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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-β (Aβ) is the major component of aggregates located in the brain of AD patients. The 40-residue-containing peptide ($A\beta_{40}$) or the 42-residue-containing peptide ($A\beta_{42}$) 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 Aβ in the brain and soluble Aβ oligomers are now widely recognized as key pathogenic structures in AD. Therefore, extracellular soluble Aβ oligomers are believed to cause synaptic and cognitive dysfunction in AD (Klein et al., 2001; Selkoe, 2002). Aβ peptide is derived from proteolytic cleavage of β-amyloid precursor protein (APP). Three secretases, α, β, and γ, are involved in APP processing. Sequential cleavage of APP by β- and γ-secretases yields either $A\beta_{1-40}$ or $A\beta_{1-42}$ peptide (Walter et al., 2001; Selkoe, 2004). Aβ 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 Aβ, and bapineuzumab, targeting amyloid plaques, prompted expert comments that drug discovery efforts in Alzheimer's disease should focus on soluble forms of Aβ rather than fibrillar Aβ deposits found in amyloid plaques. Accumulating scientific data suggest that soluble Aβ oligomers represent the optimal intervention target within the