Austin Alzheimer's and Parkinson's Disease

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Review Article

# Alzheimer's Disease and the Compounds of Ligusticum Wallichii

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**Abstract**

*Ligusticum wallichii*, a famous hemorheologic agent of Chinese medicinal herb, was used to treat headache, rheumatic arthralgia, irregular menses and other diseases during ancient years. Today dozens of chemical compositions in this herb have been isolated and identified including butylphthalides, terpene, organic acid, alkaloid, polysaccharide and others compounds. These compounds contain many active ingredients such as tramethylpyrazine, ligustilide, ferulic acid, protocatechuic acid, and β-sit sterol. Interestingly, more and more studies showed that *Ligusticum wallichii* and its active ingredients can ameliorate cognitive function through increasing mitochondrial biogenesis, ameliorating cerebral ischemia, resisting oxidative stress, purging inflammatory reaction and anti-apoptotic. This paper reviews the current research findings about the active ingredients of *Ligusticum wallichii* to treat Alzheimer's disease and discusses the potential measures to intervene mild cognitive impairment or Alzheimer's disease.

**Keywords:** *Ligusticum wallichii*; Alzheimer's disease; Chinese herb

## Introduction

Alzheimer's disease (AD) is an aging neurodegenerative disease, accompanied by the distinctive pathology-senile plaque and Neuro Fibriler Tangles (NFTs). However, the pathogenesis is still unclear. Though there are many hypotheses for the pathogenesis of AD, they can't still explain some pathological changes and solve some needs in clinic. For example, β-amyloid cascade hypothesis is the mainstream hypothesis, National Institutes of Health (NIH) and others leading pharmaceutical companies have invested heavy to study potential drugs to intervene AD according to Immunotherapy which aim to anti-β-amyloid,

But unfortunately these drugs were losing in clinical tests [1]. It suggests that mono-target drugs can't cure these difficult miscellaneous diseases like AD, whereas drugs combination according to clinical symptom may be an available medium. Fortunately, Traditional Chinese medicine has exhibited distinctive advantages to prevent or cure those diseases. Not only many classic prescriptions such as Huanglian jiedu tang [2], Danggui Saoyao san [3] and smart soup [4] but also many Chinese herbs like ginseng or theirs compounds [5,6] can obviously ameliorate some symptom in AD patients or animal models.

*Ligusticum wallichii*, a famous hemorheologic agent of traditional Chinese medicine, has been used more than two thousand years to treating headache, rheumatic arthralgia, irregular menses and other diseases. Modern pharmacological researches show that it contains many pharmacological actions including enhance vascular endothelial function, ameliorate coronary blood flow, anti-thrombosis, resist oxidative stress, purge inflammatory reaction and neuro-protective. Thus, it always acts on cardio cerebral vascular system, nervous system, respiratory system and other related systems [7]. Moreover, a lot of chemical composites has been isolated and identified, they are used to intervene some miscellaneous diseases as a result of they owns their distinctive active ingredient. It is worth mentioning that Alzheimer's disease is an important research direction in those miscellaneous diseases. The paper reviewed recently findings of *Ligusticum wallichii* and their compounds in treat AD by searching key words Ligustrazine, tetramethylpyrazine, protocatechuic acid, β-sitosterol, oxidative stress, β-amyloid or Alzheimer's disease in PubMed.

### Anti-oxidative stress and Alzheimer's disease

β-amyloid is the central pathologic feature, but it may not the first factor in the development of AD became of there aren't statistical difference in increasing of senile plaques and NFTs in Mild Cognitive Impairment (MCI) [8], but the lipid peroxidation like isoprostane 8,12-iso-iPF(2alpha)-VI increased obviously in cerebrospinal fluid, plasma, and urine [9]. What's more, oxidation of protein such as Protein carbonyls and 3-nitrotyrosine were be observed in hippocampus, middle superior temporal gyrus and cerebrospinal fluid [10-12] in AD patients; Reactive aldehydes, the other lipid oxide, like Malon Di Aldehyde (MDA), 4-hydroxynonal, 2-propenal were also detected in hippocampus, temporal cortex, amygdala and other areas [13-15]. Besides, oxidation of DNA/RNA such as 8-hydrOxydeoxyguanosine and 8-hydroxyguanosine were certified distributes in hippocampus and cerebral cortex. These evidences indicate that oxidative stress may be the vital factor. Therefore, abnormal active oxygen species (aROS) may play a leading role in the development of AD, and purging aROS could be the first step to intervene Alzheimer's disease.

Normally Ligustrazine or tetramethylpyrazine is considered as the major active ingredient in *Ligusticum wallichii*. Ligustrazine hydrochloride or phosphate has been used in clinic to treat some obliterative vascular disease [16] like cerebral ischemia, cerebral embolism, vasculitis, coronary heart disease. Emerging researches




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implicates tetramethylpyrazine can enhance Nuclear factor erythroid 2-related factor 2 (Nrf2)-Glu-tamyl Cysteine Ligase (GCLs) mediate GSH activities, and suppress Hypoxia-Inducible Factor 1α (HIF-1α) -NADPH oxidase-2(NOX2) mediated ROS generation to maintains redox balance and neuroprotectiv activities [17]. Ferulic acid, an important active ingredient of *Ligusticum wallichii*n and Radix Angelica sinensis,can increase antioxidase activity to suppress oxidative stress [18-19]. Ligustilide, like ferulic acid that comes from *Ligusticum wallichii* or *Radix Angelica sinensis*, can also defense oxidative stress by improving cellular antioxidant activities [20] and up-regulating Klotho expression to protect neuron [21]. In addition, protocatechuic acid and β-sitosterol are also ameliorate cognitive function *via* alleviating oxidative stress. However, The former (protocatechuic acid) inhabited oxidative stress through up-regulating the expression of hallmark antioxidant enzymes and decreasing the levels of malondialdehyde [22]. But the antioxidant effect of β-sitosterol was associated with estrogen receptor mediated Phosphatidyl Inositol 3-Kinase (PIK3) / Glycogen Synthase Kinase 3 (GSK-3β) signaling [23]. Together, these researches suggest that antioxidant effect of those compounds mainly rely on three pathways: (1) increasing the activities of antioxidase; (2) enhancing the expression of Nrf2; (3) regulating estrogen receptor-PIK3/GSK-3β signaling.

### Amyloid beta and Alzheimer's disease

Though β-amyloid cascade hypothesis can't explain why there aren't statistical differences in increasing of senile plaques and NFTs in MCI [8], and why the metabolic disease like atherosclerosis [24], obesity [25] and type 2 diabetes mellitus [26] may the primary risks in the development of AD. It is still play a vital role in the pathogenesis of Alzheimer's disease. Recently, a new study shows that the complement-dependent pathway and microglia were inappropriately activated and mediated synapse loss in AD [27]. It is worth noting that even C1q had increased in J20 a mouse at 1 month old that precedes plaque deposition [28] but punctate β-amyloid was also found at the same time [27]. Although this research suggests that complement and microglia are the potential early therapeutic targets in AD and other neurodegenerative diseases involving synaptic dysfunction and memory decline [27], pruning oligomeric β-amyloid or inhabiting its generation are still the pivotal way to intervene or treat AD.

More and more evidences show that high cholesterol is closely related to the pathogenesis of AD [29]. What's more, high cholesterol can increase activities of β- and γ-secretase and promote β-amyloid generation. Amazingly, a recently study suggests that β-sitosterol can inhabit β-amyloid release through maintaining of membrane cholesterol homeostasis [29], and more subsequent experiments indicate that β-sitosterol can enter the brain and accumulate in the plasma membrane of brain cells. Besides, it can promote nonamyloidogenic processing of Amyloid Precursor Protein (APP) without affecting membrane fluidity [30]. Attenuating the neurotoxicity induced by β-amyloid was the other important segment. Among the active ingredient of *Ligusticum wallichii*, ligustilide, ferulic acid and protocatechuic acid can ameliorate those lesions in different ways. Firstly, ligustilide improved the pathology relied on modulating TNF-alpha-activated NF-κB signaling pathway [31]. Secondly, ferulic acid weakened the lesions through three pathways: (1) inhibiting the aggregation of Aβ42 oligomers by blocking the hydrogen bond with the forming β-sheets [32,33]; (2) decreasing cleavage of the β-carboxyl-terminal APP fragment and reducing β-site APP cleaving enzyme 1 protein stability and activity [34]; (3) attenuating phosphorylation of ERK1/2 and modulating oxidative stress *via* reducing cytochrome C release and increasing the expression of Peroxiredoxin [35]. Finally, like ligustilide, protocatechuic acid reduced neurotoxicity involving inflammatory response and brain derived neurotrophic factor [36]. Together, mediating β-amyloid generation and oligomerize, modulating oxidative stress and inflammatory response are the chief targets to suppress β-amyloid and reduce its neurotoxicity in these compounds.

### Is β-amyloid the essentially pathogenic factor?

There is no doubting senile plaque caused by β-amyloid is the central pathologic feature and β-amyloid can induce oxidative stress, inflammatory, mitochondrial dysfunction etc. However, the question is raise what activates β- and γ-secretase, especially β-secretase? Many factors such as oxidative stress, inflammatory are really the downstream effect of β-amyloid or Tau [37]? At first, according to many studies we can find that many transgenic model like APP/PS1 mice, PDAPP, Tg2576, APP23, TgCRND8 and J20 [38] were used to research pathogenesis of AD. Spontaneously, those results show β-amyloid play the pivotal role in the pathogenesis. In fact, what these transgenic animals imitate is Familial Alzheimer's Disease (FAD) not the sporadic Alzheimer's disease. Secondly, increasing evidences indicate cardiovascular diseases can increase risk of AD [39-40]. Interestingly, oxydate particularly oxidized low-density lipoproteins play a important role in the incidence of these diseases like atherosclerosis [41]. So ROS induced oxidative stress may be the leading risk, and it is noteworthy that ROS can from normal physiological activity that called endogenous ROS (enROS) and external environment which named exogenous ROS (exROS) [42], the former can be clean up in time, but the later may not purge in time and many researchers have suggested that exposing to particulate matter for a long time obviously damaged oxidative imbalance, promoted lipid or protein oxidation products [43,44]and even destroy DNA [45,46], thus exROS could be the essential risk. Together, whether exROS is the leading factor in AD, more and more task needs to carry out.

## Conclusion

Chinese medicine is an important constituent part of traditional Chinese medicine, and it become more and more popular. Many compounds like artemisinin, vinblastine, and L-3-n- Butylphthalide that separated from Chinese herbs own their particular pharmacological action to treat a few difficult miscellaneous diseases such as helopyra, tumour and cerebrovascular disease. Though many Chinese herbs and their compounds have been affirm to ameliorate some pathology of AD, like cancer or Acquired Immune Deficiency Syndrome (AIDS), AD isn't an ordinary disease. Drugs combination may lead a direction to treat AD. Thus, exploring the pathogenesis of AD, discovering new medicine and dealing with the relationship among these drugs rationally are still the primary task.

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