia. Amyloid beta and tau proteins are primitively component of plaques and tangles. Recently, researcher focused on the tau inhibitors because of letdown of amyloid beta targeting treatment. At initial, tau inhibitors shown action by inhibiting of kinase or aggregation tau or stabilization of microtubules but these approach obsolete due to its toxicity and lack of efficacy. Currently, many tau aggregator inhibitors in clinical trials as an immunotherapies, which shown potential preclinical studies.

Table 1: Enlist of Tau inhibitors in clinical trials

S. No.	Agents	Mechanism of class	Clinical Trial Phase
1	TRx0237 (LMTX)	Tau protein aggregation inhibitor	III
2	AADvac1	Active immunotherapy	II
3	ABBV-8E12	Monoclonal antibody	II
4	BIIB092	Monoclonal antibody	II
5	IONIS MAPTRx	Microtubule-associated tau (MAPT) RNA inhibitor; antisense oligonucleotides	I
6	ANAVEX 2-73	GSK-3β inhibitor	II
7	Methylene Blue	Tau protein aggregation inhibitor	II
8	RO7105705	Monoclonal antibody	II
9	Nicotinamide (Vitamin B_3)	Histone deacetylase inhibitor	II
10	Nilotinib	Tyrosine kinase inhibitor	II
11	Tideglusib	Tau aggregation inhibitor	II
12	AZD0530 (Saracatinib)	Tyrosine kinase Fyn inhibitor	II
13	JNJ-63733657	Hyper phosphorylated tau peptide	I
14	RO7105705	Hyper phosphorylated tau peptide	II
15	TPI-287	Hyper phosphorylated tau peptide	I
16	BIIB-080	Hyper phosphorylated tau peptide	I
17	LY3303560	Immunotherapy binds and neutralizes tau	II
18	Minocycline	Hyper phosphorylated tau peptide	II

CONCLUSION

This natural product-based fundamental review article provided a thorough focus over the Alzheimer's disease, history, underlined causes, stages, pathogenesis, the role of environmental factors, paired helical filaments, the role of genes, gene organization, splicing, along with the structure and role of Tau-protein. The article moreover focuses on various natural products [Plant-derived (paclitaxel, curcumin, oleocanthal, diallyl disulfide, emodin, S-allyl cysteine, cinnamaldehyde, tanshinone-IIA,myricanone, and rosmarinic acid); Microbes-derived (adriamycin, daunorubicin, geldanamycin, rubellin-B, rubellin-D, rubellin-E, minocycline, epithilone-D, and fulvic acid); and Marine macroorganism-derived (peloruside-A, manzamine-A, palinurin, and hymenialdisine)] that acts as tau-protein aggregation inhibitors. This fascinating literature concluded that the low molecular-weight natural inhibitors will positively provide research information or serve as a futuristic lead to enthusiastic medicinal chemists and curious pharmacologists in managing Alzheimer's disease by opening application avenues via pharmacotherapeutic approach.

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Conflict of Interest

The authors stated No Conflict of Interest for the Publication of this review article in the Journal.

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Authors' Contribution

KRD: Physically authored the whole manuscript

ASM: Complete literature survey performed

DKM: Made Figures, Wrote Structured Abstract, Drawn Graphical Abstract, Set References

UNM: Final reviewing of this manuscript, provided suggestions, and corrected few errors

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