Role of Tau Protein in Alzheimer Disease and its Inhibitors from Plants

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Abstract
Alzheimer is a common neurodegenerative disease that affects 45 million people worldwide. Pathogenesis usually begins with formation of plaques and neurofibrillary tangles due to abnormal folding of amyloid beta and tau proteins. Tau proteins are important member of microtubule associated proteins and involved in constitution of microtubules network in neurons which play major role in progression of Alzheimer disease. Hyper phosphorylation and aggregation of Tau protein on chromosome 17 may be the sign of several neurodegenerative pathologies like Alzheimer disease (AD), Parkinsonism, fronto-temporal dementia and Pick disease. The complete cure of AD is not possible be with already marketed drugs. From this review article it is concluded that Tau protein is an important biomarker of Alzheimer disease. Usage of extracts from various plants i.e Danggui Longhui Wang, Hymenialdisine, Morin, Salvia officinalis, Ginseng helps in effective treatment of disease and hence a step forward to reduce the prevalence of Alzheimer disease.

1 Introduction
Alzheimer disease is a common neurodegenerative disease that silently starts with impairments in episodic memory and involving 45 million people worldwide as its potential target¹. Alzheimer disease is mostly linked with age which means that after 65 years of age the prevalence of AD will be double with every 5 years increase in age. Loss of memory begins in mesial temporal region of brain². Pathogenesis usually begins with formation of plaques and neurofibrillary tangles due to abnormal folding of amyloid beta and tau proteins³. E4 allele of apolipoprotein (APOE) is also an important genetic risk factor⁴. Diagnosis of Alzheimer disease is usually associated with patient history with some advanced diagnostic tools like positron emission tomography (PET), magnetic resonance imaging (MRI) and computed tomography (CT scan)⁵. Prognosis of AD is usually poor because life expectancy progressively decreases with symptoms and only less than 3% people lives life with more than 14 years⁶-⁷. AD not only involves affected person as its target but sometimes it also cause difficulties for caregivers specially when caregiver is spouse or patient is treated at home⁸.

Neuropathology of AD involves degeneration in temporal and parietal lobes followed by frontal cortex atrophy due to progressive loss of neurons in these regions⁹. Biochemistry studies on AD shows that it is commonly a proteopathic disease in which two important proteins amyloid beta and Tau protein abnormally folded in various parts of brain¹⁰. Reduction in release of neurotransmitter acetylcholine in brain is also one of important contributing factor in AD¹¹. Beta amyloid peptides accumulate in brain that are toxic to neurons and it leads to apoptosis by disturbing calcium ion homeoeostasis¹². Excess production of free radicals in certain regions of brain leads to imbalance between normal anti-oxidative mechanisms is also major pathway in mechanism of AD¹³. Diet rich in fats and carbohydrates have higher risk of AD while caffeine and red wine is considered as protectants or have low risks of AD¹⁴-¹⁶. Life style changes like engaging in activities like reading, board games, crosswords puzzles and interaction with people show significant improvements in disease progression¹⁷. Although there is increased research on AD but exact treatment is not yet been developed and only five drugs are currently available in market which includes Glantamine, Rivastigmine, Tacrine,
Donepezil and memantine. Behavioral and psychological interventions are also effective along with pharmacological interventions in management of AD. It was brief introduction of Alzheimer Disease with some risk factors, its management and Pathophysiological mechanisms. This mini review article will also focus on Tau proteins and their role in progression of AD.

1.1 Role of Tau proteins in Alzheimer Disease

Tau proteins are important member of microtubule associated proteins and involved in constitution of microtubules network in neurons. Normally six isoforms of Tau proteins are produced in human by RNA splicing through single gene. Normal role of Tau proteins in brain is the polymerization and stabilization of microtubules but exact mechanism of this polymerization in not known yet. One of isoform of Tau phosphoprotein contains 79 serine and threonine phosphorylation sites. RNA splicing occur at exon 2, 3 and 10 of Tau gene and different isoforms are generated. Tau protein is heat stable protein which was identified in 1975. Hyper phosphorylation and aggregation of Tau protein on chromosome 17 may be the sign of several neurodegenerative pathologies like AD, Parkinsonism, fronto-temporal dementia and Pick disease.

For purification of Tau Protein polymerization and de polymerization cycles of tubulin with Tau protein were performed and protein was isolated by using phosphocellulose chromatography. Gel electrophoresis was performed which showed four bands which were analyzed by using electron microscopy. Elevated levels of Tau protein were found with 90% polymerizable tubulin in microtubules. Beef extract was used for preparation of microtubule protein in which 35% ammonium sulfate was used for saturation and subject to centrifugation. After centrifugation different methods were applied for detection of Tau protein. But overall it was found that only 8-10mg Tau protein is obtained from 1 kg of brain. It was also found that Tau protein is soluble in 2.5% perchloric acid but insoluble in 25% glycerol which provide a new foundation in purification methods of Tau protein.

Gene associated with Tau protein is commonly known as MAPT gene and found on q arm of chromosome 17. MAPT gene has two haplotype genes in inverted position which are H1 and H2. H1 is mostly involved in promoting certain neurodegenerative diseases like AD. Tau protein in phosphorylated form is detected in cerebrospinal fluid which provides basis for accurate diagnosis as in any neurodegenerative disease levels of abnormal Tau protein becomes significantly elevated in various regions of brain. Intensity of phosphorylation also vary among developmental stages which means it is more phosphorylated in embryonic CNS and less phosphorylated in adult CNS. Neurons contain 2-3 moles phosphate/mole of Tau protein. Tau protein is also involved in traumatic brain injury and chronic traumatic encephalopathy in which twisting of Tau protein into confused mass occurs. Hyper phosphorylation of Tau protein is mediated by three sets of enzymes Glycogen synthase kinase (GSK3), Mitogen activated protein kinase and neuronal cdc like kinase which all occurs at multiple sites in cells. Structure elucidation of Tau protein revealed that it has three sets of 18 amino acids in different sequences which are believed to be the binding sites for tubulin. Stability of cytoskeleton network in neurons is the responsibility of Tau protein so any changes in Tau protein leads to severe neurodegenerative disease.

In AD extracellular deposits of amyloid beta peptide and intraneuronal straight or paired helical filaments of phosphorylated Tau proteins are seen. When tau protein forms clumps and develop into lesions it constitute characteristic neuropathology of AD. When paired helical filaments (PHFs) of Tau protein were prepared from brain of AD patient 3 modified forms of Tau protein bands different from 6 isoforms bands of normal Tau protein were found. These modified bands were difficult to analyze so they were dephosphorylated and labeled at high temperature which were detected by using antibodies from isoforms. Tau protein is an important biomarker in AD so attempt to modify Tau protein was performed in which active vaccine AADvac1 has been developed and is in Phase 1 trial. Tau hypothesis for AD also states that Tau protein has six isoforms which contain 352-441 amino acids which when mutated leads to hyper phosphorylation of Tau protein with altered function and cell death.

2 Medicinal plants that Inhibit Tau protein Hyper-phosphorylation

2.1 Danggui Longhui Wang

It is a traditional Chinese herb which is used commonly in treatment of leukemia by inhibiting various kinase enzymes like tyrosine kinase and glycogen synthase kinase. Indirubin is considered as active constituent of Danggui Longhui Wang. Glycogen synthase kinase is also involved in hyper phosphorylation of Tau protein in AD. Activity of Indirubin was tested in-vitro for the treatment of AD and it was found that indirubin has potential as candidate of lead compound that is effective in treatment of AD. It was recommended that further evaluation should be carried out for effective results.

2.2 Hymenialdisine

Hymenialdisine is a substance found in marine sponges particularly in Agelasidae, Axinellidae and Halichondriidae families of marine sponges. It is also inhibitor of glycogen synthase kinase and tyrosine kinase recepotor. In vivo studies showed that Hymenialdisine efficiently inhibit hyper phosphorylation of Tau proteins.

2.3 Morin

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Morin is a yellow colored flavonol that can be found in *Maclura pomifera, Maclura tinctoria* and *Psidium guajava*. When Morin was tested in mice suffered from AD it was found that it effectively inhibit Hyper phosphorylation of Tau protein.

2.4 *Salvia officinalis*

*Salvia officinalis* commonly known as sage with major constituent Rosamirinic acid has shown beneficial effects on human brain activity but due to lack of evidences no conclusion regarding its activity against AD has been made yet. Leaves extract of *S. officinalis* leaves was evaluated on rat cultured pheochromosyotoma cells (PC12) cell lines which was incubated for 24 hours with Æ-ß amyloid proteins and Tau proteins. After incubation it was found that Rosamirinic acid reduced the Hyper phosphorylation of these proteins.

2.5 *Ginseng*

Panax ginseng is a traditional Chinese medicine that have been used over centuries for treatment of various diseases. Extract of *P. ginseng* with various ginsenosides was prepared and tested in vitro and in vivo. Results have shown that significant of improvements were seen against AD.

3 Conclusion

Tau protein is an important biomarker of Alzheimer disease. Usage of extracts from various plants i.e. *Danggui Longhui Wang*, *Hymenialdisine*, Morin, *Salvia officinalis*, Ginseng, helps in effective treatment of disease and hence a step forward to reduce the prevalence of Alzheimer disease.

4 Recommendation

It is recommended that the extracts from *Danggui Longhui Wang*, *Hymenialdisine*, Morin, *Salvia officinalis*, Ginseng, can be included for the management of Alzheimer disease.

5 Conflict of interest

Nil

6 Author’s contributions

AA: Topic selection References gathering for literature review, Abstract writing, Writing details of significance of plant extracts for Alzheimer’s disease

HZ: Corresponding author, Writing details of Alzheimer’s disease and role of Tau proteins, Final formatting of entire manuscript

MW: Topic selection, References gathering for literature review, Writing details of significance of plant extracts for Alzheimer’s disease

7 References


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