



Progress of Essential Oils in Prevention and Treatment of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a type of disease featured in progressive deterioration of the memory and loss of the acquired knowledge. Essential oil (EO) is a secondary metabolite of plant, which has certain health and medical value. This study selects and summarizes four kinds of nosogenesis of AD that are accepted in recent years. EO is widely used for its good permeability. With the people's living quality improving and environmental awareness strengthening, the anti-AD function of EO has attracted more and more attention.

Key Words: EO, AD, Acetylcholinesterase, β -amyloid protein, Free Radical Injury, Nerve Cell

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Introduction

AD is a neurodegenerative disease characterized by progressive deterioration of the memory and loss of the acquired knowledge until complete loss of activities of daily living, which often attacks the elderly (Christensen *et al.*, 2007). AD is difficult to cure, which has become the fourth major cause of death in the elderly following heart disease, cancer, and stroke. According to the statistics from Alzheimer's Disease International (ADI), nearly 50 million people worldwide suffered from AD in 2015, and the number is predicted to reach 75 million by 2030 and amount to 131.5 million in 2050 (Prince *et al.*, 2015). In China and India, the number of patients suffering from AD is increasing faster. AD can be divided into two types, early onset and late onset, of which the early onset is a familial disease determined by chromosomes, which is generally rare. The late onset AD is common, which is a complex disease with multiple factors, so its causes and mechanisms have not been clear (Blennow *et al.*, 2006). There have been some theories, such as cholinergic theory (Lee *et al.*, 2004), β -amyloid protein theory (Barger *et al.*, 2008), free radical injury theory (Smith *et al.*,

2000) and neurodegeneration theory (Yuan *et al.*, 2000). At present, the clinic treatment of AD mainly relies on acetylcholinesterase inhibitors (AChEIs), N-methyl-D-aspartate receptors (NMDARs) antagonists, antioxidants, and non-steroidal anti-inflammatory drugs, but these clinical drugs can only alleviate the symptoms of the disease but can't prevent its progress (Smith *et al.*, 2015; Huang *et al.*, 2012). Therefore, the research and development of new effective therapeutic drugs has become a global focus.

EO, also called volatile oil, is a secondary metabolite of plant, which presents in flowers, leaves, stems, roots, or fruits of plants. The volatile oily liquid material can be extracted through steam distillation method, extrusion method, cold-maceration or solvent extraction method (Lubbe *et al.*, 2011). The related research progress in recent years is summarized as follows. EO is one of the effective components of plants with complex components, mainly including small molecular aldehydes, ester compounds, monoterpenes, sesquiterpenes compounds and small molecular aromatic compounds (Li *et al.*, 2009).

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EO boasts the advantages of multiple targets and relatively small adverse reactions. For its small molecular weight and strong fat solubility, it is easy for it to pass through the biofilm and go into the brain tissue through the blood brain barrier to play a therapeutic role in AD. In recent years, a series of plant essential oil has been found to exhibit potential therapeutic effects on the prevention and treatment of AD. The related research progress in recent years is summarized as follows.

EO activity of traditional Chinese medicine based on cholinergic theory

ACh is closely related to memory. The activity of acetylcholinesterase (AChE), as well as the synthesis and release function of ACh decreases in the brain of AD patients. The loss of ACh is the key cause of AD and the key to the control of the cholinergic system is AChE (Perry *et al.*, 1997; Perry *et al.*, 1978; Atack *et al.*, 1983; Fishman *et al.*, 1986). Therefore, the use of acetylcholinesterase inhibitor (AChEI) is considered to be one of the most promising strategies to cure AD. AChEI can prevent the degradation speed of ACh neurotransmitters in the synaptic space and increase the level and action time of ACh neurotransmitters accordingly. AChEI is the most successful cholinergic enhancer at present, which has a definite effect on the improvement of learning, memory and cognitive function. AChEI has been proved to be the most feasible way for AD treatment (Singh *et al.*, 2013).

In 1996, Perry *et al.*, found that EO of *Salvia officinalis* L. could inhibit AChE in human brain and AChE in cattle's erythrocyte with IC₅₀ of 0.07 mg/mL and 0.03-5 mg/mL respectively. The activity of AChE in striatum could be decreased by oral administration of EO of *Salvia officinalis* L. (once a day, 5 days) under low dose of EO, and the activity of AChE in striatum and digitationes hippocampi could be inhibited under high dose of EO. The two doses won't change the activity of AChE in cortex.

Song (2012) ground *Radix angelicae pubescentis* by a pulverizer, added into a double amount of water for soaking and extracted volatile oil. Then he conducted the AChE inhibition experiment. The experimental result shows that when the concentration of the *Radix angelicae pubescentis* volatile oil is 1 μ L/mL, the inhibition rate of AChE reaches 92.38%.

Miyazawa *et al.*, (2001) extracted nootkatone from citrus grapefruit which has the

activity of AChE to inhibit red blood cell. Ren *et al.*, (2004) extracted Dihydranshinone (IC₅₀: 1.0 μ mol/L) and Cryptotanshinone (IC₅₀: 7.0 μ mol/L) from *Salvia miltiorrhiza* Bunge, both of which gave strong inhibitory activity of AChE.

When rats are given different doses of EO, it is found that noradrenaline, dopamine and 5-hydroxytryptamine increase while activity of AChE decreases. In the experiment under the influence of rosemary EO, the ability of task completion can be enhanced, the ability of overall memory can be enhanced, and the speed of memory can also be improved (Zhang *et al.*, 2007).

EO activity of traditional Chinese medicine based on β -amyloid protein theory

A large number of researches have verified that the abnormal metabolism and deposition of β -amyloid protein (A β) in brain tissue is the central link in the pathogenesis of AD (Kozikowski *et al.*, 1991). Deposition of A β and its further formation of senile plaque (SP), neurofibrillary tangles caused by intracellular hyperphosphorylated proteins and nutrition necrosis of neurons (Duyckaerts *et al.*, 2009) have toxic effects on the surrounding brain parenchyma, which can lead to synaptic dysfunction and synaptic loss. Reducing or alleviating β deposition in the brain can reduce the toxic effect on nerve cells and improve cognitive function so as to achieve prevention or treatment.

Cioanca *et al.*, (2013) gave a certain concentration of inhaled coriander volatile oil to A β (1-42) rat model of AD continuously, it was found that A β (1-42) treated rats had positive effects on spatial memory formation. It may be that the Inhaled coriander volatile oil improves spatial dysmnesia induced by A β (1-42) by alleviating oxidative stress in hippocampi of rats.

Batarseh *et al.*, (2016) found that extra-virgin olive oil could reduce A β load in a rat model of AD, have a significant clearance effect on A β , and reduce the overall inflammation load in the brain.

Cioanca *et al.*, (2014) also reported that *Juniperus communis* L. volatile oil extracted from *Juniperus formosana* of cypress family was used to evaluate the effect of inhaled volatile oil (1 day and 3%, every day, and 21 days) on spatial memory extracted from *J. communis* L from the abamectin A β (1-42) rat model. The *Juniperus communis* L. volatile oil can improve dysmnesia induced by amyloid protein in AD model.



Zhu *et al.*, (2012) used amygdala to inject A β 25-35 to induce AD rat model. The water maze spatial memory ability was observed in Qingxin Kaiqiao Prescription Oil group (two weeks in succession). The expressions of GFAP, A β and β APP in the cortex were studied by immunohistochemistry. Qingxin Kaiqiao Prescription can obviously improve the learning and memory ability of AD rats, which may be related to decrease in the expressions of GFAP, A β , β APP and IL6 in the cortex. The expression of A β in the cortex decreased by 12% in Qingxin Kaiqiao Prescription Oil group compared with that in the model group.

Majlessi *et al.*, (2012) found that Zataria multiflora Boiss EO would influence cognitive function in rats at different doses (50, 100, 200 μ L/kg). The principle may be that A β reverses the damage under the action of ZM EO. The activity of anti-oxidation, anti-inflammation and anti-cholinesterase of ZM or its main components may contribute to its beneficial effect.

EO activity of traditional Chinese medicine based on free radical injury theory

Lipid peroxidation and increase of free radicals in the brain tissue of AD patients lead to damage of cell nucleus and mitochondrial DNA. Oxygen free radical accumulates too much so that lipofuscin (senile pigment or SP) can't be eliminated effectively, which causes hypofunction in brain cell. This suggests that free radical scavenging system may play an important role in preventing AD (Noguchi *et al.*, 2000).

There are many mechanisms of excessive free radical scavenging in cells. Enzymes and antioxidants are the main factors to eliminate the damage and stabilize cell differentiation (Box *et al.*, 1997). Many natural plants, such as ginseng, *Chinese angelica*, *Lucid ganoderma*, *Salvia chinensis*, *Acanthopanax gracilistylus* W. W. Smith, Chinese wolfberry and *salvia miltiorrhiza*, have been considered to have anti-aging effect for a long time. EO of many plants has anti-free radical effect.

Inhaled coriander volatile oil (Cioanca *et al.*, 2013) can enhance the activity of SOD and GSH-Px and reduce the level of MDA in rat brain tissue of AD model so that the level of oxidative stress in brain tissue is decreased. At the same time, it is found that the dysmnnesia and cognitive ability of the model rats are significantly improved.

Cioanca *et al.*, (2015) found that EO of *Salvia officinalis* L. had strong inhibitory activity on superoxide dismutase (IC₅₀=478 μ L/mL) and radical scavenging (IC₅₀10.5 μ L/mL). In vivo testing, EO is given to rats to induce AD by inhalation and brain tissue samples are analyzed. Daily exposure EO of *Salvia officinalis* L. increases antioxidant enzyme activity, suggesting that the main mechanism of preventing neurodegeneration is related to antioxidant properties.

Hancianu *et al.*, (2013) studied the cerebral protective effect of aromatherapy with inhaled lavender oil on scopolamine-induced dementia in rats. The results showed that inhaled laver oil showed good anti-oxidation and anti-apoptosis activity in superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT) and reduced glutathione (GSH) and malondialdehyde (MDA).

EO activity of traditional Chinese medicine based on nerve cellular damage

PCI2 cell is a differentiated cell line of rat adrenal medulla pheochromocytoma. PCI2 cell is a catecholamine cell, which can synthesize, store and release certain amount of catecholamine (mainly dopamine and norepinephrine). PCI2 cell has typical nerve cell characteristics and is commonly used in the study of death manner of nerve cell and neurotoxicity damage (Das *et al.*, 2003). Various kinds of damage PCI2 cell models have been widely used in the screening of natural drugs with neuroprotective effect.

Liu *et al.*, (2017) has found that Chinese angelica has abundant angelica oil, which is rich in phthalide derivatives, has a variety of biological activities. The *vitro* activity screening of angelica oil finds that it also shows protective activity against glutamate-induced injury of PC12 cells in both low and high concentrations of cytotoxicity. The result shows that angelica oil and its main chemical constituents have protective effects on the damaged neurons in the proper concentration range. According to Xiong's report (Xiong *et al.*, 2014), *Lignum aquilariae resinatum* EO has protective effect on oxidative damage of PC12 cells injured by H₂O₂. In the experiment, the cell damage model of H₂O₂ is cultured in vitro first. From the testing of cell viability, the cell membrane potential (MMP) and the content of active oxygen, the content of MDA, the activity of SOD and GSH-Px, it is found that the content of ROS and MDA are significantly decreased



($P < 0.01$) while the cell survival rate, SOD and GSH-Px activity are significantly increased ($P < 0.01$), indicating that *Lignum aquilariae resinatum* EO has protective effect on oxidative damage of PC12 cells induced by H₂O₂ in a certain dose range.

The study on Ligusticum chuanxiong oil by Wang *et al.*, (2017) showed that the survival rate of PC12 cells damaged by cobalt chloride could be significantly increased and the level of lactate dehydrogenase could be decreased in a certain concentration range so as to inhibit apoptosis in PC12 cells. Nafar *et al.*, (2014) found that coconut oil could promote the survival of nerve cells and reduce the release of mitochondria induced by A β , thus protecting PC12 cells.

Conclusions

EO, as one of the effective constituents of natural plants, is more and more recognized by people for its medicinal value and health care value. Through the analysis of different pathogenic mechanisms of AD, the anti-oxidation of EO against acetylcholinesterase inhibition, A β depolymerization, free radical injury and the protection of PC12 injured cells, it can be seen that EO of various plants has the activity of preventing and treating AD. The use of EO has many kinds of ways, such as oral administration, fumigation, smearing and so on. Combined with its excellent anti-AD activity, EO has the potential value of developing natural drugs for the treatment of neurogenic diseases.

At present, more studies on anti-AD activity of EO are ongoing, but we haven't made clear the key components of many plants' essential oil, the synergetic effect of each component in EO, and in-depth anti-AD mechanism, which needs more researches.

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