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Pathogenesis and Treatments of Alzheimer's Disease

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Abstract. Alzheimer's Disease (AD) is a kind of neurodegenerative disease, and it usually occurs in senility. The number of people suffering from this disease is increasing every year, which makes AD become a major global public health problem. Once a person is diagnosed with AD, it's really hard to heal. The early symptoms of AD include memory loss, difficulty with problem solving and planning, confusion about time and place and so on. The moderate symptoms include personality and behavioral changes, restlessness and wandering. The late stage symptoms include physical decline, severe memory loss, and increased vulnerability to infections. So, it's important to write a review paper about it. This paper presents Pathogenesis of AD including A β hypothesis, Tau protein hypothesis, mitochondrial dysfunction, neuroinflammation hypothesis, cholinergic hypothesis and oxidative stress hypothesis. It also presents treatments of AD including RNAi therapeutics, ketogenic diet, probiotic interventions. Lastly, the paper suggests corresponding therapies for each pathogenesis.

Keywords: Alzheimer's Disease, pathogenesis, treatment.

1. Introduction

Alzheimer's Disease is a primary degenerative encephalopathy that occurs in old age and early senile period, and refers to a persistent disorder of higher neurological activity, that is, in the absence of consciousness disorders, disorders in memory, thinking, analysis and judgment, visuospatial recognition, emotion, etc. The onset of AD is concealed. However, once it happens, the development of AD is irreversible. At the early stage of AD, the symptom includes near memory loss, personality change, mental decline, poor spacial orientation. The patients do not know the way back, or have reduced motivation and emotional instability, but can still maintain their daily life. As it further develops, patients would experience cognitive decline, aphasia, agnosia, and sometimes impaired consciousness. At this stage, people can no longer take care of themselves in daily life, and they often have shameless behaviors and changes in ethical and moral behaviors. Auditory and visual hallucinations, delusions mania and depression may also occur. In the late stage, patients have comprehensive intellectual disability. The symptoms in this stage include lack of voluntary movement, silent or fragmented speech. In this stage, patient cannot take care of themselves at all, and eventually, they will die due to complications. The etiology of AD is complex, and its occurrence is the result of multiple factors. Genetics is one of factors of AD. Molecular biology shows that There are abnormal loci on chromosomes 21, 19, 14, and 1, and these affected genes encode proteins: β amyloid (β-AP), apolipoprotein E (Apo E), procasein-1, and progerin-2. Mutations and polypeptide alterations in these genes are associated with the onset of AD. β-AP is produced by the abnormal cleavage of β-amyloid precursor protein (β-APP) and is a major

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component of age plaque formation. Apo E gene is one of the most important genetic factors affecting the aging pathway, and the risk of late-onset familial AD and sporadic AD is dependent on the amount of Apo E4 allele [1]. Cholinergic hypothesis states that Decreased acetylcholinetransferase activity in the cerebral cortex and hippocampus directly influences acetylcholine synthesis and functions of the cholinergic system, which occurs in AD patients' brains. The accumulation of Aβ is one of the main causes of AD since Aβ can bind to synapses and then inhibit their functions. When synapses functions are inhibited, they contribute to memorial decline since synapses interactions are indispensable in memory formation. Eventually it will lead to AD. Phosphorylated tau is another main cause of AD. Tau is a kind of protein that is supposed to support the structure of axon. If it is phosphorylating, it will pair up with another tau. Eventually, nerve fiber tangles are formed in nerve cells, which leads to collapse of axon. So, neurons interactions will decline and then it will lead to AD. Based on these hypotheses, treatments for AD are developing. According to Aβ hypothesis, this harmful protein reduces interactions between neurons, which leads to AD. So, there are some medicines that are emerged to reduce this kind of protein. However, some recent research show that mice that have AD and receive the treatment do not have significant changes. So, people start to doubt whether Aβ has direct cause of AD. Based on cholinergic hypothesis, there are some medicines for cholinergic systems to increase its acetylcholine synthesis. Additionally, there are some non-medicine treatments. For instance, bright light therapy can be used to treat sleeping and behaviour disorder of patients. The sleep-wake rhythm of AD patients is fragmented, with more sleep time during the day and less sleep time at night. Here are the treatment details: Every day at 9-11 o'clock in the morning, the use of 3000-5000LX full-spectrum fluorescent lamp irradiation, lamp distance of 1m, for 4 weeks, can improve the level of alertness, reduce the daytime sleep time, so that night sleep can be integrated, and reduce the abnormal actions caused [2]. Using a right therapy to treat AD is really important, so this paper presents pathogenesis and treatments of AD, and suggest corresponding treatments of AD based on particular pathogenesis.

2. Pathogenesis of Alzheimer's disease

2.1. Aβ Hypothesis

Alzheimer's Disease have symbolic characteristics, such as neurofibrillary tangles (NFTs) which can reduce blood cells and neurons. Amyloid beta precursor proteins (APP) are existed in all cells. The APP that has amino acid numbers between 39-43 are highly cohesive. Aβ can produce soluble oligomers, and oligomers can be turned into insoluble fibers. Aβ is the most neuronal toxic molecule since it inhibits signal transmit between neurons and reduces synapses plasticity, which blocks memory formation. Additionally, Aβ can recognize CD36 and toll-like receptors on glial cells, which activates them include microglial cells and astrocytes, and then these cells will produce inflammatory factors, which leads to cascade inflammatory response in central nervous system [3]. In AD, Aβ can over activate glial cells and causing the disability of glial cells to engulf Aβ and leads more release of inflammatory response, which reduces synapse. Aβ can also lead to oxidative stress. When oxidant and antioxidant are losing balance, it can break oxidative signals, which will lead to increase of oxidant. When there is too much oxidative stress, it will hurt macromolecule including protein, DNA, RNA, lipid, etc. In fact, the N-terminal metal binding domains of Aβ and APP have zinc and copper. Since coppers are effective in oxidative reactions, they can accumulate oxidative stress and then hurt the brain.

Hardy and Higgins concluded that Aβ causes increase of NFTs and destruction of blood vessels and neuron number decline. Subsequently, Aβ synthesis leads to increase of calcium, and then pohsporylated tau will increase, which increases AD severity.

Cholesteral which is produced by glial cells is necessary for neuron. While, Aβ can decrease cholesteral formation and transmission. Therefore, neurons will be decreased. In the early stage of AD, Aβ activates FPR. With the interaction of RXR and PPARα, it stimulates astrocytes produce more ABCA1 and ABCG1 which can encourage increase of cholesteral [4]. However, in the late stage of AD, ABCA1 and ABCG1 transmission is decreased. With the accumulation of Aβ, it inhibits cholesteral formation.

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Too many ROS can cause increased Aβ formation. Combining the effect of MDA AND 4-HNE, more calcium channels on cell membrane will open, causing increased calcium flow into cells. Too much calcium will over activate protein kinase, and increase phosphorylation of tau.

In a nutshell, Aβ can over activate inflammation reaction, cause oxidative stress, inhibit cholesteral synthesis which is important for neural stability, and cause increased phosphorylated tau. All these factors are detrimental for neurons. So Aβ is regarded as one of the major causes of AD.

According to World Health Organization, currently, more than 55 million people worldwide suffer from dementia, more than 60% of whom live in low- and middle-income countries. There are nearly 10 million new cases every year. Dementia is caused by various diseases and injuries that affect the brain. Alzheimer's disease is the most common form of dementia and may account for 60-70% of cases. So, the therapies for AD are a hot research topic nowadays. Some studies show some new drugs that can reduce Aβ synthesis. For instance, Gang Cao and other researchers found out that Ginsenosides Re can reduce BACE1 mRNA and protein levels and inhibit BACE1 activity in N2a/APP695 cells, which ultimately reduces the production of Aβ1-40 and Aβ1-42.

2.2. Tau hypothesis

Tau protein is a soluble tubulin that is widely found in the central and peripheral nervous systems. In a normal physiological condition, tau exist within the microtubules in the axon. It can bind with tubulin, and can regulate microtubule aggregation, movement, and spatial distribution. It also plays a big role in maintaining neuronal axonal transport, dendrigenesis and synaptic plasticity, and nuclear DNA stability. While in pathological conditions, this kind of protein has hyperphosphorylation, and detach from microtubules, then it forms insoluble tau protein aggregates. Then, specific neural inclusions are subsequently generated, and neuronal fiber tangles are formed after forming paired spiral filaments. Tau aggregates to produce pairs of spiral fibers (PHF) and further transform into fibrous tangle (NFT), resulting in a decrease in microtubule stability, the disappearance of microtubules in dendrites and synapses, synapse loss, impairment of neuronal function, and eventually lead to neurodegeneration and neuronal death. Another study reported that tau gene mutations can also cause tau aggregation, causing dementia. Tau gene is located on chromosome17 17q21 and can express Tau [4]. Tau gene in AD patients is mutated, and tau can be abnormally modified with hyperglycosylation, phosphorylation and ubiquitination.

In healthy neurons, as a microtubule-associated protein, tau can maintain the stability of cells, and plays an important role in stabilizing neurons. But in pathological conditions, tau is over phosphorylated, and then misfold and aggregation occurs and form insoluble neurofiberillary tangles that are accumulated inside the neurons. Neurofiberillary tangle (NFT) not only block transmission between neurons, but also damage normal function of neurons. Eventually it will cause death of neurons. The hyperphosphorylation of tau form PHF and NFT. NFT is fibroid content within the brain cone cells. Clinical studies have been demonstrated that the number of NFT is positively correlated with the degree of cognitive decline in AD patients so it is a pathological marker of AD severity. The main content of NFT is a kind of PHF that is formed by hyperphosphorylated tau, and a part of hyperphosphorylated tau is soluble, while the other part of it is insoluble, called PHF tau, and its deposition in the brain leads to neuronal degeneration. The discovery of these pathological process is instructive for exploring new therapeutic targets and approaches.

Tau hypothesis suggests that tau is the major factor of AD pathogenesis, and tau tangle is closely related to AD. So, therapeutics targeting tau are expected to be an effective approach for AD. For example, the degree of phosphorylation of tau can be used as an evaluation indicator of AD disease progression and prognosis, and the study of AD-related biomarker content in human CSF shows that the ratio of Aβ-42/total tau and Aβ42/P-tau can be used as a detection index to distinguish normal individuals from AD patients. For the various mechanisms of tau proteins, various studies have been proposed to remove pathological tau proteins and reduce tau phosphorylation. Although tau aggregation inhibitors and tau antibody agents have not shown efficacy on AD endpoints, active or passive immunotherapies for this mechanism and alternation strategies to regulate post-translational

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modification of tau proteins are still under development. Currently, a variety of tau antibodies have entered to preclinical testing phase.

The current focus is on how to inhibit the abnormal production and deposition of Aβ proteins by gene therapy or immunotherapy, and how to prevent the abnormal phosphorylation and aggregation of tau. To be more specific, Aβ triggers degeneration in cultured nerve cells and also causes cognitive deficits in mice with AD-like disease, and increasedoxidative stress, impaired folding of endoplasmic reticulum proteins, protease and autolysosme-mediated clearance are all associated with aging and can accelerate Aβ and tau accumulation in the brain which has AD. Drugs that counteract these changes are still not available, but trials of small molecule inhibitors of amyloidogenic protein and tau oxidation and aggregation inhibitors are ongoing. Polyphenolic extracts from grape seeds can stimulate aging suppressor genes and are becoming therapeutic agents. These studies provide new strategies to slow the pathological progression of AD and reduce the risk of disease, which will hopefully bring more effective treatment options for AD patients in the future and improve their cognitive function and quality of life.

2.3. Mitochondrial dysfunction

Oxidative stress and neuronal death caused by the mitochondrial cascade are an important link in the pathogenesis if AD. The mitochondrial cascade hypothesis assumes that Aβ or tau cannot drive AD pathogenesis, and it argues that mitochondria play an important role in AD pathogenesis and that mitochondria are crucial in promoting the development of AD pathology with increasing age. According to the mitochondrial cascade hypothesis, mitochondrial dysfunction drives the pathogenesis of AD, as baseline mitochondrial function and the rate of mitochondrial change influence the progression of cognitive decline. Mitochondria play a key and central role in the maintenance of optimal neuronal and synaptic function. So, mitochondrial dysfunction may be a major cause of AD and is a promising target for novel therapeutic strategies.

Mitochondrial structure and function changes may cause neuronal iron death (ferroptosis), which is an important link in the pathogenic mechanism of AD. Iron death (ferroptosis) is a newly defined programmed cell death with iron-dependent, lipid-dependent and iron-dependent properties [5]. The imbalance in iron homeostasis not only leads to iron death but is also an important factor in mitochondrial dysfunction. Usually, diseases caused by mitochondrial dysfunction (such as tumors, chronic inflammation, neurodegenerative diseases, etc.) are caused by the excessive production of free radicals in mitochondria, while the imbalance of iron homeostasis may lead to increased levels of free radicals, resulting in more damage to mitochondria. For example, an imbalance in iron homeostasis leads to increased ROS, and ROS can resolve enzymes on mitochondrial membranes and disrupt mitochondrial membranes, leading to decreased mitochondrial membrane potential. At the same time, the iron ions in mitochondria may also combine with sulfur groups to form free radicals, further strengthening the oxidative stress response, leading to the destruction of the structure and function of enzymes on the mitochondrial membrane, thus triggering cell death. Therefore, an imbalance in iron homeostasis may aggravate mitochondrial dysfunction by increasing ROS [6]. The close association between mitochondria and calcium ions enables them to be responsible for many metabolic functions quickly, and the concentration of calcium ions can affect the activity of enzymes in mitochondria and affect mitochondria function. This process is called mitochondrial cascade reaction (mitochondrial cascade hypothesis) [3]. However, the cascade may cause vulnerability to the nervous system and cause a range of diseases, such as Alzheimer's disease. The homeostatic imbalance of iron ions may also interfere with the intracellular calcium ion concentration, causing the interaction between calcium and mitochondria to be affected, resulting in uncontrolled mitochondria and cell dysfunction. Therefore, the imbalance of iron homeostasis may cause mitochondrial dysfunction through multiple pathways and thus regulate the development of a variety of neurological diseases, including AD.

Mitochondrial dysfunction also plays an important role in the pathogenesis of AD since mitochondria are not only the core of cellular energy metabolism, but also an important organ to maintain the balance of calcium ions and produce reactive oxygen species. In AD, mitochondria are and abnormal, and these abnormalities may be one of the factors driving the pathological changes in AD.

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The interplay of mitochondrial dysfunction, calcium imbalance and oxidative stress constitutes a complex pathological network in AD. How to slow down or stop the pathological process of AD by promoting mitophagy in mitochondria, increasing the number of mitochondria and antioxidant therapy are being explored currently. The success of these strategies will bring new hope for the treatment of AD.

3. Treatments of Alzheimer's Disease

3.1. RNAi therapeutics

RNAi refers to the phenomenon in which double-stranded RNA (dsRNA) mediates homologous sequence mRNA-specific degradation in multiple biological cells, resulting in post-transcriptional gene silencing (gene silencing). RNAi is mainly achieved by cleavage of dsRNA into small interfering RNA (SiRNA) by dsRNA mediated recognition and targeted cleavage of cognate mRNA molecules. The phenomenon of RNAi is widely found in eukaryotic cells. With the deepening of the research on RNAi, its mechanism of action is gradually being clarified, and the RNAi technology is becoming increasingly mature and perfect [7].

In 2002, Krichevsky found that using a specific neuronal transfection reagent, TransMessenger transfection reagent, could effectively address this problem. In contrast to previous conventional transfection reagents, TransMessenger transfection reagent has a high affinity to neurons to efficiently transfect plasmid or siRNA into primary cultured rat hippocampal cortical neurons without apparent neuronal death [8]. The high transfection rate and high survival rate of this new transfection reagent greatly extends the research field of view of RNAi technology in the CNS. At present, different companies have developed special transfection reagents for nerve cells and converted them into commodities, accelerating the application of RNAi in the study of neuronal gene function. Kao showed that transfection of chemically synthesized siRNA targeting BACE 1 into mouse neurons disrupted endogenous BACE 1 gene expression and inhibition of BACE 1 gene with siRNA did not result in major defects in the cells [8].

At present, promising progress has been made in the experimental study of using RNAi to treat AD in animals. On August 28,2005, Singer published in Nature Neuroscience that they used APP transgenic mice as an animal model to construct BACE1 SiRNA expression vector into the hippocampus of transgenic mice, followed by A series of Aβ and BACE 1 levels [9]. The results showed that the level of BACE 1 and Aβ generation were significantly decreased in the hippocampus, and the behavioral defects of the transgenic mice were also improved. This is the first pioneering experiment of RNAi technology in animal models to inhibit BACE 1 expression for therapeutic purposes, and it marks that RNAi technology is approaching the ultimate goal of conquering human AD [9].

3.2. Ketogenic diet

The ketogenic diet (KD) is one of the ways to treat the disease. KD is a formula diet with high fat (80%~90%), low carbohydrate, low protein (6%~8%) and other nutrients, which can improve brain energy metabolism, relieve oxidative stress, regulate neurotransmitters and improve blood-cerebrospinal fluid barrier function. Adjust the proportion of nutrient intake to reduce glucose production and increase the production of ketone bodies, this is a metabolic state known as "nutritional ketosis" [7]. The ketogenic diet can affect the course of the disease by regulating inflammation, controlling the balance between pro-inflammatory and antioxidant, and changing the gut microbial composition. Advantages of ketogenic dietary intervention: affecting the progression of AD by regulating inflammation, controlling the balance between pro-inflammatory and antioxidant, and changing the gut microbial composition. Clinically, it is mainly used in the treatment of epilepsy, amyotrophic lateral sclerosis, cerebral ischemia, ischemia and hypoxia, traumatic brain injury and other diseases, and can achieve certain efficacy.

The brain, which accounts for about 2% of body weight, is the most energetic organ in the body and can be powered by two different mechanisms: glucose and ketone body metabolism. Glucose metabolism is impaired in the brain of AD patients, and ketone bodies can serve as an alternative fuel

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for brain capacitation [10]. A recent small randomized crossover trial in New Zealand found that a ketogenic diet improved daily functioning and quality of life in patients with AD [10]. In ketogenic diet-fed mice, the number of Lactobacillus and mucophilin-Ackermania increased, and the frequency of seizures decreased, improved cerebral vascular function and reduced the risk of AD, which also demonstrated the important impact of intestinal microbial homeostasis on nervous system function. Davis showed that the metabolites of KD is ketones and its derivatives, can prevent Aβ-42 into neurons, inhibit Aβ-42 accumulation in cells [11], reduce the phosphorylation of Tau, enhance mitochondrial function, neuroprotection against neurons, and improve the cognitive function of AD patients, but given the study sample size is small, the efficacy of KD needs to be further verified [2].

Ketogenic diet is expected to be a feasible strategy for AD, but larger and more long-term research, the recovery of abnormal glucose and energy metabolism in animal models and different AD patients still need further research, in addition, further graduate ketone diet on nutritional status, overall health and progress of AD, this new metabolic therapy needs further clinical research. KD can be used as a potential treatment for AD, providing a new idea for improving AD symptoms.

3.3. Probiotic interventions

Probiotics are beneficial and biologically active bacteria that maintain the balance of the intestinal flora. The brain-gut axis is mainly composed of the central nervous system, autonomic nervous system, hypothalamic-pituitary-adrenal axis, enteric nervous system and other structures, which is an important bridge between the brain and intestinal flora [2]. The gut microflora produces monoamines, methionine, glutamate, and homocysteine, which reach the central neurons through the lymph and the circulatory system and influence their activity, which may manifest as behavioral changes. In addition, gut bacteria are sensitive to information the brain sends through neurotransmitters [11]. Therefore, some studies have called this bidirectional information regulatory system the "gut bacteria-gut-brain axis". Because of the existence of the brain-gut axis, there is a conjecture that probiotics can treat cognitive dysfunction and even AD, that is, the intestinal flora through probiotics to achieve a stable and balanced state, and then the stable intestinal flora regulates the central nervous system through the brain-gut axis.

Intestinal microbial imbalance is associated with an increase in proinflammatory cytokines and oxidative stress, and changes in gut microbiota can be detected in neurodegenerative diseases such as AD, and treatment with probiotics can rebalance the intestinal flora and reduce inflammation. The endogenous cross-over influence between the gut microbiota and the brain is known as the microbiota gut brain axis (MGBA) [2]. Alterations in MGBA can significantly affect the course of neurodegenerative diseases such as AD, with mechanisms including increased gastrointestinal barrier permeability and systemic inflammation due to excessive immune activation, thereby damaging the blood – brain barrier and ultimately leading to neurodegenerative lesions [12].

Studies have shown that intervention in the AD model with probiotics can reduce inflammatory factors, increase antioxidant enzyme levels, and reduce Aβ deposition, as well as Tau hyperphosphorylation. Hermonium extract also significantly improved rat learning and memory capacity and downregulated the expression of AD-related markers Tau and Aβ-42. Gut flora 16S rRNA sequencing results show that the diversity and stability of the microbial community, can reduce intestinal inflammation, regulate metabolism and immunity, to slow down the process of AD, in a randomized, double-blind, controlled trial, containing lactobacillus acidophilus, lactobacillus casei, bifidobacteria and lactobacillus fermented probiotics yogurt after 12 weeks, can significantly improve the cognitive ability of AD patients [2].

Related studies showed that the patients included in the study had mild cognitive impairment, and most of them improved after taking probiotics, indicating that probiotics have a certain effect on the improvement of patients with mild cognitive impairment. However, whether probiotics are able to treat Alzheimer's disease needs further research. The treatment of Alzheimer's disease with probiotics is still in its early stages, and there are some unsuccessful cases in the published literature. Benton found that after 3 weeks of taking milk containing probiotics, no mood changes significantly, but memory was negatively affected [11]. Nonetheless, more results support the positive effects of probiotics on

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psychology and cognition. Therefore, further research on the interaction between probiotics [10], gut bacteria and AD, is needed to make probiotics play a prominent role in the prognosis of AD earlier. Although multiple probiotics show significant anti-inflammatory effects and cognitive benefits on the body, their effects on AD pathology and physiology still need to be explored. probiotics have potential clinical applications, but an effective and safe probiotics formula is developed to prevent AD.

4. Conclusion

At present, the clinical research results of anti-AD drugs are mostly not ideal, and patients urgently need effective therapeutic drugs to be put on the market. Indeed, the treatment of this disease requires an understanding of the detailed mechanisms of AD pathogenesis, and therefore, a better understanding of neurodegeneration-related mechanisms and intrinsic links could provide a reference for the future evaluation and development of new AD treatment strategies. The development of stem cell technology and the use of nanotechnology have provided a theoretical basis for nerve regeneration and targeted drug delivery. In addition, due to the complexity of AD pathology, multimodal synergistic therapy may be needed, including drug targeting at the lesion site, stimulation of endogenous neurogenesis and synaptogenesis, exogenous nerve replacement, and improvement of diet and sleep. In the future, it can have a deeper understanding of the pathogenesis of AD and provide new ideas for the prevention and treatment of AD.

Nowadays, AD drugs on the market, including ChEIs and NMDA antagonists, are not able to change the progression of the disease, so it is necessary to develop new drugs and use new therapeutic strategies. A large number of preventive treatments, especially those designed to avoid oxidative stress (e. g., antioxidants) and neuroinflammation, do provide some prospective treatments in the stage of clinical trials. Similarly, immunotherapeutic antibodies that stabilize mitochondrial function, inhibit LH production, and hyperphosphorylated tau, hindering the influence of adverse factors, may also play a role. Further elucidation of the relationship between glucagon and AD, whether the hypothesis of type 3 diabetes holds. The continuous discovery of susceptibility genes and the gradual widespread application of genetic interference technology will find a new way for the treatment of AD. In any case, finding more ways, rather than blindly pursuing a clear pathological process positioning, is a worthwhile and logical approach.

Currently, the clinical treatment of AD is still mainly based on drug treatment, which can effectively improve the symptoms of patients and delay the development of the disease. However, drug treatment is not conducive to frail elderly patients, leading to more and more patients inclined to non-drug means. If non-drug and drug therapy are combined, or multiple non-drug therapy means are combined to improve the cognitive ability of AD patients, whether better results need to be confirmed in further clinical studies.

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