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The Research Progress of Drugs for Treatment of Alzheimer'S Disease

Yuchen Zhang[1,a,*]

[1]*Beijing Camford Royal School, Beijing, China*
a. ArielZ0860@outlook.com
**corresponding author*

Abstract: In this society, Alzheimer's disease represents a significant public health concern. Nevertheless, the market offers only two FDA-approved drugs, which are capable of only partially inhibiting the symptoms. It is imperative that both patients and researchers are made aware of the mechanism by which AD is triggered and the fundamental logic underlying the action of each drug. This should include an understanding of how the drug reacts with the body and the ingredients that it contains. This section primarily discusses the therapeutic options for Alzheimer's disease, encompassing both the drugs and mechanisms that are currently available on the market and those that have not yet been approved but are theoretically feasible. This passage will introduce a number of potential treatments for Alzheimer's disease, including Chinese patent medicine, acetylcholinesterase inhibitors, NMDA receptor antagonists, Aduhelm, Leqembi, anti-amyloid therapies and Aβ immunotherapies. Despite the existence of these treatments for many years, it is still not possible to cure Alzheimer's disease completely or to delay or prevent its progression. This passage aims to provide insights into the future direction of pharmaceutical research and the selection of appropriate medications.

Keywords: Alzheimer's disease, drug therapy, research progress

1. Introduction

Alzheimer's disease (AD) is a degenerative disease of the central nervous system. In 1906, Alzheimer published the initial observation, treatment, and research of a 51-year-old woman with a degenerative disease of brain function. In 1910, it was incorporated into the textbook of psychology, Alzheimer's Disease. The primary clinical manifestations of Alzheimer's disease (AD) include deficits in emotional regulation, memory function, and daily mobility. As reported by USA Today, A significant proportion of individuals aged over 80 years old have been infected with AD, with a prevalence exceeding 50% [1]. In China, individuals aged 65 and above have a prevalence of severe AD exceeding 5%, with an increasing incidence with advancing age. The precise mechanism by which AD is triggered remains unclear. Some research has demonstrated that the brain tissue of AD patients is markedly atrophied, particularly the hippocampus, which is associated with memory, and the loss of neurons in the pars basalis of the telencephalon. Additionally, the connectivity of the hippocampus and the encephalic region in AD patients has been observed to be impaired. The primary pathogenic factor is the aberrant deposition of amyloid Aβ and hyperphosphorylation of intracellular Tau protein, which have been identified as key targets for therapeutic intervention [2]. The current status of

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treatment is not optimistic, as the drugs that have been approved for sale on the market are unable to cure AD from its source. It is notable that only a select few of the available pharmacological agents have demonstrated efficacy in alleviating the symptoms of Alzheimer's disease. These include Chinese medicinal inhibitors of acetylcholinesterase, antibody drugs, and NMDA receptor antagonists. Nevertheless, numerous prospective therapeutic agents and pharmaceutical compounds have been developed by various research groups, and some of these have demonstrated efficacy in preclinical models of AD. These findings will be discussed in this section. This passage primarily discusses the characteristics and mechanisms of existing therapeutic approaches and drugs that are currently being used to treat Alzheimer's disease (AD), as well as drugs that are currently in clinical trials and have demonstrated theoretical potential for efficacy.

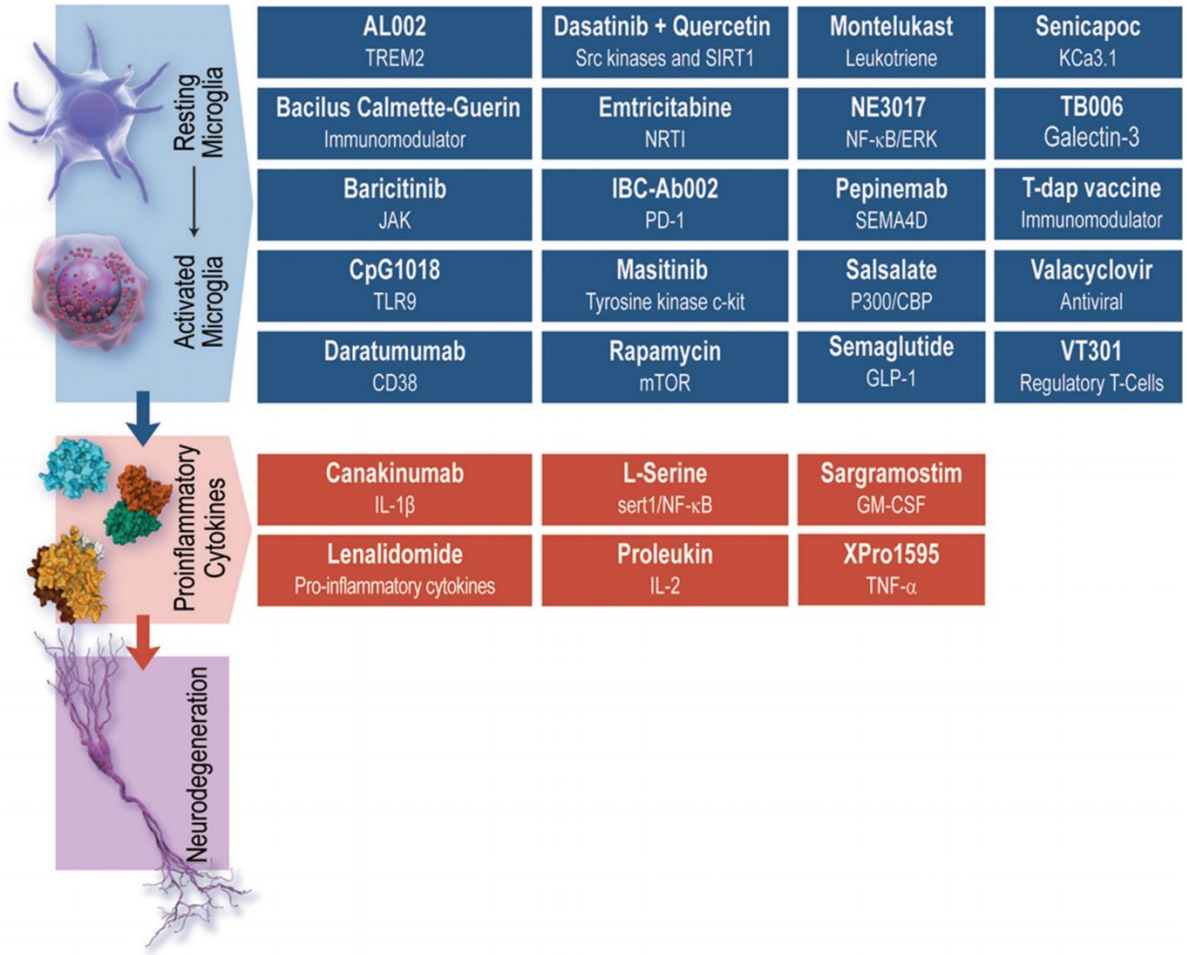


Figure 1: Key targets in treatment and relative drugs [3].

2. Chinese medicine can improve AD in some degree

The compound Cistanche Puzzle Capsules are composed of the following ingredients: lotus leaf, cistanche, lumbricus and Uniflower Swisscentaury Root. It has been demonstrated that this compound can have a beneficial effect on the liver, and may also assist in the treatment of insomnia and cognitive impairment caused by cerebral ischemia, which is characterised by the blockage of cerebral arteries.

The practice of traditional Chinese medicine has been demonstrated to facilitate improvements in cerebral circulation and the expansion of blood vessels. However, it is important to note that this approach can only be employed as an adjuvant therapy and is not a standalone cure.

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Astragalus has been demonstrated to function as an immune enhancer and regulator. The effective constituents are astragaloside and astragalus polysaccharide [4]. It has been demonstrated that this substance can expand blood vessels, inhibit platelet clotting, reduce blood viscosity, and improve blood circulation and brain perfusion. Additionally, the supplement contains micronutrients such as zinc, which have been demonstrated to enhance cognitive function in individuals with Alzheimer's disease (AD). In a study conducted by Yuepeng Wu, astragaloside was administered to mice with learning disabilities induced by scopolamine. The results demonstrated a notable improvement in learning and memory behaviour [5]. The principal mechanism of action is the enhancement of superoxide dismutase (SOD) activity and the reduction of malondialdehyde (MDA) generation and expression in brain tissue [5]. Hui Yao's research demonstrates that astragalus polysaccharide can enhance the learning and memory abilities of aged rats. The observed decline in their learning and memory abilities may be associated with the aberrant expression of proteins involved in neuroplasticity in the hippocampus [6].

Ginseng has been demonstrated to possess a number of beneficial effects, including the capacity to enhance the function of the kidneys and liver, and to induce a state of calm. Additionally, it has been demonstrated to enhance superoxide dismutase (SOD) activity, a crucial antioxidant enzyme, and to inhibit the development of arteriosclerosis and cardiovascular disease. A research on the effects of ginsenoside Rb1/Rg1 on Alzheimer's disease (AD). Injecting ginsenoside Rb1/Rg1 into transgenic mice (APP (Tg mAPP) and SAMP8) over a three-month period resulted in a significant improvement in the mice's visuo-spatial working memory abilities [7]. The research has demonstrated that ginsenoside Rb1/Rg1 is effective in reducing neuroinflammatory plaque deposits in the hippocampus and cortical tissue, as well as reducing the levels of Aβ(1-40) and Aβ(1-42) [7]. The mechanism by which ginsenoside Rb1/Rg1 exerts its effect on Alzheimer's disease (AD) and the impact of Rg1-induced synaptic plasticity in neurons: Rg1 has been demonstrated to facilitate the release of Aβ(1-42) from its inhibitory effect on the PKA-CREB signal path, thereby increasing protein expression of BDNF.

3. Inhibitor of acetylcholinesterase

The reversible inhibition of acetylcholinesterase at synapses results in an increase in the effect of acetylcholine (ACh). Furthermore, it has been demonstrated to diminish the accumulation of amyloid proteins within the brain.

Tacrine was first employed in clinical trials in 1993, where it was observed to exert an inhibitory effect on AChE in plasma and tissues [6]. Additionally, it has been demonstrated to enhance cognitive performance by traversing the blood-brain barrier. However, its hepatotoxicity limits its clinical applicability [6]. Further research is being conducted into the ramifications of tacrine, with a particular focus on developing medicines that have therapeutic effects but few side effects. For example, Tacrine ramification ZLWT-37, which is employed as a potent anti-proliferative agent, has a marked inhibitory effect on CDK9 activity and does not exert any deleterious effects on the liver and kidneys.

Donepezil is a commonly prescribed medication due to its favourable tolerability profile. It has been demonstrated to enhance memory abilities and elevate central acetylcholine levels [6]. The research indicates that patients who consistently take donepezil 10 milligrams per day for a period of six months demonstrate enhanced cognitive function, including memory and daily activity abilities, in comparison to those who receive a placebo [8]. Furthermore, no adverse effects on behaviour or quality of life have been observed.

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4. NMDA receptor antagonist

The NMDA receptor antagonist represents the most proximate receptor contact with AD. Upon interaction with the receptor, the excitatory amino acid (EAA) triggers a significant influx of cations, particularly calcium ions, leading to a substantial number of neuronal apoptosis [6].

Memantine is an excitatory amino acid receptor antagonist that can effectively block the NMDA receptor. It has been demonstrated that memantine can prevent damage caused by calcium ion overload of nerve cells, prevent the loss of neurons and play a role in protecting the nerve [6]. The research indicates that memantine has the potential to alleviate the symptoms of severe AD to a certain extent; however, it has no discernible effect on mild AD [9]. Furthermore, it is necessary to coordinate with other medications due to the clinical diversity of the drug. A further study compared the efficacy and safety of memantine hydrochloride and donepezil in the treatment of Alzheimer's disease (AD). The findings indicated that both medications were effective in improving patients' cognitive function, daily living activities, and cognitive-related disorders. However, memantine demonstrated superior safety profiles [10]. The objective of the research is to examine the relationship between the NMDA receptor subtypes NR2A, NR2B, and NR2D and the long-term potentiation (LTP) inhibiting effect of Aβ [11]. The study revealed that the selective antagonist of the NMDA receptor subtype NR2D and NR2B can reverse the damage caused to long-term potentiation (LTP) by Aβ (1-42) mediation. However, no such effect was observed with NR2A [11].

5. Antibody drugs

The primary focus of antibody therapy for Alzheimer's disease (AD) is on the clearance of Aβ protein deposits. These sediments represent a significant pathological feature. Aduhelm (Aducanumab) and Leqembi (Lecunemab) are monoclonal antibodies (MAB) that target amyloid proteins in the brains of patients with Alzheimer's disease (AD). They represent the first class of drugs designed to intervene in the underlying biological processes of the disease, with the goal of delaying clinical failure. The mechanism of action of these two drugs is based on the amyloid cascade hypothesis, which posits that the aberrant generation and accumulation of Aβ amyloid protein represents a critical link in the pathogenesis of AD, triggering a cascade of events that culminate in neurodegenerative changes. Aduhelm represents the first novel therapeutic agent to be approved by the FDA for the treatment of AD since 2003. Its mechanism of action involves the clearance of β-amyloid protein from the brain. The approval of Aduhelm is contingent upon the findings of the EMERGE and ENGAGE studies. The EMERGE trial demonstrated that Aduhelm exhibited a more pronounced efficacy in reducing amyloid protein accumulation compared to the placebo, with a reduction of approximately 71%. It is a humanised monoclonal antibody that is capable of targeting the Aβ plaque and facilitating clearance. Nevertheless, one potential adverse effect of Aduhelm is amyloid-related imaging abnormalities (ARIA), which may manifest as cerebral haemorrhage and encephalopathy. While these symptoms may not be immediately apparent, they can be serious. The medical personnel responsible for the patient's care will conduct magnetic resonance imaging (MRI) scans of the patient both before and after the administration of the treatment in order to ascertain the presence of ARIA. The approval of Leqembi is based on the results of the pivotal Phase III clinical trial, CLARIFY-AD. The results demonstrate that after 18 months of Leqembi administration, the rate of decline in cognitive and memory function has been reduced by 17%. The mechanism of action of Leqembi is to inhibit the development of Alzheimer's disease by selectively binding to soluble Aβ aggregates, thereby reducing the formation of Aβ plaques in the brain. The side effects of Leqembi include ARIA, headaches and adverse effects associated with the infusion, such as flu-like symptoms, nausea, vomiting and changes in blood pressure.

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6. Therapeutic drugs in the clinical stage

6.1. Anti-amyloid therapy

The principal pathological feature of AD patients is the bulk deposition of β-amyloid protein in the brain. Amyloid precursor protein (APP) has three known effects on the decomposition process: Aβ, β-secretase and γ-secretase are involved in the abnormal cleavage of APP. Bapineuzumab is a humanised monoclonal antibody that targets the amino terminal of Aβ. In animal experiments, it has been shown to reduce AD levels; however, in clinical tests, it has not been effective in removing Aβ plaques or improving recognition ability [12]. In the clinical trials of Bapineuzumab 301 and 302, there were 1,121 cases of APOEε4 carriers and 1,331 non-carriers [12]. Nevertheless, the findings indicate that, in comparison to the placebo, Bapineuzumab does not exhibit a notable distinction in terms of ADAS-cog11 score and dementia disability score (DAD). Solanezumab is another humanised monoclonal antibody that has been shown to bind with soluble Aβ, thereby improving the clearance rate of clear Aβ from the brain in clinical trials.

6.2. Aβ immunotherapy

The administration of the β amyloid protein vaccine serves to remove the accumulation of Aβ in the brain by stimulating the body's immune system. The AN1792 vaccine was the first to be tested in a clinical setting, but it was halted due to the occurrence of meningitis in 6% of patients. The experiment demonstrated that 59 of the 300 subjects who exhibited a cure response to AN1792 (QS-21) also demonstrated an antibody response. No significant difference was observed between the antibody response and placebo groups with regard to ADAS-Cog and Mini-Mental State Examination (MMSE) scores. However, the z-score of NTB indicates that the group with antibody response exhibited superior statistical outcomes. In subjects who underwent cerebrospinal fluid (CSF) testing, antibody responses were observed to decline more rapidly than in the placebo group, accompanied by a reduction in tau protein levels in the CSF. A total of 985 and 980 individuals were enrolled in the GRADUATE I and II experiments, respectively. The baseline CDR-SB score for GRADUATE I is 3.7, while that for GRADUATE II is 3.6. A total of 116 weeks later, a notable change was observed in the CDR-SB score for the gantenerumab group, which exhibited a score of 3.35, while the placebo group demonstrated a score of 3.01 [13]. Similarly, the CDR-SB score in GRADUATE II also demonstrated a change: the gantenerumab group exhibited a score of 2.82, while the placebo group demonstrated a score of 3.01 [13]. The results demonstrate that patients who received gantenerumab exhibited a decline in amyloid protein accumulation after 115 weeks [13].

6.3. Tau protein targeted therapy

Tau is a protein that is present in nerve cells and plays a crucial role in maintaining the stability of the canaliculus [6]. The principal mechanism of action of these drugs is the prevention of Tau protein phosphorylation, thereby enhancing the stability of the canaliculus. Sodium valproate and lithium carbonate are inhibitors of GSK-3, capable of weakening the phosphorylation of Tau protein by inhibiting kinase activity [14]. In a retrospective study, Terao and his colleague observed that patients who received lithium treatment exhibited a lower degree of decline in recognition ability, as measured by the MMSE. The study revealed that, in comparison to the efficacy of lithium in treating bipolar disorder, the use of lithium in the treatment of Alzheimer's disease demonstrated a significantly lower reduction in the incidence of the disease (3%) than in individuals who had never been exposed to lithium (19%). The present study demonstrates that long-term lithium treatment can effectively prevent the onset of Alzheimer's disease.

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7. Conclusion

In conclusion, the eradication of Alzheimer's disease (AD) will facilitate the creation of a supportive society for the elderly. According to preliminary estimates, over 40% of AD patients lack the financial resources to pursue long-term therapeutic options. In essence, the disease necessitates pharmacological intervention, psychotherapy, exercise, and a nutritionally balanced diet. The intricate regulatory framework may prove detrimental to both patients and their families over time. The only means of preventing the onset of Alzheimer's disease is through a healthy lifestyle, comprising a balanced diet, regular exercise and a regular sleep-wake cycle. The pharmaceutical agents currently available have numerous deficiencies and their efficacy is limited. Furthermore, the therapies that have been included in clinical trials have also demonstrated some limitations in their efficacy, or have been associated with significant adverse effects. Despite significant advances in research, there is still no definitive cure for Alzheimer's disease. The path to a cure is a lengthy one, with numerous challenges and uncertainties along the way.

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