

Current Drug Treatments in Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a global common concerned neurodegenerative disease, leading to an increase in death and social problems. The pathological mechanism of AD is complicated and still unclear, and it may be affected by various epigenetic factors. So far, drugs such as cholinesterase inhibitors and glutamate receptor antagonists have been approved for clinical treatment to improve the cognitive ability of patients who suffers Alzheimer's disease. Meanwhile, natural medicines including traditional Chinese medicine have attracted attention for their function in reducing oxidant stress, suppressing inflammation in the neuron system, and regulating gut microbiota homeostasis. The mechanism of natural medicines for AD treatment is still under investigation of the complicity of chemical ingredients in natural medicines. However, experiments and clinical trials show promising advantages of natural medicine to treat and prevent AD. The curative effect and safety of natural medicine on AD will be gradually confirmed with the development of research and clinic trials in the near future.

Keywords: Alzheimer's disease, Drug treatments, Natural medicines.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease first described by doctor Alois Alzheimer, leading to cognitive and functional impairment [1]. Alzheimer's disease patients are people over 65 years of age as the majority and minor cases are people between 30s to 60s of age. AD patients at an early stage are difficulty remembering events, then disorientation, loss of motivation, mood swings, self-neglect, and other behavioral disorders at the advanced stage, and AD ultimately cause the death of patients [2]. What's worse, the decline of memories and direction-sense generates the patients' withdrawal from family and society, boosting the deterioration of the living quality of AD patients. By 2021, Alzheimer's disease-associated death is the sixth reason for death in the USA. Above 6.2 million people over 65 age suffer from Alzheimer's disease-associated dementia in the US and hundred-thousands of cases die from AD are recorded every year. The prevalence of AD can reach 3.5% in China, causing over 5.69 million patients in 2010. The case number of Alzheimer's disease has been significantly increasing since the last decade and the mortality of AD were potentially exacerbated by the COVID-19 pandemic since 2020. Alzheimer's disease has become a major health issue around the world.

The development of AD is associated with aging and environmental or genetic factors. However, the mechanism that caused Alzheimer's disease is still under investigation. The allele of Apolipoprotein E (ApoE) [3], hypocretin receptors 2 (HCRTR2), and Presenilin (PSEN1 and PSEN2) [4] are confirmed genetic factors of AD. Head injury, chronic inflammation, high blood pressure, and depression are the other possible risk factors for AD [1]. Diffuse brain atrophy and cortical cell cluster alternation is the key neuropathologic evaluation of Alzheimer's disease. Neurofibrillary tangles, loss of neuronal connections, and amyloid plaques in the brain are the common feature of Alzheimer's disease, however, the diagnosis based on such features can only be conducted after death [5]. In this case, the diagnosis of possible AD is mainly based on medical imaging (CT, SPECT, PET, and MRI), blood test, and cognitive testing.

Unfortunately, no medications and supplements can reverse or stop the progression and decrease the risk of Alzheimer's disease. The therapy and medicine are also limited for slowing the development or mitigating symptoms of AD. Antipsychotics are applied to extend the progression of AD, but such therapy may increase the risk of early death. Fortunately, six drugs including cholinesterase inhibitors and glutamate receptor antagonists have been approved by FDA and the

Aduhelm (Aducanumab) targeting β -amyloid shows a promising function for improving cognitive symptoms by eliminating β -amyloid accumulation in the brain. Meanwhile, promising future treatments currently in clinical trials of AD are conducted around the world as shown in Figure 1.

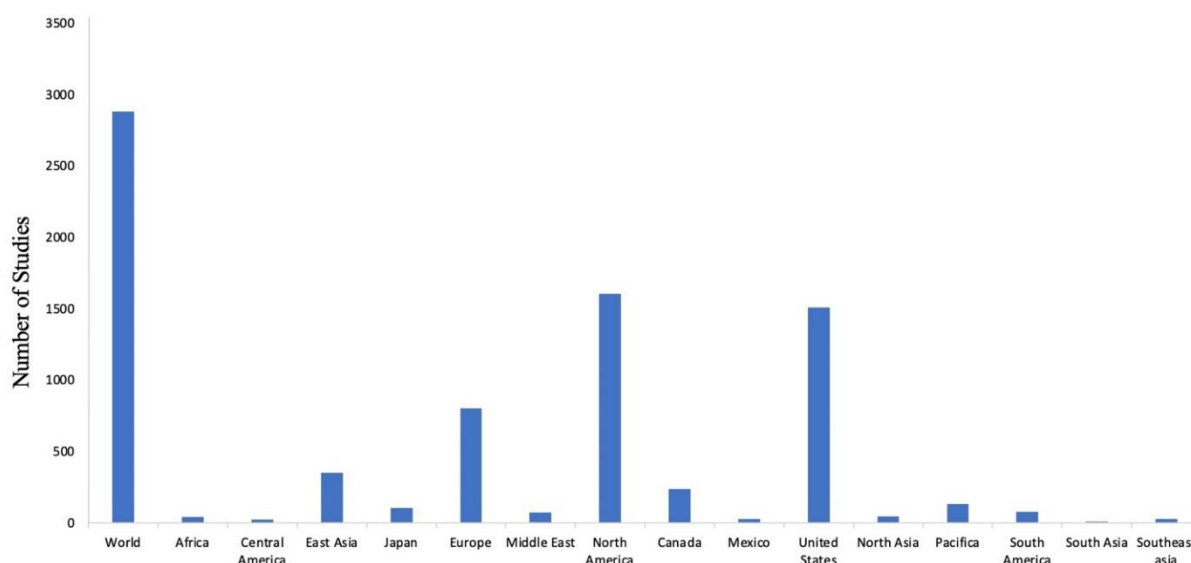


Figure 1. Number of clinical trials targeting AD around the world

Nonpharmacologic therapies can improve the symptom and living quality of AD patients, which also benefit depression, wandering, agitation, apathy, and aggression [6]. Aerobic and non-aerobic exercise combination shows positive effects on cognitive function among AD patients. The positive effects of cognitive stimulation such as music-based therapies and psychological treatment can improve depression, anxiety, and other potential AD-associated cognitive impairments have been reviewed [7]. This review not only summarizes the current drug treatments of AD, including approved drug treatment and natural medicines, but also gives an insight into future directions to overcome limitations.

2. Approved Drug Treatment

2.1. Cholinesterase inhibitors

Cholinesterase inhibitors (ChEIs) are molecules that inhibit the degradation of the neurotransmitter acetylcholine or butyrylcholine, promoting the accumulation of such neurotransmitters in the synaptic cleft to stabilize signals between neurons [8]. ChEIs are approved for Alzheimer's disease clinical treatment by the U.S. Food and Drug Administration (FDA) for their ability to mitigate symptoms. Donepezil (Aricept), Rivastigmine (Exelon), and Galantamine (Razadyne) are three approved cholinesterase inhibitors for mild to severe stage AD treatment to optimize symptoms and cognitive function related to memory, thinking, judgment of AD patients. Donepezil targets acetylcholinesterase as a reversible noncompetitive inhibitor improving the cognition and behavior of AD patients without altering the progress of AD. Donepezil has shown efficiency and safety in AD patients and may impact AD biomarkers including β -amyloid and tau protein [9]. Rivastigmine is another selective acetylcholinesterase inhibitor that inhibits acetylcholine metabolism in postsynaptic clefts mainly in the central nervous system. Rivastigmine was applied for the improvement of AD-associated dementia in 2007. The beneficitation of Rivastigmine for patients suffering from mild to moderate AD was confirmed by several clinical trials [10]. Galantamine is another approved cholinesterase inhibitor for AD treatment with a similar mechanism to Donepezil and Rivastigmine, however, the results of clinical trials of Galantamine are conflicting: no studies suggest Galantamine has improvements with compared drugs [11].

2.2. Glutamate receptor antagonists

Glutamate receptor antagonists are a series of chemical substrates belonging to the excitatory amino acid receptor antagonist family antagonizing one or more of the glutamate receptors. L-glutamate is the main excitatory neurotransmitter and can cause excitotoxicity in the brain leading to neurodegeneration. Moreover, soluble β -amyloid oligomers damage synaptic plasticity and signal transmission via a non-excitotoxic glutamatergic pathway and the production of β -amyloid oligomers is stimulated by glutamate receptors [12]. In this case, glutamate receptor antagonists can inhibit neurodegeneration mediated by β -amyloid oligomers by inhibiting the production of β -amyloid oligomers. As an example of glutamate receptor antagonists applied to AD treatment, memantine is an FDA-approved glutamate receptor antagonist for AD treatment by suppressing the extrasynaptic NMDAR signaling, which shows clinical beneficitation in moderate to severe AD cases [13]. Natural Medicines including traditional Chinese herbs and traditional Chinese medicine may also play an essential role in AD treatment. Traditional Chinese medicine believed that the pathogenesis of cognitive impairment involves not only the brain, but also other organs such as kidneys, heart, liver, and spleen. Clinical trials have shown the abilities of traditional Chinese herbs on improving neuropsychological function, optimizing AD symptoms, and the life quality of patients. Research also suggests that traditional Chinese herbs can reduce the accumulation of β -amyloid deposits and tau protein [14]. However, the exact mechanism and safety of natural medicines are still unclear due to the complexity of chemical ingredients and their interaction. The mechanisms of Chinese medicines for cognitive dysfunction improvement are complicated. Such improvements can be achieved by anti- β -amyloid effect, antioxidant stress, anti-inflammatory, improving gut microbiota and et al.

3. Natural Medicines

Natural Medicines including traditional Chinese herbs and traditional Chinese medicine also show positive effective in Alzheimer's disease treatment. Traditional Chinese medicine believed that the pathogenesis of cognitive impairment involves not only the brain, but also other organs such as kidneys, heart, liver, and spleen. Clinical trials have shown the abilities of traditional Chinese herbs on improving neuropsychological function, optimizing AD symptoms, and the life quality of patients. Research also suggests that traditional Chinese herbs can reduce the accumulation of β -amyloid deposits and tau protein [14]. However, the exact mechanism and safety of natural medicines are still unclear due to the complexity of chemical ingredients and their interaction. The mechanisms of Chinese medicines for cognitive dysfunction improvement are complicated. Such improvements can be achieved by anti- β -amyloid effect, antioxidant stress, anti-inflammatory, improving gut microbiota and et al.

3.1. Anti- β -amyloid effect

Traditional Chinese medicines can target multiple factors to improve AD symptoms. Traditional Chinese medicine can prevent the generation of β -amyloid oligomers. An iso quinoline alkaloid isolated from Coptidis rhizome named Berberine shows the ability to reduce the accumulation of β -amyloid protein, potentially by regulating the metabolism of APP protein. Additionally, berberine could work as an beta-site APP cleaving enzyme 1 (BACE1) with high affinity, reducing the expression of BACE1 and inhibiting the formation of β -amyloid oligomers. Taken together, berberine can reduce the accumulation of β -amyloid oligomers in multiple ways.

3.2. Antioxidant stress

Oxidative stress is another pathological hallmark and target for the treatment of Alzheimer's disease. The hypothesis assumed oxidative damage plays as an early event in Alzheimer's disease [15]. The oxidative stress in the brain can be suppressed by coumarins, melatonin, flavonoids, vitamin C, and other antioxidant molecules through reactive oxygen species-scavenging mechanisms [15]. Herbal drugs that are rich in flavonoids and other antioxidant molecules can be candidates for the

treatment of AD. Jung et al. have reported that Coptidis Rhizoma-groenlandicine, palmatine, and berberine may inhibit the progress of AD of its antioxidant capacities to reduce the pressure of RNS and ROS. Moreover, Ginkgo biloba and silibinin have been reported to inhibit beta-amyloid aggregation and reduce amyloid precursor protein accumulation and cognitive improvement since they contain flavonoids, terpenoids, and other antioxidant molecules. The KleeB Bua Daeng formula also shows the ability for brain health promotion and potential beneficitation for AD treatment for its antioxidant compounds. Quercetin and baicalein gain attention as nutraceutical antioxidants for AD treatment for their ability to prevent oxidative damage, inhibit excitotoxicity, against apoptosis, and stimulate differentiation and neurogenesis action.

3.3. Anti-inflammatory

Inflammation, especially systemic inflammation, is strongly related to the pathogenesis of Alzheimer's disease supported by a great deal of clinical evidences including activated microglia within senile plaques and epidemiological research. Inflammation in the neuron system is considered to be a key contributor to AD formation in the early stage and may impact AD progression by interacting with other factors. Anti-inflammatory therapy is believed to reduce the incidence of AD by epidemiological studies, however, anti-inflammatory drugs have shown no positive effect on AD progression in current clinical trials. Nevertheless, formulated Chinese medicine Shaoyao Gancao Tang has shown the effect on cognitive improvement and neuroprotection in vivo and it successfully reduced NLRP1 and NLRP3 in AD-associated cells in vitro. The correlation between the anti-inflammatory effect and cognitive improvement in AD is still believed since Shaoyao Gancao Tang also has the effect of anti-inflammation. Moreover, a study discovered the potential connection between traditional Chinese medicine and inflammation in the NF- κ B signaling pathway, which may have an impact on AD formation. The hypothesis illustrates that neuro-inflammation is a triggering event in the early stage of AD, thereby, anti-inflammation drugs may not have a significant effect on improving AD but preventing the formation of AD.

3.4. Improving gut microbiota

Gut microbiota homeostasis is an important factor for human health. Intestinal flora may affect the brain activity and cause brain dysfunction, thereby, it may have an dual-role impact on AD. The blood-brain and gut barrier can be altered by microbiota dysbiosis thereby affecting or mediating AD pathogenesis or other neurodegenerative diseases. Sodium oligomannate that works as an AD improvement agent targeting gut microbiota has been approved by CFDA for AD treatment in China. The therapeutic effect of Chinese medicine compound and monomer on AD was recognized mainly based on gut microbiota regulation. For instance, Quercetin which is widely present in fruits and vegetables may expand gut microbial diversity to optimize the cognitive function of Alzheimer's disease patients. Some herbal formulas such as Danggui Shanyao poder, Huanglian Jiedu decoction, Kaixin powder, and Liuwei Dihuang Decoction have the function of optimizing gut microbiota by restoring intestinal barrier function, activating anti-carcinogenesis-associated pathway, anti-inflammatory and antioxidant, and other pathways. Natural medicines may also impact gut microbiota homeostasis indirectly such as by increasing cardiovascular function and digestion function.

3.5. Anti- β -amyloid effect

Some traditional Chinese herbs contain compounds that work as cholinesterase inhibitors for AD treatment. Huperzine A exhibits robust anti-acetylcholinesterase activity, thus it can stabilize inter-neuron signals as Donepezil. A clinical analysis indicates Huperzine A shows a positive result in cognitive function improvement among AD patients.

Traditional Chinese medicines can also improve homeostasis by protecting blood vessels and facilitating cerebral microcirculation. Clinical trials have revealed that traditional Chinese herbs are able to optimize blood circulation, which benefits intervening in the damage to the heart, blood vessels, brain, and other organs. Ginkgolide may inhibit the platelet-activating factor (PAF) receptor

as a potent antagonist, which can reduce platelet aggregation in blood vessels and regulate thrombosis formation. Additionally, the Ginkgo extract may inhibit the arachidonic acid metabolic pathway, improve micro-cerebral vascular circulation to ameliorate brain hypoperfusion, and downregulate internal inflammatory responses.

Traditional Chinese medicines can also stimulate the mitochondrial function of neurons and prevent cell apoptosis in the hippocampus, where the early stage of AD happens. Research has shown that Dihuangyinzi could increase anti-oxidize agent activities such as catalase (CAT), glutathione peroxidase (GSH-Px), and SOD in the serum and brain tissue, reducing the pressure of reactive oxygen species to reduce cell damage. Astragalus extract can increase cell survival rate and decrease the concentration of cytosolic calcium. Thus such compounds in traditional Chinese medicines have a protective effect on neuronal cells in the hippocampus.

4. Conclusions

Alzheimer's disease has already become a major health issue around the world, causing hundred-thousands of death cases directly or indirectly each year. Although several hypotheses explaining the formation and progression of AD have come up for years, the accurate pathological pathway of AD is still unclear. The formation of AD-associated factors may be accumulated far before the symptom can be diagnosed, and the causative factors of AD can be complicated. Thus, no therapeutic strategy for overturning or preventing the progression has been developed for successful clinic trials. The diagnosis and precaution of AD are even more important to delay the formation of AD. The traditional Chinese medicines and traditional Chinese herbs may systemically optimize the symptom among AD patients and act as precaution agents for their multiple functions including anti-inflammatory, anti-oxidate, and gut microbiota regulation effects. Research on improving the cognitive function of traditional Chinese medicine has significantly increased in recent years and the mechanism of traditional Chinese medicine affecting brain function and homeostasis is going to be more clarified in the near future. The curative effect and safety of traditional Chinese medicine on AD will be gradually confirmed by research and clinic trials. Taken together, early diagnosis is of utmost significance currently since no treatment can halt or reverse AD progression, additional studies investigating novel treatments for AD should continue to be performed.

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