



Review

## The treatment of Alzheimer's disease using Chinese Medicinal Plants: From disease models to potential clinical applications



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### ABSTRACT

**Ethnopharmacological relevance:** Alzheimer's disease (AD) is characterized by the sustained higher nervous disorders of the activities and functions of the brain. Due to its heavy burden on society and the patients' families, it is urgent to review the treatments for AD to provide basic data for further research and new drug development. Among these treatments, Chinese Material Medica (CMM) has been traditionally clinical used in China to treat AD for a long time with obvious efficacy. With the further research reports of CMM, new therapeutic materials may be recovered from troves of CMM. However, So far, little or no review work has been reported to conclude anti-AD drugs from CMM in literature. Therefore, a systematic introduction of CMM anti-AD research progress is of great importance and necessity. This paper strives to systematically describe the progress of CMM in the treatment of AD, and lays a basis data for anti-AD drug development from CMM, and provides the essential theoretical support for the further development and utilization of CMM resources through a more comprehensive research of the variety of databases regarding CMM anti-AD effects reports.

**Material and methods:** Literature survey was performed via electronic search (SciFinder®, Pubmed®, Google Scholar and Web of Science) on papers and patents and by systematic research in ethnopharmacological literature at various university libraries.

**Results:** This review mainly introduces the current research on the Chinese Material Medica (CMM) theoretical research on Alzheimer's disease (AD), anti-AD active constituent of CMM, anti-AD effects on AD models, anti-AD mechanism of CMM, and anti-AD effect of CMM formula.

**Conclusion:** Scholars around the world have made studies on the anti-AD molecular mechanism of CMM from different pathways, and have made substantial progress. The progress not only enriched the anti-AD theory of CMM, but also provided clinical practical significance and development prospects in using CMM to treat AD. Western pure drugs cannot replace the advantages of CMM in the anti-AD aspect. Therefore, in the near future, the development of CMM anti-AD drugs with a more clearly role and practical data will be a major trend in the field of AD drug development, and it will promote the use of CMM.

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**Abbreviations:** AD, Alzheimer's disease; CMM, Chinese Materia Medica; NFT, neurofibrillary tangle; CHEI, cholinesterase inhibitor; AChE, acetylcholinesterase; APP, amyloid protein precursor; Ach, acetylcholine; AchEI, acetylcholinesterase inhibitor; MDA, malondialdehyde; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase

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## 1. Introduction

Alzheimer's disease (AD) was first described by the German psychiatrist, Alois Alzheimer, in 1907 (Alzheimer et al., 1907). The disease appeared less common in the early decades of the 20th century. Nowadays, however, dementia is a very common illness in the elderly (Heinrich and Teoh, 2004). As a degenerative disease of the brain, AD is characterized by the sustained higher nervous disorders of the activities and functions of the brain. It means that there are obstacles of memory thinking, analysis judgment, visual identity, emotions, and so on. As the population ages, the prevalence of AD and related dementias is also increasing. In the Kame project, a population-based cohort study of Japanese-Americans living in King County, Washington, the prevalence of AD increased from 1.4% among those aged 70–74 to 50.2% among those aged 90–94 (Graves et al., 1996). Nearly three fourths of individuals over the age of 95 were found to be demented. Due to the occurrence and irreversibility of AD, it has increased the heavy burden on society and the patients' families. Unfortunately, at present the pathogenesis of AD is not completely elucidated. In recent years, several treatment options have become available to improve the prognosis in AD patients (Sierpina et al., 2005; Birks, 2006). The effect of symptomatic treatment with cholinesterase inhibitor (ChEI) and N-methyl-D-aspartate receptor agonists has been evaluated in numerous randomized controlled trials (Ito et al., 2010). At present, with the further research reports of CMM, new therapeutic materials may be recovered from troves of CMM (Uabundita et al., 2010). Currently, more attention has been focused on the development of anti-AD drugs from CMM for their multi-component features, including the ability to affect multiple targets and levels signaling pathways. Therefore, based on these reports, this review strives to introduce the research progress systemically and generally on the treatment of AD derived from CMM, including their basic theory, chemical constituents, AD models, mechanisms, prescription research, and their drug development in order to further study anti-AD drugs from CMM in the right and meaningful direction, and to provide original data and theoretical basis for developing new anti-AD CMM drugs.

## 2. Research progress in treatment of AD

The most common symptom of AD is the difficulty to remember recent events, as well as behavior and thinking abilities. As

the disease develops, symptoms include confusion, irritability, aggression, mood swings, trouble with language, and long-term memory loss. Thus, sufferers often withdraw from their families and society. Therefore, the treatments of AD become more urgent for both patients and their families. At present, researching and developing new anti-AD drugs are attracting the attention in the medical field. Substantial research on neurophysiology, biochemistry and pharmacology of aging has led to continuous progress in the development and research of relevant drugs.

On the one hand, loss of cholinergic neurons in the brain is linked to cognitive decline, thus reduction in cholinergic neurons in brain of AD patients leads directly to cognitive deficiency and memory loss, which means that the supplement of acetyl choline is expected to alleviate symptoms of AD. ChEI is considered to be one of the most effective drugs in treatment of AD. It could inhibit the activity of acetylcholinesterase (AChE) to reduce the hydrolysis of acetylcholine and also activate the nicotinic receptor or mACh-receptor on the presynaptic membrane and the postsynaptic membrane, to enhance the function of the cholinergic neurons. At present, there are three ChEI drugs, namely donepezil (Geldmacher, 2004; Benjamin and Burns, 2007), rivastigmine (Onor et al., 2007) and galantamine (Villarroya et al., 2007).

On the other hand, Amyloid- $\beta$  (A $\beta$ ) is the major component of aggregates located in the brain of AD patients. The 40-residue-containing peptide (A $\beta$ <sub>40</sub>) or the 42-residue-containing peptide (A $\beta$ <sub>42</sub>) is a fragment of the membrane-associated amyloid precursor protein (Glenner and Wong, 1984; Selkoe et al., 1986). AD is characterized by overproduction and deposition of A $\beta$  in the brain and soluble A $\beta$  oligomers are now widely recognized as key pathogenic structures in AD. Therefore, extracellular soluble A $\beta$  oligomers are believed to cause synaptic and cognitive dysfunction in AD (Klein et al., 2001; Selkoe, 2002). A $\beta$  peptide is derived from proteolytic cleavage of  $\beta$ -amyloid precursor protein (APP). Three secretases,  $\alpha$ ,  $\beta$ , and  $\gamma$ , are involved in APP processing. Sequential cleavage of APP by  $\beta$ - and  $\gamma$ -secretases yields either A $\beta$ <sub>1–40</sub> or A $\beta$ <sub>1–42</sub> peptide (Walter et al., 2001; Selkoe, 2004). A $\beta$  inhibits synaptic function, leading to early memory deficits and synaptic degeneration, and it triggers the downstream neuronal signaling responsible for phospho-tau Alzheimer's pathology. The marginal effects observed in recent clinical studies of solanezumab, targeting monomeric A $\beta$ , and bapineuzumab, targeting amyloid plaques, prompted expert comments that drug discovery efforts in Alzheimer's disease should focus on soluble forms of A $\beta$  rather than fibrillar A $\beta$  deposits found in amyloid plaques. Accumulating scientific data suggest that soluble A $\beta$  oligomers represent the optimal intervention target within the

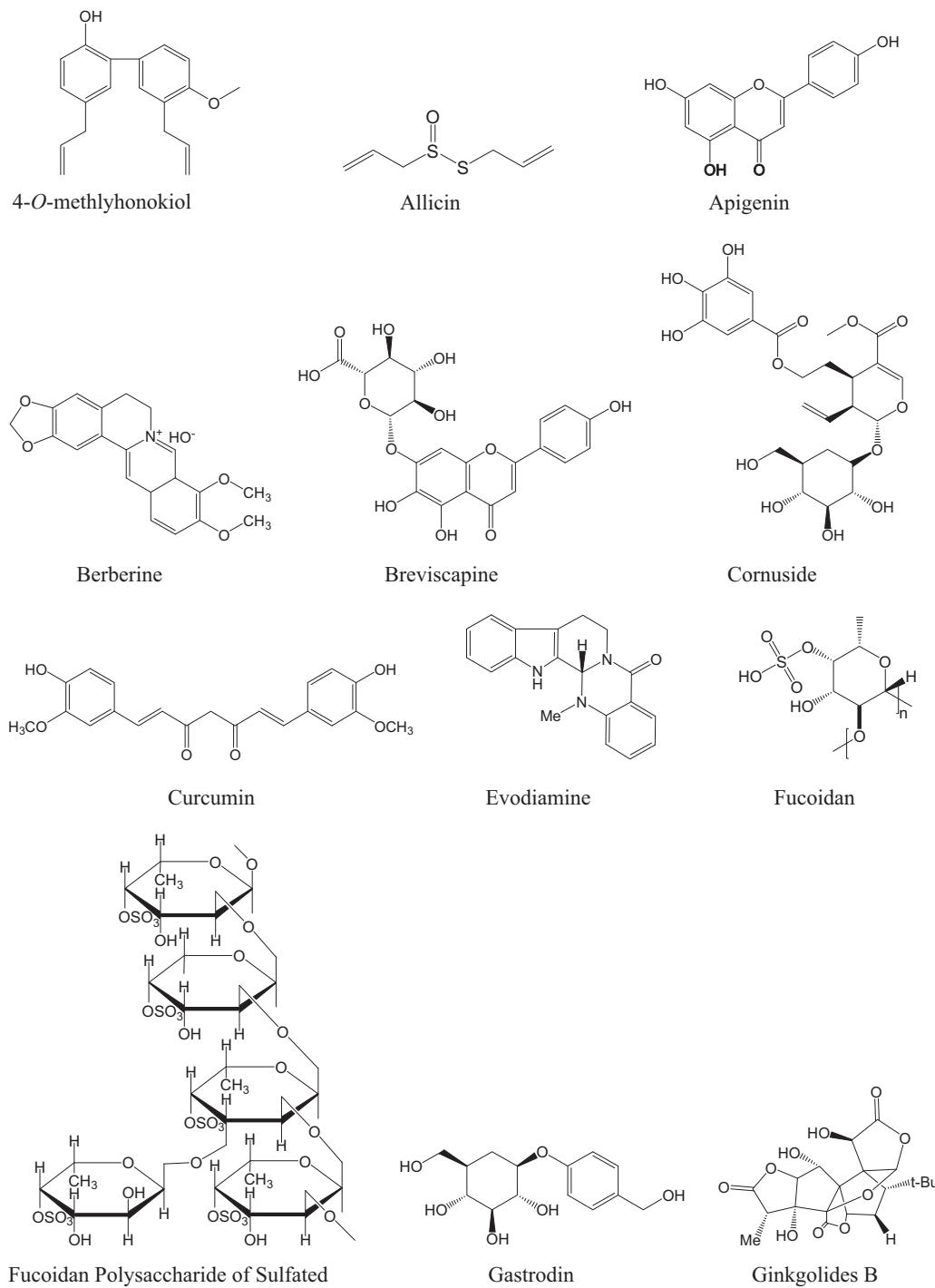
amyloid manifold. Active drug discovery approaches include antibodies that selectively capture soluble A $\beta$  oligomers, selective modifiers of oligomer assembly, and receptor antagonists (Franz et al., 2013).

Moreover, with the continuous development of CMM, treatment of AD using CMM has become an important area of research. In this field, China has the exceptional advantages with CMM information from which numerous databases could be used. Because CMM exerts their pharmacological effects through a multi-component and multi-target way in addition to their fewer side effects, CMM provides the advantages and wide application possibilities compared with the pure drug with limited efficacy

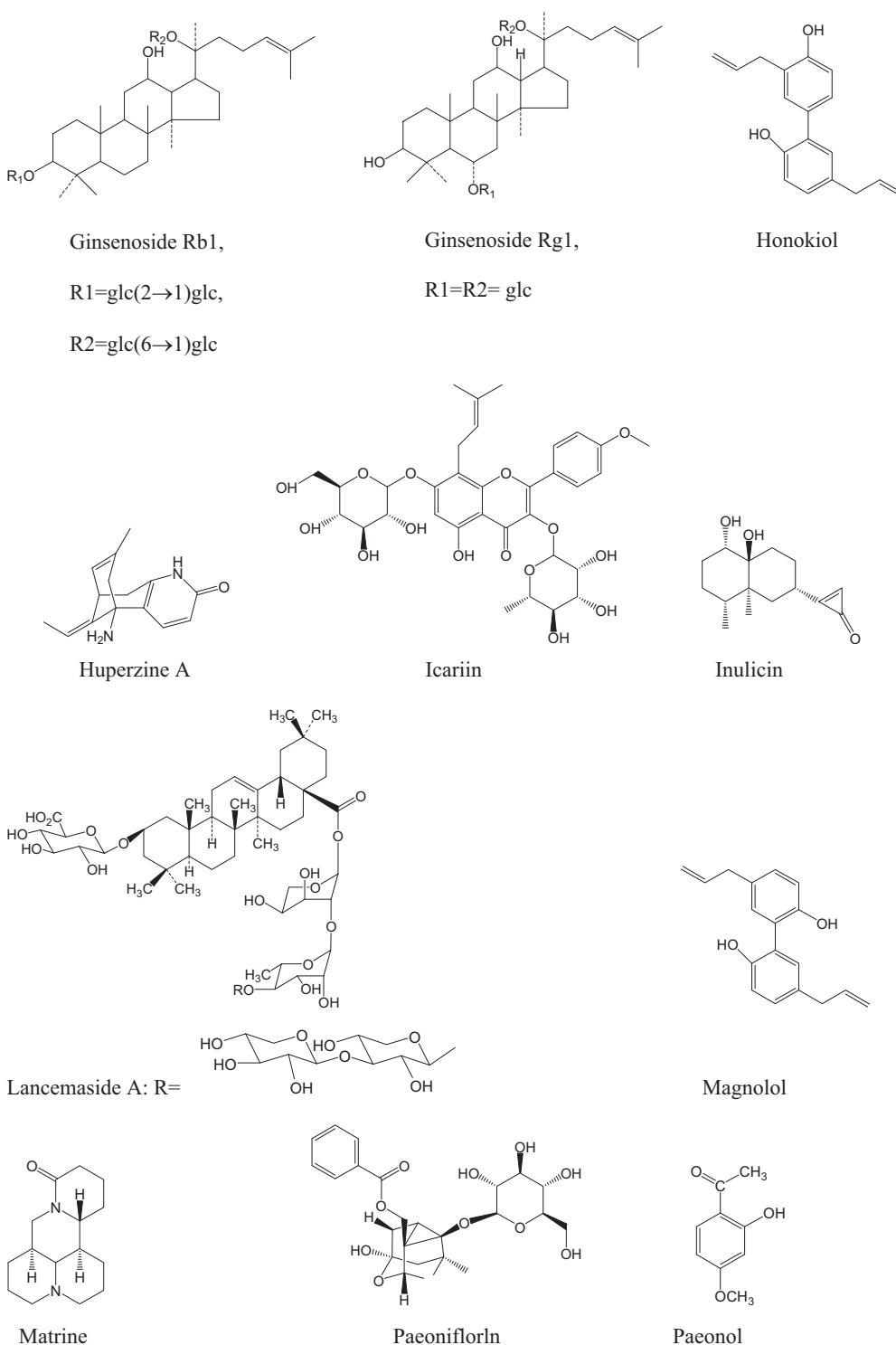
and some side effects. At present, tens of thousands of AD patients are looking forward to safe, effective and inexpensive drugs, which are considered to have a potential market and a very good development prospect.

### 3. CMM theoretical research on AD

AD is a common degenerative disease of central nervous system, with the main neuropsychiatric symptoms, such as progressive memory disorders, cognitive dysfunction, and personality changes. Western medicine considers that aging, shrinkage, and



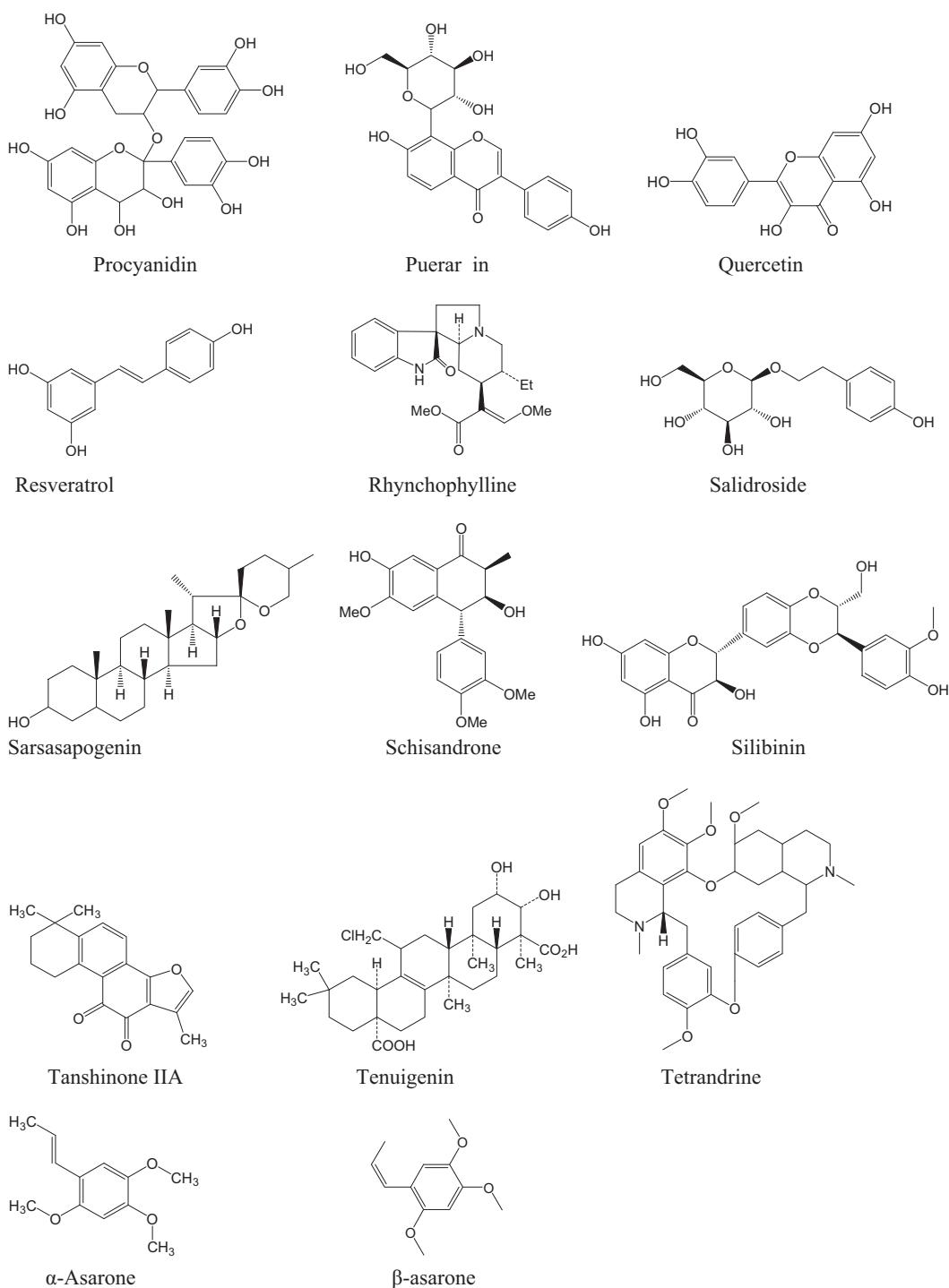
**Fig. 1.** Important compounds with anti-AD activities from CMM.

**Fig. 1. (continued)**

degeneration of the brain tissue are the foundation of AD occurrence, which may be a principle that the older the patients were, the higher the incidence was. In the CMM theory, some symptoms are similar to those of AD, such as dementia, amnesia and so on. CMM holds that these diseases belong to aging illness and are linked with the “asthenic disease of five organs”, especially the deficiency of the kidney essence (Li and Wang, 2010).

In the CMM theory, it has been recognized that the kidney essence is an important role in life's activities. On the one hand,

the kidney essence is the main substance that controls the process of life and determines the life span and the quality of life. Kidney essence is considered as the source of human life. When the kidney essence is sufficient in the body, it will be full of energy, which leads to endless vitality. But with deficiency of the kidney essence, growth retardations occur in children, and young and middle-aged people show signs of premature aging, and people grow old rapidly. On the other hand, the kidney essence has also a very close relationship with the brain and sanity. When one's

**Fig. 1. (continued)**

kidney essence is sufficient, the brain will also be sufficient, and thus one can hear and see well. Deficiency of the kidney essence can cause the dystrophy of brains, and with the passing of time, the marrow will be exhausted and the brain will be deficient. This will result in dementia, muscle rigidity and movement disorder, which are similar to the neurodegenerative disease symptoms and signs. In TCM, the AD clinical treatment take "Tonifying the kidney essence" as the basic principle of treatment of AD. Experimental studies have demonstrated that this therapy is effective in the treatment of cognitive impairment, and early and moderate Alzheimer's disease.

One clinical trial used randomized, double-blind, double-dummy and parallel-controlled design has been investigated to explore the clinical efficacy and safety of Chinese medicine for tonifying the kidney in the treatment of AD patients. This clinical trial showed that after 12 weeks, both Chinese medicine group and the donepezil group can improve global cognition in patients. Furthermore, Chinese medicine is safe for patients (Miao et al., 2012).

To sum up, CMM holds that kidney essence is a basic component of the human body, and which has a close relationship with human's life process. By reviewing the results of method by

nourishing the kidney essence used in delaying aging and prevention of AD *in vivo* and *in vitro* in recent years, and by reviewing its clinical research on the treatment of AD and other age-related neurodegenerative diseases, the important role of this method in the prevention and treatment of AD is further affirmed.

Therefore, in the CMM theory, due to the important role of kidney essence in physiology and pathology of CMM, the method of nourishing the kidney essence is mostly used in the treatment of aging diseases. From the CMM theory's perspective, the occurrence and development of AD have close relationship with the aging procedure, started by deficiency of the kidney essence. The

CMM Theory pays much attention to nourish the kidney, which has very important practical value for AD.

#### 4. Research on active constituent of CMM against AD

Currently, the active anti-AD compounds (see Fig. 1), namely the effective components including alkaloids, polysaccharides, flavonoids, etc. (see Table 1) and extracts from CMM, have been reported with their effects against AD. The effects against AD have been described in the section "mechanism research of CMM

**Table 1**  
Anti-AD active ingredients of CMM.

Classifications	Components	CMM	Pinyin	Refs.
Alkaloids	Tetrandrine	Dried root of <i>Stephania tetrandra</i> S. Moore	Han Fang Ji (汉防己)	He et al. (2011)
	Berberine	Roots from <i>Coptis chinensis</i> Franch	Huang Lian (黄连)	Durairajan et al. (2012)
	Huperzine A	Whole herb of <i>Huperzia serrata</i> (Thunb.) Trev.	Qian Ceng Ta (千层塔)	He et al. (2003)
	Evodiamine	The fruit of <i>Evodia rutaecarpa</i> Bentham	Wu Zhu Yu (吴茱萸)	Yuan et al. (2011)
	Dehydroevodiamine hydrochloride	The fruit of <i>Evodia rutaecarpa</i> Bentham	Wu Zhu Yu (吴茱萸)	Park et al. (1996)
	Rhynchophylline; isorhynchophylline	Roots of <i>Uncaria rhynchophylla</i> (Miq.) ex Havil	Gou Teng (钩藤)	Xian et al. (2012a)
	isorhynchophylline	Roots of <i>Uncaria rhynchophylla</i> (Miq.) ex Havil	Gou Teng (钩藤)	Xian et al. (2012b); Zhou and Zhou (2010)
	Icariin	Aerial part of <i>Epimedium davidii</i> Franch	Yin Yang Huo (淫羊藿)	Wu et al. (2012)
	Brevicapine	Roots of <i>Erigeron breviscapus</i> (Vant.) Hand Mazz.	Xi Xin (细辛)	Mei et al. (2012)
	Quercetin	Whole herb of <i>Ruta graveolens</i> Linn.	Lu Ding (芦丁)	Li et al. (2003)
Flavonoids	Puerarin	Roots of <i>Pueraria lobata</i> (Willd.) Ohwi	Ge Gen (葛根)	Zhang, H.Y. et al. (2011)
	Apigenin	Leaf of <i>Apium graveolens</i> Linn.	Han Qin (旱芹)	Zhao et al. (2005)
	Proanthocyanidin	Leaf of <i>Vaccinium uliginosum</i> Linn.	Yue Ju (越橘)	Cai et al. (2011)
	Isoflavone	Fruits of <i>Glycine max</i> (Linn.) Merr.	Da Dou (大豆)	Cai et al. (2012); Cai et al. (2013); Yang et al. (2005)
	Silibinin	Seed coat of <i>Silybum marianum</i> Gaertn.	Shui Fei Ji (水飞蓟)	Bi et al. (2012)
	Tanshinone II A	Bulbus of <i>Salvia miltiorrhiza</i> Bunge	Dan Shen (丹参)	Jiang et al. (2010)
	Turmerone	Rhizome of <i>Curcuma longa</i> Linn.	Jiang Huang (姜黄)	Meng et al. (2012)
	Schisandrone	Fruit of <i>Schisandra sphenanthera</i> Rehd et Wils	Hua Zhong Wu Wei Zi (华中五味子)	Lv et al. (2007)
	Allitridium	Bulb of <i>Allium sativum</i> Linn.	Da Suan (大蒜)	Hu et al. (2010)
	Inulinicin	Inflorescence of <i>Inula japonica</i> Thunb.	Xuan Fu Hua (旋覆花)	Wang et al. (2008)
Ketones	Ginkgolides	Leaf of <i>Ginkgo biloba</i> Linn.	Yin Xing (银杏)	Li, N. et al. (2007); Li, Q.C. et al. (2007)
	Magnolol and honokiol	Bark of <i>Magnolia officinalis</i> et Wils	Hou Po (厚朴)	Hoi et al. (2012)
	4-O-methylhonokiol	Bark of <i>Magnolia officinalis</i> et Wils	Hou Po (厚朴)	Lee et al. (2010)
	Polyphenols	Leaves of <i>Camellia sinensis</i> Linn.	Lv Cha (绿茶)	Xu and Zhang (2008)
	Resveratrol	Roots of <i>Veratrum nigrum</i> Linn.	Li Lu (藜芦)	Lin et al. (2009)
	Paeonol	Velamen of <i>Paeonia suffruticosa</i> Andrews	Mu Dan (牡丹)	Zhou J. et al. (2011)
	Salidroside	Whole herb of <i>Rhodiola sachalinensis</i> A.Bor	Hong Jing Tian (红景天)	Zhang et al. (2012)
	Gastrodin	Tuber of <i>Gastrodia elata</i> Blume	Tian Ma (天麻)	Liu and Wang (2012)
	Paeoniflorin	Roots of <i>Paeonia lactiflora</i> Pall.	Chi Shao (赤芍)	Li, S.M. et al. (2012)
	Iridoid glycosid	Flesh fruit of <i>Cornus officinalis</i> Sieb. et Zucc	Shan Zhu Yu (山茱萸)	Chu et al. (2009)
Polysaccharides	Polysaccharides	Roots of <i>Millettia pulchra</i> (Benth.) Kurz var. laxior (Dunn) Z. Wei	Long Yan Shen (龙眼参)	Huang, Z.S. et al. (2008)
	Fucoidan	Whole herb of <i>Ecklonia kurome</i> Okam.	Kun Bu (昆布)	Zhao et al. (2010)
	Polysaccharide	Whole herb of <i>Sargassum fusiforme</i> (Hary) Seichell	Yang Xi Cai (羊栖菜)	Tang et al. (2012)
	Polysaccharide	Mycelium of <i>Ganoderma lucidum</i> (Leyss. ex Fr.) Karst.	Ling Zhi (灵芝)	Guo et al. (2006)
	Caltrop saponin	Fruits of <i>Tribulus terrestris</i> Linn.	Ji Li (蒺藜)	Ma and Qu (2009)
	Seed saponin	Fruits of <i>Litchi chinensis</i> var. <i>euspontanea</i> Hsue	Li Zhi (荔枝)	Li and Wang (2012)
	Gypenosides	Roots of <i>Gynostemma pentaphyllum</i> (Thunb.) Makino.	Jiao Gu Lan (绞股蓝)	Zhou et al. (2012)
	Tenuigargin	Roots of <i>Polygala tenuifolia</i> Willd.	Yuan Zhi (远志)	Jia et al. (2004)
	Ginsenoside Rb1, Rg1	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Yang et al. (2008); Xu and Lai (2007)
	Gross saponins	Fruits of <i>Tribulus terrestris</i> Linn.	Ji Li (蒺藜)	Zhang J. et al. (2011)
Saponins	Lancemaside A	Rhizome of <i>Codonopsis lanceolata</i>	Yang Ru (羊乳)	Jung et al. (2012)
	Ginsenoside Rg2	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Li, N. et al. (2007); Li, Q.C. et al. (2007)
	Ginsenoside Rg3	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Yang et al. (2009)
	Ginsenoside Rd	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Liu et al. (2012)
	Ginsenoside Rb1	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Lv et al. (2012); Xie, C.M. et al. (2010); Xie, X. et al. (2010); Cheng et al., 2005

against AD". This section will describe the structures and sources from various compounds.

Both the diversity structures of CMM on treating AD and their extensive effects are not common in anti-AD synthesis drugs. Considering the close relationship between mechanisms and active constituents of CMM against AD, this result has attracted the researches' attention, and more active constituents from CMM will be developed to be anti-AD drugs with wide applications.

## 5. CMM anti-AD effects on AD models

At present, there are a variety of *in vitro* and *in vivo* AD models, but the most commonly used models are inducers models, aging models and transgenic models. This section strives to introduce these models mentioned above (see Table 2).

### 5.1. AD model induced by D-galactose

D-galactose is a physiological nutrient ingredient in human metabolic process. It is involved in sugar metabolism and can be converted into glucose (Xu and Ma, 1998). Injection of excessive D-galactose to animals could induce AD model with the features of abnormal glucose, lipid metabolism and the pathological features, including brain aging (Chu and Li, 2003). The main performance is the reduction of learning, memory and cognitive ability. Meantime, it is accompanied by the index of abnormal free radical expression and blood rheology. For instance, Tan et al. used this model to study the improving learning and memory effects and mechanisms of the aerial part of *Verbena officinalis* Linn. (马鞭草). Results showed that this medicine plant can significantly prolong the step-through latency of the AD mice and reduce errors number. Additionally, A $\beta$  content in brain tissue and serum also decreased significantly (Tan and Wang, 2011).

### 5.2. APP transgenic AD animal model

With structure features of cell surface receptors, A $\beta$ -precursor protein (APP) is the precursor protein of A $\beta$ , consisting of 695–720 amino acids with numerous subtypes (such as APP 695, APP 751, and APP 770). A $\beta$  is a cleavage product of the APP by the  $\beta$ - and  $\gamma$ -secretases (Bryan and Debomoy, 2011). Cleavage of APP by  $\beta$ -secretase or  $\beta$ -site APP cleaving enzyme 1 (BACE1) releases the large extracellular domain of APP (Hussain et al., 1999; Sinha et al., 1999; Vassar et al., 1999; Yan et al., 1999), and subsequent cleavage by  $\gamma$ -secretase releases A $\beta$  and the APP intracellular domain fragment (AICD) (Kimberly et al., 2001). Coding sequence mutations in the APP gene are linked to autosomally dominant AD (Selkoe and Schenk, 2003). The concentration and deposition of A $\beta$  can be used for the quantitative analysis to reflect the severity of brain levels of A $\beta$  and A $\beta$  deposition. For instance, APPV71I transgenic mice were developed by Chinese Academy of Medical Sciences. Its spatial learning and memory ability decreased in 4–6 months animals and A $\beta$  deposition began to appear significantly in 10 month animals (Qin et al., 2000a, 2000b). Meantime, data showed that ginsenoside, derived from the roots of *Panax ginseng* C.A. Mey. 人參, significantly increased the expression of synaptophysin in this model, revealing that ginsenoside dose-dependent improved synaptophysin expression to prevent A $\beta$  protein deposition (Li, 2013).

### 5.3. AD animal model by injection of A $\beta$ protein

A $\beta$ , a peptide of 39–43 amino acids, was considered to induce inflammation and oxidative stress in the brain. These factors have been postulated to play very important roles in the pathogenesis

of AD with property of learning and memory ability impairment (Ding et al., 2011). Researchers have found that the senile plaques were infiltrated by reactive microglias and astrocytes in brain of AD patients (Schwab and McGeer, 2008), suggesting inflammation contributes to the pathogenesis of AD. Therefore, injection of A $\beta$  protein into the animal brain can directly establish AD animal model (Ding et al., 2011). When such inflammation affects hippocampus function even without apparent neuron death, learning and memory impairment could occur (McGeer et al., 2006; Tanaka et al., 2006). Because A $\beta$  deposition in brain can damage neurons, inducing neuronal apoptosis and reduction, which is one of the most important mechanisms of AD. There are generally three kinds of A $\beta$  proteins, namely A $\beta_{1-42}$ , A $\beta_{1-40}$  and A $\beta_{25-35}$ . Zhou Jun injected A $\beta_{1-42}$  into rat brain to prepare AD model. The main pathological features included cell growth activity decreasing obviously, neurons damaging, and apoptotic morphological concentration increasing. Then, this model was used to explore the treatment of the paeoniflorin, extracted from the roots of *Paeonia lactiflora* Pall. (赤芍). The results showed that, compared with the model group, cortical injury degree of the paeoniflorin group was significantly reduced, and the apoptosis cells significantly decreased. Above data showed that paeoniflorin can antagonize the pathology of AD model by inducing A $\beta_{1-42}$  expression, including morphology, biochemistry and behavior change. Therefore, paeoniflorin can be used as an effective drug to develop in the treatment of AD pathological process (Zhou, J. et al., 2011).

### 5.4. Natural aging animal model of AD

Aging is one of the factors leading to the dysfunction of the normal cellular regulation, affecting both central nervous and immune systems (Kawakami et al., 1999). It is an important risk factor of various chronic diseases, including cancer, cardiovascular diseases and neurodegenerative diseases such as AD (Yua et al., 2005). Aging accounts for more than 50% cases for sporadic AD (Holliday, 1996). Cognitive impairment and other neurological functional changes also occur naturally in the natural aging AD animal model. Therefore, the change of real pathology of this model is more close to the human AD disease. Current studies suggest that development of anti-aging drugs from Chinese medicinal herbs may be one of the possible interventions (Bastianetto and Quirion, 2002; Chang, 2001; Lei et al., 2003). Oriental herbal medicine has been widely investigated for drug development because it has fewer side effects and it is much safer to be used than that of synthetic compounds (Wong et al., 1994). In China, Epimedium is widely used for the treatment of age related diseases, and icariin, isolated from aerial part of *Epimedium davidii* Franch. (淫羊藿), is one of the active components. For example, Wu Bin et al. found that by using the natural aging animal model, compared with the model group, icariin has an obvious positive effect on cognition result, and at the same time, neural stem cell activities has also been increased significantly. Therefore, icariin can also be developed as a candidate drug for the treatment of AD (Wu et al., 2012).

### 5.5. Learning and memory improvement

AD is a chronic neurodegenerative disease, seriously harming the physical and mental health of the elderly population. Its primary symptoms are the irreversible degenerations of intelligence, memory, sensory orientation ability, thinking ability and language sense. Studies have confirmed that a variety of CMM can improve the animal learning and memory function on the normal and disease models. For instance, Yu Hong et al. confirmed that apigenin, isolated from the leaf of *Apium graveolens* Linn. (旱芹) could improve the learning and memory ability of AD rats made by

**Table 2**  
Cell and animal models for CMM with anti-AD activity.

Inducer	Object	Components or extracts	CMM	Pinyin	Refs.
$\text{A}\beta_{1-40}$	Wistar rats	Grape seed proanthocyanidin	Leaf of <i>Vaccinium uliginosum</i> Linn.	Yue Ju (越橘)	Cai et al. (2011)
	SD rats	Ethanol extract and water extract	Dry stems of <i>Eleocharis dulcis</i> (Burm. F.) Trin. Ex Henschel	Tong Tian Cao (通天草)	Li, B.L. et al. (2012)
		Gastrodin	Tuber of <i>Gastrodia elata</i> Blume	Tian Ma (天麻)	Liu and Wang (2012)
		Salidroside	Whole herb of <i>Rodiola sachalinensis</i> A. Bor	Hong Jing Tian (红景天)	Zhang et al. (2012)
		Granules	Dry roots of <i>Angelica biserrata</i> (Shan et Yuan) Yuan et Shan	Du Huo (独活)	Zhu et al. (2011)
		Tanshinone II A extract	Bulbus of <i>Salvia miltiorrhiza</i> Bunge	Dan Shen (丹参)	Jiang et al. (2010)
		Turmerone	Roots of <i>Boschniakia rossica</i> P.E.	Cao Cong Rong (草苁蓉)	Fu et al. (2011); Zhou et al. (2009)
		Water, ethanol and acetone extract	Rhizome of <i>Curcuma longa</i> Linn.	Jiang Huang (姜黄)	Meng et al. (2012)
		Ginsenoside Rd	Seeds of <i>Juglans regia</i> L.	He Tao Ren (核桃仁)	Zhou, L.S. et al. (2011)
	Kunming mice	Fucoidan	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Liu et al. (2012)
$\text{A}\beta_{1-42}$	HEK293sw cells	Huperzine A	Whole herb of <i>Ecklonia kurome</i> Okam.	Kun Bu (昆布)	Zhao et al. (2010)
	PC-12 cells	Magnolol and honokiol	Velamen of <i>Magnolia officinalis</i> et Wils	She Zu Shi Shan (蛇足石杉)	Zhang et al. (2004)
	SD rats	Paeonol	Bark of <i>Paeonia suffruticosa</i> Andr.	Hou Po (厚朴)	Hoi et al. (2012)
		Tetrandrine	Dried root of <i>Stephania tetrandra</i> S. Moore	Mu Dan Pi (牡丹皮)	Zhou J. et al. (2011)
		Brevicarpine	Roots of <i>Erigeron breviscapus</i> (Vant.) Hand Mazz.	Han Fang Ji (汉防己)	He et al. (2011)
$\text{A}\beta_{25-35}$	Wistar rats	Decoction, decoctum without oil and essential oil	Rhizoma of <i>Acorus gramineus</i> Soland.	Xi Xin (细辛)	Mei et al (2012)
	Kunming mice			Shi Chang Fu (石菖蒲)	Tian et al. (2012)
	Male ICR mice	4-O-methylhonokiol	Bark of <i>Magnolia officinalis</i> et Wils	Hou Po (厚朴)	Lee et al. (2010)
	Primary cortical neuron	Catalpol	Bulbus of <i>Salvia miltiorrhiza</i> Bunge	Dan Shen (丹参)	Liang et al. (2009)
	SD rats	Inulinicin	Inflorescence of <i>Inula japonica</i> Thunb.	Xuan Fu Hua (旋覆花)	Wang et al. (2008)
		Polysaccharide	Mycelium of <i>Ganoderma lucidum</i> (Leyss. ex Fr.) Karst.	Ling Zhi (灵芝)	Guo et al. (2006)
		Extract	Roots of <i>Astragalus membranaceus</i> (Fisch.) bge.	Huang Qi (黄芪)	Zhang et al. (2007)
		Schisandrone	Fruit of <i>Schisandra sphenanthera</i> Rehd et Wils	Hua Zhong Wu Wei Zi (华中五味子)	Lv et al. (2007)
			Fruits of <i>Glycine max</i> (Linn.) Merr.	Da Dou (大豆)	Cai et al. (2012); Cai et al. (2013); Yang et al. (2005)
				Ji Li (蒺藜)	Zhang J. et al. (2011)
$\text{AlCl}_3$	Wistar rats	Isoflavone	Fruits of <i>Tribulus terrestris</i> Linn.	Di Huang (地黄)	Wang et al. (2009)
	Kunming mice	Gross saponins	Roots of <i>Rehmannia glutinosa</i> (Gaertn.) Libosch. ex Fisch. et Mey.	Dan Shen (丹参)	Zhou, Y.Q. et al. (2011)
		Catalpol	Bulbus of <i>Salvia miltiorrhiza</i> Bunge	Ren Shen (人参)	Xie, C.M. et al. (2010); Xie, X. et al. (2010)
	PC-12 cells	Tanshinones	Roots of <i>Panax ginseng</i> C.A. Mey.	Gou Teng (钩藤)	Xian et al. (2012a)
		Ginsenoside Rb1	Roots of <i>Uncaria rhynchophylla</i> (Miq.) ex Havil	Gou Teng (钩藤)	Xian et al. (2012b)
		Rhynchophylline; isorhynchophylline	Roots of <i>Uncaria rhynchophylla</i> (Miq.) ex Havil	Mu Dan (牡丹)	Li, S.P. et al. (2012)
		Isorhynchophylline	Velamen of <i>Paeonia suffruticosa</i> Andrews	Chi Shao (赤芍)	Li, S.M. et al. (2012)
	SD rats	Paeonol	Roots of <i>Paeonia lactiflora</i> Pall.	Zang Hong Hua (藏红花)	Shati, et al. (2011)
		Paeoniflorin	Dried red stigma of <i>Crocos sativus</i> L.	Yuan Zhi (远志)	Jia et al. (2004)
		Aqueous extract	Roots of <i>Polygala tenuifolia</i> Willd.	Huang Lian (黄连)	Asai et al. (2007)
App	Balb/c and C57BL/6 mice	Tenuigargin	Rhizome of <i>Coptis chinensis</i> Franch.	Jiang Huang (姜黄)	Wang et al. (2011)
	SH-SY5Y APP 695 cells	Berberine	Rhizome of <i>Curcuma longa</i> Linn.	Zhi Zi (梔子)	Li (2013)
	APP <sub>NL</sub> -H4 cells	Turnerone	Fruits of <i>Gardenia jasminoides</i> Ellis		
	Appsw/PS1dE9 Mice	Gardenoside	Dry roots of <i>Rodiola sachalinensis</i> A.Bor.	Hong Jing Tian (红景天)	Zhu et al. (2004)
	Heterozygous APP V717I transgenic mice		The fruit of <i>Evodia rutaecarpa</i> Benthem	Wu Zhu Yu (吴茱萸)	Yuan et al. (2011)
Arac	APP-C100 transgenic mice	Drug Rhodiola	Aerial part of <i>Epimedium davidii</i> Franch	Yin Yang Huo (淫羊藿)	Wu et al. (2012)
	APP <sup>swe</sup> /PS1 <sup>ΔE9</sup> double-transgenic mouse	Evodiamine	Fruits of <i>Litchi chinensis</i> var. <i>eupsonstanea</i> Hsue	Li Zhi (荔枝)	Li and Wang (2012)
D-Galactose	Aging rats and quiescent neural stem cells	Icariin	Whole herb of <i>Sargassum fusiforme</i> (Hary) Seichert	Yang Xi Cai (羊栖菜)	Tang et al. (2012)
	SD rats	Saponin			
		Polysaccharide			

		Huang Jing Drug	Dry rhizoma of <i>Polygonatum sibiricum</i> Red.	Huang Jing (黄精)	Ma (2011)
		95% Ethanol extract	Dry rhizoma <i>Valeriana amurensis</i> Smir. ex Komarov in Bull.	Hei Shui Xie Cao (黑水缬草)	Zhang et al. (2010); Zuo et al. (2010)
		Water extract	Roots of <i>Astragalus mongolicus</i> Bge	Huang Qi (黄芪)	Wan et al. (2011)
		Catalpol	Roots of <i>Rehmannia glutinosa</i> (Gaertn.) Libosch.ex Fisch.et Mey.	Di Huang (地黄)	Zhang et al. (2008a); Zhang et al. (2008b)
		Flavonoids	Dry secretions of <i>Apis mellifera</i> L.	Feng Jiao (蜂胶)	Su et al. (2010)
		Extract	Fermented culture materials of <i>Hericium erinaceus</i> (Rull ex F.) Pers.	Hou Tou Jun (猴头菌)	Liu and Jiang (2010)
		Decoction	Dry aerial parts of <i>Verbena officinalis</i> Linn.	Ma Bian Cao (马鞭草)	Tan and Wang (2011)
		Water extract	Dry roots of <i>Psychotria rubra</i> (Lour.) Poir	Shan Da Yan(山大颜)	(Zhang J.H. et al., 2011)
		Allitridium	Bulb of <i>Allium sativum</i> Linn.	Da Suan (大蒜)	Hu et al. (2010)
		Gypenosides	Roots of <i>Gynostemma pentaphyllum</i> (Thunb.) Makino.	Jiao Gu Lan (绞股蓝)	Zhou et al. (2012)
		Polyphehols	Leaves of <i>Camellia sinensis</i> Linn.	Lv Cha (绿茶)	Xu and Zhang (2008)
d-Galactose, AlCl <sub>3</sub>	SD rats	Ginsenoside Rb1, Rg1	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Yang et al. (2008); Xu and Lai (2007)
		Granules	Dry roots of <i>Rhodiola sachalinensis</i> A.Bor.	Hong Jing Tian (红景天)	Sun et al. (2012)
	Kunming mice	Resveratrol	Roots of <i>Veratrum nigrum</i> Linn.	Li Lu (藜芦)	Lin et al. (2009)
		Leaf Tablets	Leaf of <i>Ginkgo biloba</i> Linn.	Yin Xing (银杏)	Xie, C.M. et al. (2010); Xie, X. et al. (2010)
		Apigenin	Leaf of <i>Apium graveolens</i> Linn.	Han Qin (旱芹)	Zhao et al. (2005)
		HS <sub>2</sub>	Caulis of <i>Kadsura heteroclita</i> (roxb.) Craib	Hai Feng Teng (海风藤)	Xiao et al. (2004)
Ibotenicacid	SD rats	Matrine injection	Roots of <i>Sophora Flavescens</i> P.E.	Ku Shen (苦参)	Ni et al. (2006)
glutamate	PC-12 cells	Sarsasapogenin	Dry stems of <i>Anemarrhena asphodeloides</i> Bunge.	Zhi Mu (知母)	Hu et al. (2007)
Glutamic acid	Kunming mice	Ginsenoside Rg2	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Li, N. et al. (2007); Li, Q.C. et al. (2007)
Gluconic acid, aluminum	Kunming mice	Gross saponins	Fruits of <i>Tribulus terrestris</i> Linn.	Ji Li (蒺藜)	Ma and Qu (2009)
Okadaic acid	Wistar rats	Ginsenoside Rg1	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Qi and Ai (2011)
		Iridoid glycosid	Fleshoffruit of <i>Cornus officinalis</i> Sieb.et Zucc	Shan Zhu Yu (山茱萸)	Chu et al. (2009)
		Ginkgolides	Leaf of <i>Ginkgo biloba</i> Linn.	Yin Xing (银杏)	Li, N. et al. (2007); Li, Q.C. et al. (2007)
Quinolinic acid	Wistar rats	Quercetin	Whole herb of <i>Ruta graveolens</i> Linn.	Lu Ding (芦丁)	Li et al. (2003)
Scopolamine	SD rats	Silibinin	Seed coat of <i>Silybum marianum</i> Gaertn.	Shui Fei Ji (水飞蓟)	Bi et al. (2012)
	Swiss mice	Standardized extracts	Leaf of <i>Ginkgo biloba</i> Linn.	Yin Xing (银杏)	Das et al. (2002)
	SD rats	Dehydroevodiamine hydrochloride	the fruit of <i>Evodia rutaecarpa</i> Bentham	Wu Zhu Yu (吴茱萸)	Park et al. (1996)
	Male ICR mice	Lancemaside A	Rhizome of <i>Codonopsis lanceolata</i>	Yang Ru (羊乳)	Jung et al. (2012)
Senescence	Mice	Magnolol and honokiol	Velamen of <i>Magnolia officinalis</i> et Wils	Hou Po (厚朴)	Nobuaki et al. (2009)
SweAPP	SK-N-SH cells	Ginsenoside Rg3	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Yang et al. (2009)
-	Aging guinea pigs	Water-soluble extracts	Bulbus of <i>Salvia miltiorrhiza</i> Bunge	Dan Shen (丹参)	Hou et al. (2007)
-	Mitochondriatransgenic neuronal cell	Puerarin	Roots of <i>Pueraria lobata</i> (Willd.) Ohwi	Ge Gen (葛根)	Zhang, H.Y. et al. (2011)
-	SAMP8 mice	Polysaccharides	Roots of <i>Millettia pulchra</i> (Benth.) Kurz var. laxior (Dunn) Z. Wei	Long Yan Shen (龙眼参)	Huang, Z.S. et al. (2008)
		Evodiamine	the fruit of <i>Evodia rutaecarpa</i> Bentham	Wu Zhu Yu (吴茱萸)	Yuan et al. (2011)
-	Tgrnd8 mice	Berberine	Roots from <i>Coptis chinensis</i> Franch Franch	Huang Lian (黄连)	Durairajan et al. (2012)
-	Tg2576 mice	Ethanol extract	Bark of <i>Magnolia officinalis</i> et Wils	Hou Po (厚朴)	Lee et al. (2012)
		Ginsenoside Rg3	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	Feng et al. (2006)

D-galactose and AlCl<sub>3</sub> (Zhao et al., 2005). It could reduce the mice's learning times and improve their learning abilities.

To sum up, to a certain extent, the symptom and pathology changes of each AD animal and cell model are similar to or partly similar to AD disease, where they have a certain scope of application, the functional characteristics and their advantages and disadvantages. But at present, there is no AD model that can change completely or simulate human AD pathology and behavior. Therefore, different AD animal models can be used simultaneously in evaluation of CMM on the effectiveness and pharmacological mechanism, in order to achieve the goal of the different aspects of the prevention and treatment of AD. It is worth noting that, CMM is worthy of further experimental and clinical research on the curative effect for many scholars, and to provide more useful scientific data for research of anti-AD drugs of CMM.

## 6. Extracts and isolates with activity against AD targets *in vitro*

### 6.1. Reduction of A $\beta$ protein deposition

A $\beta$  deposition is an early and critical event in the pathogenesis of AD (Emilien et al., 2000), and it is also the core component of senile plaques in AD patients (Gervais et al., 1999). Therefore, the A $\beta$  cascade theory holds that the increase and deposition of A $\beta$  in brain is the starting factor in the pathogenesis of AD, and reducing A $\beta$  generation or increasing of A $\beta$  clearance can reduce AD upset (Golde et al., 2006). This mechanism is also one of the important methods to determine the efficacy of CMM against the AD model. As Siva et al. reported in the TgCRND8 transgenic mouse model, berberine, isolated from the roots of *Coptis chinensis* Franch (黄连) could significantly improve the learning level and spatial memory with long term, and it could also greatly reduce the A $\beta$  protein levels in brain homogenates. At the same time, berberine can inhibit the C-terminal fragment of APP and its phosphorylation in N2a-SwedAPP695 cell model. To sum up, various data showed that berberine played the neuroprotective role in TgCRND8 mouse AD model and N2a-SwedAPP695 cells AD model by adjusting the APP of the physiological processes. Thus berberine can be used as a candidate drug for the treatment of AD (Durairajan et al., 2012).

### 6.2. Inhibition of acetylcholinesterase

Acetylcholine (Ach) is an important neurotransmitter of the central cholinergic systems, and especially it plays an important role in spatial working memory, storage and extraction. In addition to the role of hydrolysis acetylcholine, acetylcholinesterase (AchE) could promote axonal growth, involved in cell interaction, with participation in axon formation to activate dopamine neurons and promote the  $\beta$  amyloid peptide like precipitation function (Soreq and Seidman, 2001). At present, the acetylcholinesterase inhibitor (AchEI) is thought to be one of the first drugs used on AD patients with FDA approval. Among them, most are derived from plants, such as huperzine and galanthamine (Lin et al., 2008). For example, Zhou Weihua et al. studied the effect of Gypenoside (isolated from the roots of *Gynostemma pentaphyllum* (Thunb.) Makino.(绞股蓝)) on the function of hippocampal cholinergic system in the AD mice model induced by D-galactose. The results showed that, compared with the model group, learning and memory functions of the AD model mice can be obviously improved by gypenosides, which could reduce the activity of AchE and improve the hippocampal cholinergic system function (Zhou et al., 2012).

### 6.3. Neuronal apoptosis inhibition

Research shows that AD is the result of pathological cell apoptosis occurring in central nervous system (Savitz, 1998), and the BCL-2 family, including promoting apoptosis gene Bax and inhibiting apoptosis gene Bcl-2, plays an important role in the regulation of neuronal apoptosis and survival (Orike et al., 2001; Zhang and Rosdahi, 2006). The over expression of Bcl-2 may reduce neuronal programmed cell death and increase the number of neurons from the specific brain region, while over expression of Bax could promote apoptosis of neurons. When Bcl-2 and Bax proteins form dimers, the changes of Bax/Bcl-2 ratio may decide caspase-3 expression, which is closely related to apoptosis and proliferation of neuronal cells. Research has shown that neuronal apoptosis could be induced by oxidative stress and modified mitochondria gene, and the Bax/Bcl-2 ratio can then be inhibited significantly after puerarin (isolated from the roots of *Pueraria lobata* (Willd.) Ohwi(葛根)) intervention, and caspase-3 expression could be further prevented. Therefore, puerarin could antagonize neuronal apoptosis induced by oxidative stress by inhibition of neuronal apoptosis (Zhang, H.Y. et al., 2011).

### 6.4. Antioxidant effect

As we all know, aging is caused by the imbalance of many factors, including oxygen free radicals, lipid peroxidation, malondialdehyde, superoxide dismutase and catalase. Among them, free radicals can damage macromolecules protein, DNA and lipid peroxidation, resulting in nerve cell apoptosis and deletion and leading learning and memory deficits, and then causing or exacerbating AD (Masaaki et al., 2005). In recent years, the relationship between the free radical and AD is attracting more and more attention from scholars, and is considered as one of the most important risk factors of AD. Malondialdehyde (MDA) levels, an index of lipid peroxidation, produced by free radicals and is the intermediate product of lipid pigment formation process. It can indirectly reflect the lipid peroxidation level, leading to nerve cells damage within the protein metabolism disorder caused by cell dysfunction, thus exhibiting memory and intellectual decline (Naghizadeh et al., 2013). Superoxide dismutase (SOD) is a natural antioxidant substance in the body. It can eliminate free radicals and resist free radical injury, reducing lipid peroxidation and MDA content, and maintaining biological membrane structure and function (Gao et al., 2012). Glutathione peroxidase (GSH-Px) is a kind of important peroxidase which exists widely in the body, being one of indexes of the anti peroxidative ability (Naghizadeh et al., 2013). Lv Jianyong et al. established AD animal model by stereotactic injection of A $\beta_{25-35}$  into lateral ventricle, and schisandrone (isolate from the fruit of *Schisandra sphenanthera* Rehd et Wils (华中五味子)) was administrated in rats for drug intervention. Compared with the model group, escape latency decreased in the schisandrone group, which was however significantly higher than AD model group in the activity of SOD and GSH-Px in the brain. Thus, schisandrone can significantly improve the learning and memory abilities of AD model rats induced by A $\beta_{25-35}$ , which may be related to the increase of the activities of the antioxidant enzyme system and the removal of oxygen free radicals in brain (Lv et al., 2007).

### 6.5. Regulation of NO content in brain

NO is a gaseous signal molecule in central nervous system, being closely related to the development of the nervous system including maturity, learning and memory abilities (Veltkamp et al., 2002). Under normal circumstances, neurons synthesize and release the right amount of NO, which can be involved in guiding

**Table 3**  
Extracts and isolates with activity against AD targets.

No.	Component	CMM	Pinyin	Learning ability	A $\beta$	AChE	ROS	caspase-3	Bax/Bcl-2 ratio	GSH-ST	SOD	MDA	iNOS	Refs.
1	Allitridium	Bulb of <i>Allium sativum</i> Linn.	Da Suan (大蒜)							↑	↓			Hu et al. (2010)
2	Apigenin	Leaf of <i>Apium graveolens</i> Linn.	Han Qin (旱芹)	↑										Zhao et al. (2005)
3	Aqueous and ethanol extract	Caulis of <i>Spatholobus suberectus</i> Dunn.	Ji Xue Teng (鸡血藤)			↓								Lin et al. (2008)
4	Aqueous extract	Dried red stigma of <i>Crocus sativus</i> L.	Zang Hong Hua (藏红花)							↑				Shati et al. (2011)
5	Berberine	Roots from <i>Coptis chinensis</i> Franch	Huang Lian (黄连)	↑		↓								Durairajan et al. (2012)
6	Breviscapine	Roots of <i>Erigeron breviscapus</i> (Vant.) Hand Mazz.	Xi Xin (细辛)	↑						↑	↑	↓		Mei et al. (2012)
7	Caltrop saponin	Fruits of <i>Tribulus terrestris</i> Linn.	Ji Li (蒺藜)							↑				Zhang, J. et al. (2011)
8	Catalpol	Roots of <i>Rehmannia glutinosa</i> (Gaertn.) Libosch.ex Fisch.et Mey.	Di Huang (地黄)		↓	↓	↓	↓	↓	↑	↑	↓		Wang et al. (2009); Liang et al. (2009); Zhang et al. (2008a); Zhang et al. (2008b)
9	Decoction	Dry aerial parts of <i>Verbena officinalis</i> Linn.	Ma Bian Cao (马鞭草)	↑		↓								Tan and Wang (2011)
10	Decoctum, decoctum without oil and essential oil	Rhizoma of <i>Acorus gramineus</i> Soland.	Shi Chang Fu (石菖蒲)								↓			Tian et al. (2012)
11	Dehydroevodiamine hydrochloride	the fruit of <i>Evodia rutaecarpa</i> Bentham	Wu Zhu Yu (吴茱萸)			↓								Park et al. (1996)
12	Ethanol extract of Magnolia officinalis et Wils	Bark of <i>Magnolia officinalis</i> et Wils	Hou Po (厚朴)	↑		↓								Lee et al. (2012)
13	Ethanol extract of Magnolia officinalis et Wils	Bark of <i>Magnolia officinalis</i> et Wils	Hou Po (厚朴)								↓			Lee et al. (2013)
14	Ethanol extract and water extract	Dry stems of <i>Eleocharis dulcis</i> (Burm. F.) Trin. Ex Henschel	Tong Tian Cao (通天草)	↑		↓				↑	↓			Li, B.L. et al. (2012)
15	Evodiamine	the fruit of <i>Evodia rutaecarpa</i> Bentham	Wu Zhu Yu (吴茱萸)	↑										Yuan et al. (2011)
16	Extract	Fermented culture materials of <i>Hericium erinaceus</i> (Rull ex F.) Pers.	Hou Tou Jun (猴头菌)		↓									Liu and Jiang (2010)
17	Extract	Roots of <i>Boschniakia rossica</i> P.E.	Cao Cong Rong (草苁蓉)	↑		↓								Fu et al. (2011); Zhou et al. (2009)
18	Extract	Roots of <i>Polygonum multiflorum</i> Thunb.	He Shou Wu (何首乌)	↑							↓			Lin (2004)
19	Extract	Roots of <i>Astragalus membranaceus</i> (Fisch.) bge.	Huang Qi (黄芪)	↑		↓	↓	↓	↓					Zhang et al. (2007); Wan et al. (2011)
20	Flavonoids	Dry secretions of <i>Apis mellifera</i> L.	Feng Jiao (蜂胶)							↑				Su et al. (2010)
21	Fucoidan	Whole herb of <i>Ecklonia kurome</i> Okam.	Kun Bu (昆布)	↑		↓								Zhao et al. (2010)
22	Gastrodin	Tuber of <i>Gastrodia elata</i> Blume	Tian Ma (天麻)	↑						↑				Liu and Wang (2012)
23	Ginkgolides	Leaf of <i>Ginkgo biloba</i> Linn.	Yin Xing (银杏)	↑										Li, N. et al. (2007); Li, Q.C. et al. (2007)
24	Ginkgo Leaf Tablets	Leaf of <i>Ginkgo biloba</i> Linn.	Yin Xing (银杏)		↓					↑	↓			Nongnut et al. (2010)
25	Ginsenoside Rb1	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)				↓	↓	↓	↑				Xie, C.M. et al. (2010); Xie, X. et al. (2010); Qian et al. (2009)
26	Ginsenoside Rb1	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)			↓								Lv et al. (2012)
27	Ginsenoside Rb1, Rg1	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)	↑	↓	↓			↓					Yang et al. (2008); Xu and Lai (2007)
28	Ginsenoside Rd	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)					↓						Liu et al. (2012)
29	Ginsenoside Rg1	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)							↑	↓			(Qi and Ai, 2011)
30	Ginsenoside Rg2	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)		↓		↓							Li, N. et al. (2007); Li, Q.C. et al. (2007)
31	Ginsenoside Rg3	Roots of <i>Panax ginseng</i> C.A. Mey.	Ren Shen (人参)		↓		↓							Yang et al. (2009); Feng et al. (2006)
32	Granules	Dry roots of <i>Angelica biserrata</i> (Shan et Yuan) Yuan et Shan	Du Huo (独活)	↑										Zhu et al. (2011)
		Dry roots of <i>Rhodiola sachalinensis</i> A. Bor.	Hong Jing Tian (红景天)	↑										Sun et al. (2012)

**Table 3** (continued)

No.	Component	CMM	Pinyin	Learning ability	A $\beta$	AChE	ROS	caspase-3	Bax/Bcl-2 ratio	GSH-ST	SOD	MDA	iNOS	Refs.
34	Gypenosides	Roots of <i>Gynostemma pentaphyllum</i> (Thunb.) Makino.	Jiao Gu Lan (绞股蓝)	↑	↓									Zhou et al. (2012)
35	HS2	Caulis of <i>Kadsura heteroclita</i> (roxb.) Craib	Hai Feng Teng (海风藤)	↑										Xiao et al. (2004)
36	Huang Jing Drug	Dry rhizoma of <i>Polygonatum sibiricum</i> Red.	Huang Jing (黄精)				↓							Ma (2011)
37	Huperzine A	Whole herb of Whole herb of <i>Huperzia serrata</i> (Thunb.) Trev.	Qian Ceng Ta (千层塔)			↓								He et al. (2003)
38	Icarin	Aerial part of <i>Epimedium davidii</i> Franch	Yin Yang Huo (淫羊藿)	↑										Wu et al. (2012)
39	Inulinicin	Inflorescence of <i>Inula japonica</i> Thunb.	Xuan Fu Hua (旋覆花)	↑							↓			Wang et al. (2008)
40	Iridoid glycosid	Fleshoffruit of <i>Cornus officinalis</i> Sieb. et Zucc	Shan Zhu Yu (山茱萸)			↓		↓						Chu et al. (2009)
41	Isoflavone	Fruits of <i>Glycine max</i> (Linn.) Merr.	Da Dou (大豆)	↑	↓					↑	↓			Cai et al. (2012); Cai et al. (2013); Yang et al. (2005)
42	Isorhynchophylline	Roots of <i>Uncaria rhynchophylla</i> (Miq.) ex Havil	Gou Teng (钩藤)				↓	↓						Xian et al. (2012b)
43	Lancemaside A	Rhizome of <i>Codonopsis lanceolata</i>	Yang Ru (羊乳)	↑										Jung et al. (2012)
44	Magnolol and honokiol	Velamen of <i>Magnolia officinalis</i> et Wils	Hou Po (厚朴)	↑	↓	↓								Nobuaki et al. (2009); Hoi et al. (2012)
45	Paeoniflorin	Roots of <i>Paeonia lactiflora</i> Pall.	Chi Shao (赤芍)	↑										Li S.M. et al. (2012)
46	Paeonol	Velamen of <i>Paeonia suffruticosa</i> Andrews	Mu Dan (牡丹)	↑				↓						Zhou J. et al. (2011)
47	Polyphenols	Leaves of <i>Camellia sinensis</i> Linn.	Lv Cha (绿茶)		↓	↓		↓		↑	↓			Xu and Zhang (2008)
48	Polysaccharide	Roots of <i>Milletia pulchra</i> (Benth.) Kurz var. laxior (Dunn) Z.Wei	Long Yan Shen (龙眼参)	↑										Huang, Z.S. et al. (2008)
49	Polysaccharide	Mycelium of <i>Ganoderma lucidum</i> (Leyss. ex Fr.) Karst.	Ling Zhi (灵芝)	↑				↓		↑	↓			Guo et al. (2006)
50	polysaccharide	Whole herb of <i>Sargasum fusiforme</i> (Hary) Seichell	Yang Xi Cai (羊栖菜)	↑				↓						Tang et al. (2012)
51	Puerarin	Roots of <i>Pueraria lobata</i> (Willd.) Ohwi	Ge Gen (葛根)			↓	↓	↓						Zhang, H.Y. et al. (2011)
52	Proanthocyanidin	Leaf of <i>Vaccinium uliginosum</i> Linn.	Yue Ju (越橘)	↑				↓		↑	↓			Cai et al. (2011)
53	Quercetin	Whole herb of <i>Ruta graveolens</i> Linn.	Lu Ding (芦丁)	↑				↓		↑	↓			Li et al. (2003)
54	Resveratrol	Roots of <i>Veratrum nigrum</i> Linn.	Li Lu (藜芦)		↓			↓		↑	↑	↓		Lin et al. (2009)
55	Salidroside	Whole herb of <i>Rhodiola sachalinensis</i> A. Bor	Hong Jing Tian (红景天)							↑	↓	↓		Zhang et al. (2012)
56	Saponin	Fruits of <i>Tribulus terrestris</i> Linn.	Ji Li (蒺藜)	↑										Ma and Qu (2009)
57	Saponin	Fruits of <i>Litchi chinensis</i> var. eupontanea Hsue	Li Zhi (荔枝)		↓									Li and Wang (2012)
58	Schisandrone	Fruit of <i>Schisandra sphenanthera</i> Rehd et Wils	Hua Zhong Wu Wei Zi (华中五味子)						↑	↑				Lv et al. (2007)
59	Silibinin	Seed coat of <i>Silybum marianum</i> Gaertn.	Shui Fei Ji (水飞蓟)	↑			↓							Bi et al. (2012)
60	Standardized extracts	Leaf of <i>Ginkgo biloba</i> Linn.	Yin Xing (银杏)		↓									Das et al. (2002)
61	Tanshinones	Bulbus of <i>Salvia miltiorrhiza</i> Bunge	Dan Shen (丹参)		↓									Zhou, Y.Q. et al. (2011)
62	Tanshinone II A	Bulbus of <i>Salvia miltiorrhiza</i> Bunge	Dan Shen (丹参)	↑	↓	↓								Jiang et al. (2010)
63	Tetrandrine	Dried root of <i>Stephanotis tetrandra</i> S. Moore	Han Fang Ji (汉防己)	↑										He et al. (2011)
64	Tenuiginin	Roots of <i>Polygala tenuifolia</i> Willd.	Yuan Zhi (远志)	↑		↓				↑	↓			Jia et al. (2004)
65	Turmerone	Rhizome of <i>Curcuma longa</i> Linn.	Jiang Huang (姜黄)	↑										Meng et al. (2012)

66	Water extract	Stem and branches of <i>Uncaria rhynchophylla</i> (Miq.) Jacks.	Gou Teng (钩藤)	Hironori et al. (2006)
67	Water extract	Dry roots of <i>Psychotria rubra</i> (Lour.) Poir	Shan Da Yan (山 大 颜)	Zhang, J.H. et al. (2011)
68	Water, ethanol and acetone extract	Seeds of <i>Juglans regia</i> L.	He Tao Ren (核 桃 仁)	Zhou, J.S. et al. (2011)
69	4-O-methylhonokiol	Bark of <i>Magnolia officinalis</i> et Wils	Hou Po 厚朴 ()	Lee et al. (2010)
70	95% ethanol extract	Dry rhizoma of <i>Valeriana amurensis</i> Smir. ex Komarov in Bull.	Hei Shui Xie Cao (黑水缬草)	Zhang et al. (2010); Zuo et al. (2010)

axonal growth and synaptic plasticity by promoting neurotransmitter release. If the nitric oxide synthase (NOS) continues to increase, releasing redundant NO, it will induce cytotoxic effects, resulting in damaged cells, and accelerating neuron apoptosis or death (Kim et al., 2005). Meanwhile, NO is also an important and typical free radical signal in the brain, generated by L-arginine catalyzed under NOS. NO generates free radicals, inhibiting the normal function of mitochondrial, by a series of reactions, and may eventually lead to cell death (Yu and Dong, 1996). Research shows that A $\beta$  could induce NOS mediated NO generation in large amounts via the activation of microglia and astrocytes, and then kill neurons in the brain (Combs et al., 2001). Jiang Ping et al. established AD rat model by A $\beta$  directly injection to study the effect of tanshinone II A (Tan II A) (isolated from bulbous of *Salvia miltiorrhiza* Bunge (丹参)) on learning and memory aspects, iNOS expression and its mechanism on free radical release. The results showed that compared with the model group, Tan II A intervention can significantly reduce NO, ONOO $^-$  and ROS content in hippocampus of AD rats, decrease the expression of iNOS and significantly improve the learning and memory ability of AD model rats. The above data showed that Tan II A can effectively alleviate the symptoms of AD, and the mechanism may be related to the inhibition of iNOS expression, reduction of the oxidation of toxic free radicals, and the damage of the inhibition of oxidative stress (Jiang et al., 2010).

On the one hand, in summary, a large number of literature and data show that, CMM plays a role against AD through different pathways and mechanisms, such as the improvement of behavior and memory, reduction of A $\beta$  protein deposition and inhibition of acetylcholinesterase activity and neuronal apoptosis, antioxidant activity and regulation of NO content in brain (see Tables 3–5). During the study on these aspects, some other mechanisms, such as anti-tumor, promoting inflammatory factors IL-1, IL-6, NF-KB, etc., anti-Tau, anti-neurofibrillary tangles, and anti-presenilin 1, are also present, but with less research data. However, these factors may have some important role in AD disease. For instance, one of the main symptoms of AD is abnormal phosphorylation of Tau protein. Recent studies have shown that compared with the abnormal deposition of A $\beta$ , the aggregation of Tau protein caused by hyperphosphorylation is more highly relevant to AD (Ludovic et al., 2013). In addition, studies show that the inflammatory reaction induced by A $\beta$  deposition also plays an important role in the pathogenesis of AD, translating the acute reaction under normal conditions into chronic inflammation through the continuous activation of inflammatory repair mechanism (Cotman et al., 1996). In this case, the immune inflammation theory on pathogenetic cause of AD indicates that anti-inflammatory drugs may play a certain role in preventing AD. Therefore, the scope of mechanism study should be expanded in the direction of future research, and researchers should not be concentrated on one of these mechanisms, but focus on different perspectives, aspects and ways in order to better illustrate the effects of anti-AD drugs.

On the other hand, AD pathogenesis has not been fully elucidated so far, although the majority of anti-AD drugs are used to improve the symptoms and slow the progression of the disease, especially in CMM field. CMM has rich theoretical and practical experiences in delaying the brain aging, with characteristics of a multiple pathological links in the treatment of the disease. Above statements and data show that CMM in the treatment of AD is through multi-targets, multiple-levels, and multiple-ways of therapy. Such features accord with complex pathogenesis of AD that with multiple links, multiple factors, and multiple ways. Meanwhile, whether from the material basis, the mechanism, or the clinical curative effect, the research needs to be interdisciplinary, using cutting-edge technology and means, to improve and solve many or more of the shortcomings.

**Table 4**  
Basic pharmacological data of anti-AD effect of CMM mentioned in the text.

CMM	Type of extract	Anti-AD experiments	Animal or cell	N	Dose range	Minimal active concentration	Model	Positive controls	Negative controls	Duration	Refs.
<i>Acorus gramineus</i> Soland (菖蒲) (Rhizoma)	$\beta$ -Asarone	Aluminum chloride( $AlCl_3$ ) and D-galactose (D-gal).	Rats	7	25–100 mg/kg	25 mg/kg	In vivo	Nimodipine	Saline water	14 d	Li, Z.Q. et al. (2012)
	Decoction	$\text{A}\beta_{1-42}$ -induced AD model	Mice	6	0.2 mL/10 g BW	0.2 mL/10 g BW	In vivo	–	Saline	3 w	Tian et al. (2012)
	Essential oil	$\text{A}\beta_{1-40}$ -induced AD model	Mice	6	0.2 mL/10 g BW	0.2 mL/10 g BW	In vivo	–	Isotonic saline solution	3 w	Limon et al. (2009)
<i>Allium sativum</i> Linn. (大蒜) (Bulb) <i>Anemarrhenes asphodeloides</i> Bunge. (知母) (Stems)	Allicin	D-galactose-induced AD model	Mice	10	0.48 g/kg	0.48 g/kg	In vivo	–	Saline	60 d	Hu et al. (2010)
	Sarsasapogenin	$\text{A}\beta_{1-40}$ -induced AD model	Rats	10	3.6–90 mg/kg	3.6 mg/kg	In vivo	Tacrine	–	60 d	Hu et al. (2007)
<i>Angelica biserrata</i> (Shan et Yuan) (独活) (Roots)	Water granula	$\text{A}\beta_{1-40}$ -induced AD model	Rats	9	0.365 mg/mL $\times$ 2 mL each rat	0.365 g/mL $\times$ 2 mL each rat	In vivo	Indometacin	Saline	28 d	Zhu et al. (2011)
<i>Apis mellifera</i> L. (蜂胶) (Dry secretions)	Propolis flavonoids	D-galactose-induced AD model	Mice	10	75–300 mg/kg	75 mg/kg	In vivo	Aniracetam capsules	Saline	7 w	Su et al. (2010)
<i>Apium graveolens</i> Linn. (旱芹) (Leaf) <i>Astragalus membranaceus</i> (Fisch.) bge. (黄芪) (Roots)	Apigenin	D-galactose-induced AD model	Mice	10	20–80 mg/kg	20 mg/kg	In vivo	Estradiol ( $E_2$ )	–	15 d	Zhao et al. (2005)
	Astragalosides	$\text{A}\beta_{25-35}$ -induced AD model	Rats	8	20–80 mg/kg	20 mg/kg	In vivo	–	0.5% CMC-Na	5 d	Zhang et al. (2007)
<i>Boschniakia rossica</i> P.E. (草苁蓉) (Roots)	Water extract	$\text{A}\beta_{1-40}$ -induced AD model	Rats	10	0.03 g/L $\times$ 1 mL–4 mL each rat	0.03 g/mL $\times$ 1 mL each rat	In vivo	–	–	28 d	Fu et al. (2011)
	Ethanol extract		Rats	10	0.03 g/ml $\times$ 1 mL–4 mL each rat	0.03 g/ml $\times$ 1 mL each rat	In vivo	–	–	24 d	Zhou et al. (2009)
<i>Codonopsis lanceolata</i> (羊乳) (Roots)	Lancemaside A	Scopolamine-induced memory and learning deficits in mice	Mice	6	10–20 mg/kg	10 mg/kg	In vivo	Donepezil	5% Tween 80	–	Jung et al. (2012)
<i>Coptis chinensis</i> Franch (黄连) (Roots)	Berberine	Alzheimer's disease transgenic mouse model	Mice	4–5	25–100 mg/kg	25 mg/kg	In vivo	–	Gavage	6 d	Durairajan et al. (2012)
<i>Cornus officinalis</i> Sieb.et Zucc (山茱萸) (Flesh fruit)	Cornel iridoid glycoside	Okadaic acid-induced AD model	Cells	–	50–200 $\mu$ g/kg	50 $\mu$ g/kg	In vitro	–	–	–	Chu et al. (2009)
<i>Crocus sativus</i> L (藏红花) (Red stigma)	Aqueous extract	$AlCl_3$	Mice	–	200 mg/kg	200 mg/kg	In vivo	Honey sirup	Saline	45 d	Shati et al. (2011)
<i>Curcuma longa</i> Linn. (姜黄) (Rhizome)	Curcumin	$\text{A}\beta_{1-40}$ -induced AD model	Rats	16	300 mg/kg	300 mg/kg	In vivo	–	Saline	7 d	Meng et al. (2012)
<i>Ecklonia kurome</i> Okam. (昆布) (Whole herb)	Fucoidan	$\text{A}\beta_{1-40}$ -induced AD model	Mice	15	50–200 mg/kg	200 mg/kg	In vivo	Donepezil	Saline	16 d	Zhao et al. (2010)
<i>Eleocharis dulcis</i> (Burm. F.) Trin. Ex Henschel (通天草) (Stems)	Ethanol extract	AD model	Rats	10	0.94–3.96 g/kg	0.94 g/kg	In vivo	Piracetam tablets	Saline	28 d	Li B.L. et al. (2012)
	water extract	AD model	Rats	10	0.50–2.00 g/kg	0.50 g/kg	In vivo	Piracetam tablets	–	28 d	
<i>Epimedium davidii</i> Franch (淫羊藿) (Aerial part)	Icariin	Aging rats	Rats	15	0.02 g/kg	0.02 g/kg	In vivo	–	Saline	5 d	Wu et al. (2012)
<i>Erigeron breviscapus</i> (Vant.) Hand Mazz. (细辛) (Roots)	Breviscapine	$\text{A}\beta_{1-42}$ -induced AD model	Rats	10	1–4 mg/kg	1 mg/kg	In vivo	HupA	Saline	3 w	Mei et al. (2012)
<i>Evodia rutaecarpa</i> Benthham (吴茱萸) (Fruit)	Evodiamine	SAMP8 and APP <sup>swe</sup> /PS1 <sup>ΔE9</sup> transgenic mouse models	Mice	16–20	50–100 mg/kg	100 mg/kg	In vivo	Aricept	–	4 w	Yuan et al. (2011)
	Dehydroevodiamine hydrochloride	Scopolamine	SD rats	10	6.25 mg/kg	6.25 mg/kg	In vivo	DHED or tacrine	Saline	24 h	Park et al. (1996)
<i>Ganoderma lucidum</i> (Leyss. ex Fr.) Karst (灵芝) (Mycelium)	Iisorhynchophylline	PC-12 Cells	Cells	–	1–50 $\mu$ M	1 $\mu$ M	In vitro	–	–	24 h	Xian et al. (2012b)
	Polysaccharid	$\text{A}\beta_{25-35}$ -induced AD model	Rats	12	50 mg/kg	50 mg/kg	In vivo	–	–	7 d	Guo et al. (2006)
<i>Gardenia jasminoides</i> Ellis (栀子) (Fruits)	Quercetin	Quinolinic acid-induced AD model	Rats	6	50–200 mg/kg	50 mg/kg	In vivo	Ketamine	Distilled water	20 d	Li (2013)

<i>Gastrodia elata</i> Blume (天麻) (Tuber)	Gastrodin	$\text{A}\beta_{1-40}$ -induced AD model	Rats	10	200 mg/kg	200 mg/kg	<i>In vivo</i>	Huperzine A	Saline	4 w	Liu and Wang (2012)
<i>Ginkgo biloba</i> Linn. (银杏) (Leaf)	Ginkgolides	Okadaic acid-induced AD model	Rats	12	50 mg/kg	50 mg/kg	<i>In vivo</i>	–	Saline with 1% DMSO	4 w	Li, N. et al. (2007); Li, Q.C. et al. (2007)
<i>Glycine max</i> (Linn.) Merr. (大豆) (Fruit)	Soybean isoflavone	$\text{A}\beta_{25-35}$ -induced AD model	Rats	10	3–9 mg/kg	3 mg/kg	<i>In vivo</i>	Estrogen	–	21 d	Cai et al. (2012)
		D-galactose-induced AD model	Rats	9–10	3–9 mg/kg	3 mg/kg	<i>In vivo</i>	Estradiol valerate	–	21 d	Cai et al. (2013)
<i>Gynostemma pentaphyllum</i> (Thunb.) Makino. (绞股蓝) (Roots)	Gypenosides	D-galactose-induced AD model	Mice	10	50–500 mg/kg	50 mg/kg	<i>In vivo</i>	–	–	15 d	Yang et al. (2005)
<i>Hericium erinaceus</i> (Rull ex F.) Pers. (猴头菌) (Fermented culture materials)	Hericium erinaceus extract	$\text{A}\beta_{1-40}$ -induced AD model	Mice	10	2 g/kg	2 g/kg	<i>In vivo</i>	VE	Double-distilled water	4 w	Liu and Jiang (2010)
<i>Huperzia Serrata</i> P.E. (蛇足石杉) (Whole herb)	Huperzine A	$\text{A}\beta_{1-40}$ -induced AD model HEK293sw	Rats cells	3 –	0.2 mg/kg 0.1–10 $\mu\text{M}$	0.2 mg/kg 0.1 $\mu\text{M}$	<i>In vivo</i>	–	Saline	12 d	Zhang et al. (2004)
<i>Inula japonica</i> Thunb. (旋覆花) (Inflorescence)	Inulinicin	$\text{A}\beta_{25-35}$ -induced AD model	Rats	4	26 mg/kg	26 mg/kg	<i>In vivo</i>	–	Saline	21 d	Wang et al. (2008)
<i>Juglans regia</i> L. (核桃仁) (Seeds)	Water extract	$\text{A}\beta_{1-40}$ -induced AD model	Rats	10	3 g/kg	3 g/kg	<i>In vivo</i>	–	Saline	24 d	Zhou, L.S. et al. (2011)
	Alcohol extract		Rats	10	3 g/kg	3 g/kg	<i>In vivo</i>	–		24 d	
	Acetone extract		Rats	10	3 g/kg	3 g/kg	<i>In vivo</i>	–		24 d	
	HS <sub>2</sub>	D-galactose and aluminum trichloride-induced AD model	Mice	6	3.15–12.6 g/kg	3.15 g/kg	<i>In vivo</i>	–	Double-distilled water	40 d	Xiao et al. (2004)
<i>Litchi chinensis</i> var. <i>euspontanea</i> Hsue (荔枝) (Fruits)	Lychee seed saponin	D-galactose and sodium nitrite-induced AD model	Rats	10	150–600 mg/kg	150 mg/kg	<i>In vivo</i>	–	Saline	3 m	Li and Wang (2012)
<i>Magnolia officinalis</i> t Wils (厚朴) (Bark)	Magnolol and honokiol	PC-12 cells	Cells	–	10–100 $\mu\text{M}$	10 $\mu\text{M}$	<i>In vitro</i>	–	1% DMSO	24 h	Hoi et al. (2012)
	4-O-methylhonokiol	$\text{A}\beta_{1-42}$ infused mouse model Tg2576 Transgenic mice model of Alzheimer's disease	Mice	10	2.5–10 mg/kg	5 mg/kg	<i>In vivo</i>	Methyhonokiol	–	10 d	Lee et al. (2010)
			Mice	10	1 mg/kg	1.0 mg/kg	<i>In vitro</i>	–	Water	3 m	Lee et al. (2012)
	Ethanol extract	Lipopolysaccharide-induced memory deficiency	Mice	5	10 mg/kg	10 mg/kg	<i>In vivo</i>	–	Saline	28 d	Lee et al. (2012)
<i>Millettia pulchra</i> (Benth.) Kurz var. <i>laxior</i> (Dunn) Z.Wei (龙眼参) (Roots)	Polysaccharides	Senescence accelerated-prone mouse/ 8 (SAMP8)	Mice	10	45–180 mg/kg	45 mg/kg	<i>In vivo</i>	HupA	Saline	40 d	Huang, Z.S. et al. (2008)
<i>Paeonia lactiflora</i> Pall. (芍药) (Roots)	Paeoniflorin	$\text{A}\beta_{1-42}$	Rats	12	15–30 mg/kg	15 mg/kg	<i>In vivo</i>	Donepezil	–	20 d	Lan et al. (2013)
	Paeoniflorin	Aluminum trichloride-induced AD model	Rats	10	60 mg/kg	60 mg/kg	<i>In vivo</i>	–	Saline	70 d	Li, S.M. et al. (2012)
<i>Paeonia suffruticosa</i> Andrews (牡丹皮) (Velamen)	Paeonol	$\text{A}\beta_{1-42}$ -induced AD model	Rats	8	5 mg/kg	5 mg/kg	<i>In vivo</i>	–	Phosphate-buffered saline	40 d	Zhou, J. et al. (2011)
<i>Panax ginseng</i> C.A. Mey. (人参) (Roots)	Ginsenoside Rb1	D-galactose and aluminum trichloride-induced AD model	Rats	12	2.5 mg/kg	2.5 mg/kg	<i>In vivo</i>	–	Saline	4 w	Yang et al. (2008)
	Ginsenoside Rg2	PC-12 cells	Cells	–	0.05–0.2 mmol/L	0.05 mmol/L	<i>In vitro</i>	Nimodipine	DMSO	24 h	Li, N. et al. (2007); Li, Q.C. et al. (2007)
	Ginsenoside Rg3	SweAPP Transgenic mice	Cells	–	25–100 $\mu\text{m}$	25 $\mu\text{m}$	<i>In vitro</i>	–		3–4 w	Yang et al. (2009)
			Mice	9–22	25 mg/kg	25 mg/kg	<i>In vivo</i>	LY-411575		18 h	Feng et al. (2006)
	Ginsenoside Rb1	PC12 cells	Cells	–	0.01–1 mmol/L	0.1 mmol/L	<i>In vitro</i>	–		24 h	Xie, C.M. et al. (2010); Xie, X. et al. (2010)
	Ginsenoside Rg1 and Rb1	–	Mice	5, 5	5–10 mg/kg, 2.5–10 mg/kg	10 mg/kg, –	<i>In vivo</i>	–	–	21 d, 14 d	Cheng et al. (2005)
	Ginsenoside Rb1	$\text{A}\beta_{1-42}$	Cells	–	0.1–10 $\mu\text{M}$	0.1 $\mu\text{M}$	<i>In vitro</i>	–	Dimethyl sulfoxide	24 h	Qian et al. (2009)
<i>Polygonatum sibiricum</i> Red. (黄精) (Rhizoma)	Water extraction	D-galactose-induced AD model	Rats	8	5–10 g/kg	10 g/kg	<i>In vivo</i>	–	Saline	6 w	Ma (2011)
<i>Polygala tenuifolia</i> Willd. (远志) (Roots)	Tenuigenin	$\text{A}\beta$ levels of SH-SY5Y APP695 cells	Cells	–	1–4 $\mu\text{g}/\text{ml}$	1 $\mu\text{g}/\text{ml}$	<i>In vitro</i>	–	PBS	–	Jia et al. (2004)
	Onjisaponins	Roots of <i>Polygala tenuifolia</i> Willd	Cells	–	25–100 $\mu\text{g}/\text{ml}$	25 $\mu\text{g}/\text{ml}$	<i>In vitro</i>	–	PBS	24 h	Yabe et al. (2003)
	Water extract		Mice	10	50–200 mg/kg	50 mg/kg	<i>In vivo</i>	Piracetam	Saline	7 w	

**Table 4** (continued)

CMM	Type of extract	Anti-AD experiments	Animal or cell	N	Dose range	Minimal active concentration	Model	Positive controls	Negative controls	Duration	Refs.
<i>Psychotria rubra</i> (Lour.) Poir (山大願) (Roots)		D-galactose and aluminum trichloride-induced AD model									Zhang, J.H. et al. (2011)
<i>Pueraria lobata</i> (Willd.) Ohwi (葛根) (Roots)	Puerarin	Alzheimer's disease neuronal cybrids from oxidant-stress induced apoptosis	SH-SY5Y cells	–	0.1–10 μM	0.1 μM	In vitro	–	DMSO	24 h	Zhang, H.Y. et al. (2011)
<i>Ruta graveolens</i> Linn. (芸丁) (Whole herb)	Quercetin	Quinolinic acid-induced AD model	Rats	6	50–200 mg/kg	50 mg/kg	In vivo	Ketamine	PBS	20 d	Li et al. (2003)
<i>Rhodiola sachalinensis</i> A.Bor (红景天) (Whole herb)	Salidroside	Aβ <sub>1–40</sub> -induced AD model	Rats	8	25–75 mg/kg	25 mg/kg	In vivo	–	Saline	21 d	Zhang et al. (2012)
<i>Rehmannia glutinosa</i> (Gaertn.) Libosch.ex Fisch.et Mey. (地黃) (Roots)	Catalpol	Aβ <sub>25–35</sub> -induced AD model	Mice	8–10	50 mg/kg	50 mg/kg	In vivo	–	Saline	60 d	Wang et al. (2009)
<i>Stephania tetrandra</i> S. Moore (汉防己) (Roots)	Tetrandrine	Aβ <sub>1–42</sub> -induced AD model	Rats	15	20–40 mg/kg	40 mg/kg	In vivo	–	Saline	14 d	He et al. (2011)
<i>Silybum marianum</i> Gaertn. (水飞蓟) (Seed coat)	Silibinin	Scopolamine-induced AD model	Rats	10	100–400 mg/kg	100 mg/kg	In vivo	Donepezil	–	–	Bi et al. (2012)
		tBH-induced AD model	SH-SY5Y cells	–	15 μmol	15 μmol	In vitro	–	–	–	
<i>Sargasum fusiforme</i> (Hary) Seichert (羊栖菜) (Whole herb)	Polysaccharide	Aβ <sub>1–40</sub> -induced AD model	Rats	10	0.4–1.6 g/kg	0.4 g/kg	In vivo	Piracetam	–	4 w	Tang et al. (2012)
<i>Salvia miltiorrhiza</i> Bunge (丹参) (Bulbus)	Tanshinone II A	Aβ-induced AD model	Rats	15	50 mg/kg	50 mg/kg	In vivo	–	Corn oil	15 d	Jiang et al. (2010)
<i>Schisandra sphenanthera</i> Rehd et Wils (华中五味子) (Fruits)	Schisandrone	Aβ <sub>25–35</sub> -induced AD model	Rats	10	2 mol/L × 2 mL each rat	2 mmol/L × 2 mL each rat	In vivo	–	Corn oil	7 d	Lv et al. (2007)
<i>Sophora Flavescens</i> P.E. (苦参) (Roots)	Matrine	Ibotenic acid- induced AD model	Rats	8	20–80 mg/kg	20 mg/kg	In vivo	Huperzine A	–	30 d	Ni et al. (2006)
<i>Tribulus terrestris</i> Linn. (蒺藜) (Fruits)	Caltrop saponin	L-glutamic acid-induced AD model	Mice	20	50–100 mg/kg	50 mg/kg	In vivo	HupA	Distilled water	30 d	Ma and Qu (2009)
	Thistle saponins	Aβ <sub>25–35</sub> -induced AD model	Mice	15	50–450 mg/kg	150 mg/kg	In vivo	–	Normal saline	14 d	Zhang, J. et al. (2011)
<i>Vaccinium uliginosum</i> Linn. (越橘) (Leaf)	Procyanidins	Aβ <sub>1–40</sub> -induced AD model	Rats	15	20–40 mg/kg	20 mg/kg	In vivo	–	Saline	4 w	Cai et al. (2011)
<i>Veratrum nigrum</i> Linn. (藜芦) (Roots)	Resveratrol	D-galactose and aluminum trichloride-induced AD model	Mice	10	22–88 mg/kg	22 mg/kg	In vivo	–	Saline	60 d	Lin et al. (2009)
<i>Valeriana amurensis</i> Smir. ex Komarov in Bull. (黑水缬草) (Rhizoma)	95% Ethanol extract	Aβ <sub>1–40</sub> -induced AD model	Rats	10	0.52–1.04 g/kg	0.52 g/kg	In vivo	Jian nao capsules	2% Twain-80 aqueous solution	7 d	Zhang et al. (2010)
	50% Ethanol extract		Rats	10	0.26–0.52 g/kg	0.26 g/kg	In vivo	Jian nao capsules	2% Twain	7 d	Zuo et al. (2010)

**Table 5**

The main anti-AD disease from CMM formula.

CMM formula	Object	Inducer	Learning ability	AchE	Apoptosis	GSH-PX	SOD	MDA	NO	Refs.
Dihuang Drink	Wistar rat	D-galactose	↑		↓					Xie et al. (2004); Xie et al. (2005)
Dingzhi Xiaowan	Aging SD rat	—	↑		↓		↑	↓		Qu et al. (2004)
Erzhiwan	Kunming mice	D-galactose	↑			↑	↑	↓		Li and Yang (2005)
Goutengsan	SD rat	AlCl <sub>3</sub>	↑			↑	↑	↓	↑	Huang, H.C. et al. (2008)
HuangLian JieDu Tang	SD rat	Aβ <sub>1–42</sub>				↑	↑	↓		Dong et al. (2012)
HuangLian JieDu Tang	APP/PS1AD mice	—			↓		↑	↓		Qiu et al. (2011a); Qiu et al. (2011b)
Liuweidihuangwan	SD rat	Aβ <sub>1–40</sub>	↑							Yi et al. (2011)
Xiaoyaosan	Kunming mice	D-galactose	↑		↓					Wu and Wang (2010)

## 7. Anti-AD effect of CMM formula

KaiXinSan, first appeared in “Bei Ji Qian Jin Yao Fang” written by Sun Simiao and is consisting of the roots of *Polygala tenuifolia* Willd., *Panax ginseng* C.A. Mey and *Acorus calamus* Linn, the sclerotium of *Poria cocos* (Schw.) Wolf, is the representative prescription with brain fitness effect. It is a fundamental formula of Traditional Chinese Medicine for anti-dementia disease due to its nootropic, intelligent, anti-forgetful, and anti-aging effects.

It has been proven that, *in vitro* and *in vivo* studies, KaiXinSan prevents and cures AD through multi-ways, including improving memory function in AD model induced by the intracerebral injection of Aβ and intraperitoneal injection of D-galactose (Zhou et al., 2008); inhibiting Aβ production through reducing the APP expression; improving synaptic plasticity (Smriga et al., 1995); inhibiting Bax expression through reducing Bax mRNA expression, and increasing Bcl-2 expression through up-regulating Bcl-2 mRNA expression (Qian et al., 2007); improving aging caused by the oxidative stress; inhibiting brain AChE activity; protecting nerve cells through reducing brain NO and NOS (Huang et al., 2001). KaiXinSan has complex chemical compositions which produce multi-target mechanisms based on four Chinese herbs. Furthermore, a large number of studies indicate that KaiXinSan is a promising anti-aging prescription as a result of preventing and treating brain aging effects. However, in the current situation, most studies remain in the level of phenomena observed, lacking associated discussions between inner mechanisms. For example, Aβ inhibits the formation of synaptic plasticity and directly or indirectly leads to neuronal death, which is a major factor in the incidence of AD disease. However, no study reports the directly effect of KaiXinSan in detecting the content of Aβ in brain, no mechanism studied about its effect on Aβ-induced low synaptic plasticity, and no coincident results about its anti-apoptotic mechanisms. All these informations need to be confirmed in future studies in order to determine the mechanisms of KaiXinSan in treating AD disease, and develop it as an effective anti-AD drug.

## 8. Local and traditional uses

Generally speaking, each type of traditional Chinese medicine has its own local and traditional uses, such as cleansing method, cutting method, heating method and accessories processing method, etc., namely the processing methods. Herbs are called slices after processed by these processing methods. Medicinal herbs must become into slices can be made into different application and clinical preparation formulations, which is the feature and characteristics of the clinical usage of traditional Chinese medicine.

For example, it is necessary to remove the basal part of stem from the roots of *Panax ginseng* C.A. Mey. (人参), then cut the roots into slices which can be added into decoctions. Some Chinese traditional medicines have to be processed by heating, and then

make them into different preparation formulations, such as decoctions, pills, powders, and so on. Such as the dried fruits of *Gardenia jasminoides* rubiaceae (栀子), which have to be scalded in boiling water, and then dry, crush and make them into different dosage forms. In the course of processing, Chinese herbs usually accompany with some kinds of accessory agents, such as yellow rice wine, vinegar, honey, salt, ginger, licorice, etc. which are used to strengthen the effects or decrease the side-effects of Chinese herbs. For example, licorice juice is added to process the roots of *Polygala tenuifolia* Willd. (远志) in order to avoid the stimulation of throat. In general, one Chinese herb often requires the integrated use of a variety of processing methods. Here is a typical example, namely the roots of *Coptis chinensis* Franch (黄连). Firstly, the root is clear by removing the fibrous root and the silt. Secondly, we slice the root and add yellow rice wine quantificationally. Lastly, put the mixture into frying pan and heat them under gently fire until they are dry enough which can be made into various dosage forms and clinical application (Wang et al., 2000).

To sum up, all the local and traditional uses of the traditional Chinese medicine (TCM) need cleansing method, and majority of the usage need cutting method, heating method and accessories processing method. Importantly, in the most cases, one Chinese herb usually requires the integrated use of a variety of processing methods to become traditional Chinese medicine slice which will be made into various dosage forms and clinical application. Only after processing, Chinese medicine can be applied for the treatment of diseases in various formulations in order to guarantee the clinical effects.

## 9. Toxicity of TCM and the solutions

TCM system has a unique understanding of the safe application of toxic TCM. In the mainstream and ancient of TCM books, the toxicity classification of many toxic TCM (big poison, medium toxic, and small drug), medicine quality, processing agents, medicine dosages, administration ways, reasonable combination and individual differences in patients all have been involved in the safe application of CMM in clinical practice, which gradually formed the toxicity of TCM theory and effective way to control their toxicities in TCM system.

In the study of anti-AD TCM, toxicity is the intrinsic property of some TCM. They will produce side-effects if directly applied for clinical treatment. Doctors attach great importance to the toxicity of TCM, and propose the corresponding alexipharmac solutions. On the one hand, TCM processing play an important role in reducing the side effects of toxic TCM. For example, the roots of *Veratrum nigrum* Linn (藜芦) have more poison. Modern toxicology studies have shown that the steroidal alkaloids isolated from the roots of *Veratrum nigrum* Linn (藜芦) are their toxic ingredients. They have strong stimulation on the digestive mucous membrane, the central nervous system, and the medulla vagus nerve dorsal nucleus. Usually pharmacist use rice-water, one of the processing materials,

to decrease toxic of the roots of *Veratrum nigrum* Linn (藜芦) by transforming the toxic steroid alkaloid into non-toxic veratrosine in processing in order to reduce the side effects (Wang et al., 2007). On the other hand, strictly control the use dosage of toxic TCM is also an important way to solve drug toxicity. One example is the usage of roots of *Erigeron breviscapus* (Vant.) Hand Mazz. (细辛). Main toxic component in the roots of *Erigeron breviscapus* (Vant.) Hand Mazz. (细辛) is safrol which has respiratory paralysis effect and is the severe toxicity carcinogenic substance (Feng, 1999). When poisoning, cardinal symptoms include headache, neck stiffness, opisthotonus, muscle tremor, whole body tension, and then quickly move to the condition of spasticity, unconsciousness, and limb tic, finally died of respiratory paralysis (Liu and Liu, 1998). Therefore, dosage of them is between 1.0 g and 3.0 g as the oral administration agents in "Chinese pharmacopoeia", and between 0.5 g and 1.0 g as internal powder agents. Moreover, doctor should accurately use the roots to differentiation syndromes, and pharmacist should strictly deploy them according to prescriptions in order to correctly use these toxic drugs. The most important thing is that administration should be stopped immediately if patients have any adverse reaction.

In conclusion, the causes of TCM producing toxicity are manifold. To solve the problem of the safe use of toxic TCM, the researchers should not only pay attention to the study of their material foundations and biological effects, but also to the correlations between toxic effects and therapy effects of one herb. Only in these ways can researchers thoroughly indicate the scientific connotation of toxic TCM, which provide scientific support and theoretical basis for safely and effectively clinical application and sustainable development of TCM industry.

## 10. Conclusion

AchE inhibitors are the first approved anti-AD drugs by the FDA, and they are also the first and the most useful drug used in the clinical treatment of AD disease (Doody et al., 2001). However, the limitation is that they are only suitable for mild or moderate AD patients, so further researches are needed to find more advanced stages of AD. Worldwide healthcare and chemical drug development have become interested in the field of natural medicine, especially the Chinese medicine. CMM has accumulated a wealth of clinical experience about nootropics drugs. Based on the reports about anti-AD effects of CMM, it plays multi-targets, multi-systems, and multi-aspects coordinating roles as effective anti-AD drugs. Utilization of the anti-AD effects of active ingredients in CMM has become a trend in the development of new drugs internationally today. In line with the international pharmaceutical concept, of being namely safe, effective, stable and controllable, there is a promising prospect to develop and find potential therapeutic chemical compounds from traditional Chinese medicine and develop them as efficient, high selectivity and low toxicity anti-AD drugs.

However, in these studies, there are still many problems to be solved, so further studies are necessary. Mechanism research concentrated on mature indicators, rather than on cutting-edge, groundbreaking indicators, which results in low innovation and therapy results in treating AD disease. In addition, the establishment of their efficacy, material study and quality evaluation system are also not clear enough, especially in the formula study with a good therapeutic effect, which makes traditional Chinese medicine resource wasteful. And from now on, there is no specific AD model for lab research. Therefore, we should strengthen the cooperation between the multi-disciplinary and cross-over study, and carry more in-depth studies to document the process of CMM anti-AD effects in order to find out new useful targets and specific

models. Since the anti-AD drugs from CMM have their own unique advantages, they are not replaceable by western medicine. However, it is promising to improve the efficacy and explicit activity drugs from traditional Chinese medicine, which will promote the development of anti-AD medicine. In short, we must develop a vision, have innovative ideas, and integrate the international requirements of anti-AD drugs in order to make traditional Chinese medicine as an important anti-AD drug resource.

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