

# Patterns and Mechanisms of Kidney-tonifying Herbs for Alzheimer's Disease

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**Keywords:** Alzheimer disease, Chinese medicine, Herb

**Abstract: Purpose:** To explore and summarize the pharmacological characteristics and rules of kidney tonic herbs and their compound for the treatment of Alzheimer's disease (AD). **Methods:** We searched the following electronic databases: PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biological Medicine Database (CBMdisc), and Wangfang Data Knowledge Service Platform (Wangfang Data). The data ranged from the inception to December 22, 2021. Drug frequency analysis was performed using Excel 2016. **Results:** A total of 75 herbal compound prescriptions for kidney tonics were compiled, and the most frequently used drugs were deficiency tonics, blood-stasis activators, astringents and tranquilizers. According to the two main pathological features of AD are the deposition of beta amyloid-protein in the brain and the hyperphosphorylation of tau protein which leads to neurofibrillary tangles, analysing the mechanisms the top 5 herbs of kidney-tonifying. **Conclusion:** TCM kidney tonic method for AD mainly uses kidney tonics, blood circulation and blood stasis activators and tranquilizers.

## 1. Introduction

Alzheimer's disease (AD), also known as senile dementia, belongs to the category of "dementia" in Chinese medicine, with cognitive dysfunction and mental abnormalities as the main clinical manifestations[1]. Although these drugs have proven to be effective in improving the cognitive function and daily living ability of AD patients, clinical workers and researchers are looking forward to the early and individualized prevention and treatment of AD, and aim to explore a more effective and precise prevention and treatment method. In Chinese medicine, it is believed that the main cause of AD is the lack of essence and blood and the loss of nourishment of the medulla oblongata[2-4]. In order to improve the efficacy, it is necessary to use scientific methods to summarize and condense the TCM kidney tonic herbal formulas. In this study, we used data mining to explore the rules of Chinese kidney tonics for the treatment of AD and their combination characteristics, in order to efficiently analyze the data of recent studies on kidney tonics for the treatment of AD and deduce the core rules of Chinese kidney tonics for the treatment of AD. The core rules of AD treatment by TCM kidney tonic method were deduced[5, 6].

## 2. Materials and Methods

### 2.1 Data sources and searches

We searched the following electronic databases: PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biological Medicine Database (CBMdisc), and Wangfang Data Knowledge Service Platform (Wangfang Data). The data ranged from the inception to December 22, 2021[7, 8].

## 2.2 Literatures Selection

Inclusion and exclusion criteria Inclusion criteria: (1) clinical studies, medical case reports, and summaries of academic ideas of famous doctors of AD.[9] (2) clinical studies, medical case reports, summaries of academic ideas of famous doctors, etc.; (3) disease diagnosed as AD[10]. (4) The treatment/intervention was kidney tonic Chinese medicine and its compound treatment. Exclusion criteria the exclusion criteria were as follows: (1) No complete drug composition was provided; (2) Clearly diagnosed with other types of dementia[11]. (2) Diagnosis of other types of dementia.

## 2.3 Data Synthesis and Analysis

The researcher read the full text and extracted data such as literature title, source, author, year of publication, case source, treatment method, prescription name, and specific drugs. The drugs were categorized uniformly using the new century (second edition) national planning textbook of higher Chinese medicine colleges and universities "Traditional Chinese medicine" as the standard, and the Excel 2016 software was applied to establish the database, and the extracts of the Chinese medicines included in the literature were made, and the drug fields were quantified binary, with the occurrence of the drug as 1 and the absence of the drug as 0. The frequency of the drugs was used for descriptive analysis using Excel 2016, and the The frequency statistics were performed for the class, taste, and ascription of drugs.

## 3. Results

### 3.1 Drug frequency analysis

Finally, 75 prescriptions from 154 documents were included[12-19]. After combining and sorting the drugs in the 75 prescriptions, a total of 122 herbal medicines were obtained, with a total drug occurrence frequency of 1655 times. The 122 herbal medicines were classified according to the 20 categories listed in TCM, and all the other 16 categories were distributed except for the medicine for dispelling wind and dampness, the medicine for expelling worms, the medicine for gushing out vomit, and the medicine for extracting poison and resolving decay and creating muscle. In terms of drug categories, the most frequently used drugs were deficiency tonics (43 times), followed by blood-stasis activators (11 times), antiphlogistic drugs (11 times), and phlegm and cough relievers (10 times); in terms of frequency of use, the most frequently used drugs were deficiency tonics (804 times), followed by blood-stasis activators (233 times), astringent drugs (211 times), and tranquilizers (156 times).

### 3.2 Basic information of the top 33 herbs of kidney-tonifying

Among all the drug flavors, 24 flavors were used  $\geq 10$  times, which accounted for 1385 times of the total drug frequency. Among them, the most frequent drugs were *Acorus calamus* and *Radix rehmanniae*. The most frequent drugs were *Acorus calamus*, *Radix Angelicae Sinensis*, *Rhizoma Chuanxiong*, *Rhizoma Ligusticum*, *Rhizoma Polygonati*, and *Radix Rehmanniae*. The most frequent drug type was tonic for deficiency (671 times); the most frequent drug property was warm (54 times); the most frequent drug flavor was sweet (48 times); the most frequent drug meridian was kidney (54 times), and none of the herbs belonged to the Sanjiao and small intestine meridians.

Table 1. Basic information of the top 24 herbs of kidney-tonifying

Drug name	Frequency	Medicinal properties	Taste	Attribution	Drug Categories
<i>Acorus tatarinowii</i>	86	Warm	pungent,bitter	heart, stomach	Enlightening medicine
<i>Angelica sinensis</i>	79	Warm	pungent, sweet	heart, liver	tonic for deficiency
<i>Ligusticum chuanxiong</i>	74	Warm	Pungent	Liver, gallbladder, pericardium	blood-stasis activator
<i>Polygala tenuifolia</i>	58	Slightly warm	pungent, bitter	heart, kidney, lung	nourishing the heart and tranquilizing the mind
<i>Alpinia oxyphylla</i>	56	warm	pungent	kidney, spleen	tonic for deficiency
<i>Rehmannia glutinosa</i>	51	Slightly warm	sweet	liver, kidney	tonic for deficiency
<i>Cornus officinalis</i>	43	Slightly warm	sour, astringent	liver, kidney	fixing sperm, reducing urine
Shou Wu	40	Slightly warm	bitter	liver, kidney	tonic for deficiency
<i>Salvia miltiorrhiza</i>	32	Slightly Cold	Bitter	Heart, pericardium, liver	promoting blood circulation and resolving stasis
<i>Astragalus membranaceus</i>	27	Slightly warm	sweet	spleen, lung	tonic for deficiency
Poria	26	Plain	sweet, light	heart, spleen, lung	diuresis and dampness
Cistanches	25	Warm	sweet, salty	kidney, intestine	tonic for deficiency
Spleen	25	Warm	pungent, sweet	Kidney, liver	Tonic for deficiency
<i>Glycyrrhiza glabra</i>	24	Slightly cold	sweet	spleen, lung, stomach	tonic for deficiency
Fructus Lycii	24	Plain	Sweet	Liver, Kidney	tonic for deficiency
Ba Ji Tian	21	Slightly warm	Pungent, Sweet	Kidney, Liver	tonic for deficiency
Ginseng	19	Slightly warm	Sweet	Lung, Spleen, Heart, Kidney	tonic for deficiency
Mai Dong	18	Slightly cold	Slightly bitter	lung, stomach	tonic for deficiency
Wu Wei Zi	18	Warm	sweet, sour	spleen, lung, heart, kidney	astringent to the lung and intestines
Leeches	16	Plain	salty, bitter	liver	promoting blood circulation and resolving stasis
<i>Cuscuta sinensis</i>	13	Plain	pungent, sweet	kidney, liver, spleen	tonic for deficiency
Dendrobium	12	Slightly Cold	Sweet	Kidney, Stomach	tonic for deficiency
Yam	11	Plain	Sweet	Spleen, Lung, Heart, Kidney	Tonic for deficiency
<i>Radix Codonopsis Pilosulae</i>	11	Plain	pungent	Spleen, Lung	Tonic for deficiency

#### 4. Mechanisms of kidney-tonifying herbs

According to the research into the pathogenesis of AD, the two main pathological features of AD are the deposition of beta amyloid-protein in the brain and the hyperphosphorylation of tau protein which leads to neurofibrillary tangles, and also accompanied by synaptic loss, central nervous system inflammation, oxidative stress response and other activities. The treatment of AD by kidney-tonifying prescription is mainly related to A $\beta$  plaque, cholinergic system, fibrous tangles, inflammation, oxidative stress, tau protein and neuroprotection. The mechanisms the top 5 herbs of kidney-tonifying were displayed in the following part.

##### 4.1 *Acorus tatarinowii*

*Acorus tatarinowii* was recorded in *Supplementary Records of Famous Physicians* with its functions on eyes, ears and minds. It also recorded in the *Herbal Classic*, where record its functions on heart, liver, lungs, kidneys, ears and eyes. And in the clinical results of traditional Chinese medicine shown that the prescription based on *Acorus tatarinowii* was the basic structure of the prescription for the treatment of AD, ranking first in the frequency of the use of single drug, and its curative effect was confirmed. *Acorus tatarinowii* could decrease nitric oxide synthase activity in brain and hippocampus of AD patient and improve learning and memory ability. The main ingredients of *Acorus tatarinowii* found in paper in the AD treatment are  $\beta$ -asarone and eugenol.

##### $\beta$ -asarone

According to the research results, A $\beta$ 1-42 induces the activation of the RA-h and releases inflammatory factors such as IL-1 $\beta$ , TNF- $\alpha$  which aggravate the injury of PC12 cells. And the  $\beta$ -

asarone decrease the production of IL-1 $\beta$ , TNF- $\alpha$ , promote BDNF release, inhibit NF- $\kappa$ B activity and phosphorylation of ERK, p38, and JNK.[41]

Eugenol

The experiment shows that eugenol can obviously antagonize the apoptosis of PC12 cells induced by A $\beta$ 1-42. And it may be related to the inhibition of the expression of apoptosis-related factors. [37] And in this paper, writer also guessed that the antiapoptotic mechanisms of the eugenol are various. And the mechanism of its protective effects on neurons also needs more research.

#### 4.2 *Angelica sinensis*

*Angelica sinensis* recorded in the *Compendium of Materia Medica* with its functions that nourish blood and regulate menstruation, quicken blood, relieve pain, moisten intestines, and relieve constipation. And in some recent studies, it is shown that *Angelica sinensis* has functions of antioxidant, anti-inflammatory, activating neurotrophic factor. The main ingredients of *Angelica sinensis* in the AD treatment are ferulic acid (FA) and ligustilide. The treat mechanism of the ligustilide is shown in the *Ligusticum chuanxiong*.

FA

FA improves the combination of the Nrf2 and ARE through influencing the PI3K and ERK signaling pathways, thus affect the expression of the GSH and NADPH, producing the function of antioxidant. It also said that FA can not only decomposes the fibrous tangles that have formed, but also reduce the average length of fibrous by disrupting the elongation process. FA can decrease the production of the inflammasome TNF- $\alpha$  and IL-1 $\beta$  to reduce neuroinflammation. What's more, FA can improve neurological symptoms through increase the production of cAMP-responsive element binding protein (CREB) and brain-derived neurotrophic factor (BDNF). FA can also increase the expression of the gene GRP78/Bip and reduce the combination between CCAAT enhancer and CHOP to promote the processing of misfolding or unfolded proteins accumulated in the ER, so that the cell function can be restored to normal.[29]

#### 4.3 *Ligusticum chuanxiong*

*Ligusticum chuanxiong* was first recorded in the *The Commentary of Zuo* and was named xiong for the first name in *Shen Nong's Herbal Classic*. In the record, the effects of the *Ligusticum chuanxiong* are moving qi and quickening blood, dispelling wind, and relieving pain. And it frequently appears in kidney tonifying prescriptions for treat AD. In addition, it was suggested that *Ligusticum chuanxiong* had antioxidant effect, and its mechanism might be related to platelet anticoagulation, increasing the activity of superoxide dismutase (SOD) and accelerating the scavenging of oxygen free radicals. And it also has a significant effect on headache and vertigo and can cure cardiovascular and cerebrovascular diseases such as angina pectoris, ischemic stroke, and migraine by promoting blood circulation, as well as gynecological diseases such as menstrual disorders, dysmenorrhea, amenorrhea and blemishes abdominal pain, as well as rheumatic pain. The main ingredients of *Ligusticum chuanxiong* in the AD treatment are levistolide A (LA), ligustilide, ligustrazine and ferulic acid (FA), while the mechanisms of FA are mentioned in the *Angelica sinensis*.

LA

LA could reduce the concentration of A $\beta$ 1-42 in cells, thus playing a neuroprotective role and reducing the risk of AD. [31] And the reason indicated in this paper is that LA can increase the expulsion of A $\beta$ 1-42 through some specific pathway which is unknown.

Ligustilide

Ligustilide can improve its antioxidant activity through increasing the expression of SOD and CAT. In terms of anti-aging, ligustilide can play a neuroprotective role by upregulating the anti-aging gene Klotho. In the inhibition of mitochondrial apoptosis pathway, ligustilide has a protective effect on A $\beta$ 25-35-induced SH-SY5Y cytotoxicity. In terms of cognitive function, ligustilide inhibit the activity of the AchE, enhance the activity of the ChAT and the cholinergic system.[31]

Ligustrazine

Ligustrazine can improve the memory function of AD patients, enhance the activity of ChAT and AchE, and up-regulate the number of M receptor. Meanwhile, ligustrazine has the function of scavenging hydroxyl free radicals and anti-oxidation, playing an anti-aging role.[16] However, the mechanism of these functions is still unknown.

#### **4.4 *Polygala tenuifolia***

*Polygala tenuifolia*, a traditional Chinese medicine, is a famous nootropic drug, first recorded in the *Shen Nong's Herbal Classic*. It has the functions of claiming the mind, removing phlegm and reducing swelling. In this case, it can be used to treat insomnia, dreaminess, trance, breast swelling and pain caused by heart and kidney disharmony. What's more, modern pharmacological studies have shown that *Polygala tenuifolia* has the functions of intelligence, sedation, and hypnosis, antitussive and expectorant, neuronal protection, anti-oxidation, anti-dementia, anti-depression and so on. Some research indicate that oxidative stress and neuronal loss are important pathogenesis of neurodegenerative diseases. With the in-depth study of Chinese traditional medicine, it was found that *Polygala tenuifolia* has a very good effect in the treatment of neurodegenerative diseases. According to the TCMID database, we can know the ingredients of the *Polygala tenuifolia*. However, the main active ingredients found in paper for treat Alzheimer disease are tenuigenin (TEN), senegenin (SEN), oligosaccharides and alkaloids.

##### **TEN**

TEN can reduce A $\beta$  production by inhibiting BACE1 activity without affecting APP mRNA expression, full-length APP synthesis and SAPP secretion. [24] These studies indicate that TEN can reduce the production and secretion of A $\beta$  and thus play a neuroprotective role against AD. This study also point out that TEN can inhibit IL-1 $\beta$ -induced NF- $\kappa$ B activation, increase the phosphorylation of P13K and AKT, and reduce IL-1 $\beta$ -induced matrix metalloproteinase (MMP1, MMP3, MMP13) expression, thus exerting anti-inflammatory activity.[24]

##### **SEN**

SEN increases the number of the growth associated protein43 (GAP-43) and microtubule-associated protein 2 (MAP2) and BDNF, which improves the neuronal atrophy and neurite degeneration induced by A $\beta$ , and also promotes cortical neurite growth and neuronal survival to prevent the AD. [24] What's more, it also shown that SEN can significantly inhibit LPS-induced production of TNF- $\alpha$ , IL-6 and IL-1 $\beta$ . It also inhibit LPS-activated NF- $\kappa$ B and MAPK signaling pathway as well as the expression of iNOS and COX-2 and can reduce H<sub>2</sub>O<sub>2</sub>-induced production of ROS and MDA, reduce the consumption of SOD and GSH antioxidant enzyme, and up-regulate the Nrf2/Ho-1 signaling pathway. [24] These show the functions of anti-inflammation and anti-oxidation.

##### **TFSA**

Tenuifoliside A is a bioactive oligosaccharide, which can increase the phosphorylation of ERK and Akt, increase the release of BDNF, and also enhance the phosphorylation of CREB at Ser133, suggesting that TFSA plays a neurotrophic role by regulating the Akt/PI3K pathway.

#### **4.5 *Alpinia oxyphylla***

*Alpinia oxyphylla* has the effect of warming the spleen, stopping diarrhea and swallowing saliva, warming the kidney, solidifying sperm and reducing urine. Traditional Chinese medicine uses it for the treatment of kidney deficiency enuresis, urine frequency, spermatorrhea and so on. Modern Chinese medicine clinical also often used for the treatment of AD, which can effectively improve the cognitive function of AD patients. And the main ingredients of AD treat in *Alpinia oxyphylla* are Protocatechuic acid (PCA), chrysin and yakuchinone b. These ingredients have a better neuroprotective, memory and cognitive dysfunction improving effect. GO analysis shown that the treatment of AD mainly involved protein serine kinase, lyase, carbon and oxygen lyase, protein tyrosine kinase, etc., for protein serine kinases and protein tyrosine kinases can reduce the apoptosis of nerve cells, while lyase can promote the proliferation and differentiation of nerve cells. Moreover, KEGG pathway enrichment analysis results shown that PI3K-Akt, Ras, HIF-1 and other signaling pathways may be related to the treatment of nootropics for AD. Among them, PI3K-Akt and Ras

signaling pathways might be the key pathways in the treatment of AD. [23] But its mechanism of those ingredients in the treatment of AD are still not very clear and need further study.

#### 4.6 *Rehmannia glutinosa*

*Rehmannia glutinosa*, recorded in the *New Compilation of Materia Medica*. And through the research of the AD treatment, it can be found that *Rehmannia glutinosa* can inhibit the neuro apoptosis induced by A $\beta$ , which improves the learning and memory function. What's more, *Rehmannia glutinosa* can regulate the glutamic and r-aminobutyric and prevent excessive Al<sup>3+</sup> damaging the brain tissue. But the main ingredients which play the important role in AD treat and their treat mechanisms are still unknown.

### 5. Conclusion

Through the analysis of the drug use pattern and combination characteristics of the kidney tonic formula from the perspective of data mining, the more frequent drugs were deficiency tonic, blood invigorating and stasis resolving, and tranquilizing drugs, and the more core drugs were Acorus calamus, Radix rehmanniae, Cornu Cervi Pantotrichum, Radix et Rhizoma Polygoni, Rhizoma Chuanxiong, Salviae Miltiorrhizae, Radix Astragali, Poria, Herba Cistanches, Radix Rehmanniae, Fructus Lycii, Radix et Rhizoma Bidentatae, Radix et Rhizoma Ginseng, Radix Angelicae Sinensis, Radix et Rhizoma Macrocephala, and Fructus Schisandrae. Drug Categories: Mainly classified as deficiency tonic, blood circulation and blood stasis, astringent, tranquilizer, warming and orifice. The taste of medicine is mainly pungent, bitter and sweet, with the sweet taste being the main one: the sweet taste is nourishing and tonic, and the deficiency tonics are mostly sweet; the bitter taste is good at draining dampness with bitterness, lowering qi and lowering rebellion; the pungent taste can move and disperse, and is good at moving qi and invigorating blood. The properties of these medicines are: Calamus, Chuanxiong, Cistanches, Xian Ling Spleen, Angelicae and Wu Wei Zi are warm; Radix Rehmanniae, Cornu Cervi Pantotrichum, Yuan Zhi, Shou Wu, Astragalus, Ginseng and Bacopa monniera are slightly warm; Salviae, Mai Dong and Licorice are slightly cold; Poria and Lycium are calm. It can be seen that the common drugs for the treatment of AD are mainly warm in nature. From the point of view of meridians, the above drugs are concentrated in the kidney, liver and heart meridians. The kidney collects essence and produces marrow, the liver collects blood, and the heart is the master of blood, so essence and blood have the same source.

The pathological products, the loss of essence and blood, the emptiness of the brain marrow, and the stagnation of phlegm and stagnation, the mingling of positive deficiency and evil reality, and the entrapment of the brain, lead to dementia. In general, the treatment of AD takes Yin and Yang as the general outline, either by warming the kidneys to help Yang, or by nourishing the kidneys to fill the marrow, taking into account the nourishment of Qi and Blood to transform Yin and strengthen the source of essence and Blood.

In summary, the treatment of AD should strictly adhere to the pathological mechanism of "mixed deficiency and reality", and the main treatment is to tonify the kidney and fill the essence, fill the marrow, open the orifice and strengthen the brain; according to the deficiency of the five organs, the treatment is to benefit the qi and strengthen the spleen, nourish the blood and soften the liver; according to the difference of the evil and reality, the treatment is to tonify the kidney and invigorate the blood, tonify the kidney and resolve phlegm, and tonify the kidney and pacify the liver.

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