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Effects and Therapeutic Value of Ziziphi Spinosae Preparations and Haierfu on Alzheimer's Disease-Related Cerebral Secretase Activity

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Abstract: To investigate the effects of Ziziphi Spinosae preparations and traditional Chinese medicine Haierfu on β-amyloid cleaving enzyme activity in aluminum-induced Alzheimer's disease (AD) model mice, and their therapeutic effects. Sixty KM mice were randomly divided into four groups: normal group, model group, treatment group 1, and treatment group 2, with 15 mice in each group. During the modeling phase, the normal group received no treatment, while the model group and the two treatment groups were administered maltol and $AlCl_3$ via intraperitoneal injection to establish the AD mouse model. After 30 days of injection modeling, treatment group 1 mice were administered 0.3 ml/mouse of diluted Ziziphi Spinosae preparation by gavage, and treatment group 2 mice were administered 0.3 ml/mouse of diluted Haierfu solution by gavage. The normal group and model group mice were administered an equal amount of distilled water by gavage, once daily for 5 consecutive weeks. Before exposure, after exposure, and after treatment, the learning and memory abilities of the mice were assessed using the Y-maze test. After the treatment, the brain tissues of the mice were taken and made into 10% brain homogenates to determine the activities of β-amyloid cleaving enzyme (BACE), α-secretase, γ-secretase, and acetylcholinesterase (AchE) in the brain. The results of the water maze test showed that the escape latency to reach the platform was significantly prolonged in the mice after modeling ($P<0.01$), and the time required for the mice to reach the platform was significantly shortened after treatment ($P<0.01$). The results of β-secretase activity in the brains of mice showed that the β-secretase activity of the two treatment groups was significantly lower than that of the model group mice. Sorted by normal group, model group, treatment group 1, and treatment group 2, the β-secretase activities were $9.54\pm1.31^{▲}$, $9.79\pm2.22^{▲}$, 6.92 ± 2.97, 8.57 ± 2.03 (u/L), respectively ($F=2.902$, $P=0.051$, compared with treatment group 1, $^{▲}P<0.05$). The α-secretase activities were $26.98\pm5.37^{▲▲}$, 25.97 ± 3.52, $48.30\pm39.06^{▲▲}$, $24.10\pm2.80^{▲▲}$ (u/L), respectively ($F=3.973$, $P=0.013$, compared with treatment group 1, $^{▲▲}P<0.01$). The brain AchE activities were 0.08 ± 0.02, $0.16\pm0.06^{▲▲}$, $0.15\pm0.07^{▲▲}$, $0.12\pm0.05^{▲}$ (u/mg.prot), respectively ($F=6.833$, $P=0.001$, compared with the normal group, $^{▲}P<0.05$, $^{▲▲}P<0.01$). Ziziphi Spinosae preparations and traditional Chinese medicine Haierfu can reduce β-amyloid cleaving enzyme activity in the brains of mice and improve cognitive dysfunction in AD mice.

1. Introduction

Alzheimer's disease (AD) is the most common type of senile dementia. AD has an insidious and slow onset and is irreversible. Reports indicate that the number of AD patients in China is expected to exceed 30 million by 2050 and continue to increase [1]. The pathogenesis of AD is complex and diverse. Among them, the β-amyloid cascade hypothesis is one of the most widely accepted theories in the academic community. It posits that the accumulation of excessive Aβ in the brain is the original mechanism of AD and the initiating factor leading to other pathological changes in AD patients. Therefore, reducing Aβ deposition in the brain is a key measure for the prevention and treatment of AD [2]. β-secretase, as a key cleaving enzyme for Aβ generation, is of great significance for the prevention and treatment of AD by reducing β-secretase activity and thereby reducing its catalytic production of Aβ. Aluminum, as a toxic metal element that is not essential to the human body, has obvious damaging effects on the human body, especially the central nervous system. There is a current academic consensus that aluminum exposure is one of the main environmental factors leading to the occurrence of AD. Studies have proven that the incidence of AD in areas with high aluminum intake is higher than in other areas. From a pathological perspective, aluminum accumulation in the brain can cause neurotoxic events such as oxidative stress, apoptosis, excessive Aβ deposition, and the formation of neurofibrillary tangles [3,4]. Currently, there is no effective treatment to cure AD patients, and the experimental effects of clinical drugs are not ideal and have been repeatedly frustrated. Traditional Chinese medicine (TCM) chemical components have natural advantages such as multi-target effects, consideration of the whole body, and fewer side effects in the treatment of AD, and have received increasingly widespread research attention in recent years [5]. Therefore, in this experiment, an AD mouse model was established by intraperitoneally injecting aluminum maltolate solution into mice, followed by treatment with a TCM compound via gavage, to explore the intervention mechanism of its active ingredients on AD-related secretases, so as to provide a basis for the clinical diagnosis and treatment of AD and the development of new drugs.

2. Materials and Methods

2.1 Experimental Animals

Sixty healthy, specific-pathogen-free grade KM mice (30 males and 30 females), weighing between 30 and 35g, aged 2-3 months, were purchased from Changsha Tianqin Biotechnology Co., Ltd., license number: Scxk (Xiang) 2023-0013. Males and females were housed separately in aluminum-free, independent mouse cages, 5 mice per cage. Feed and water were provided by the animal laboratory of Youjiang Medical University for Nationalities.

2.2 Reagents and Drugs

Crystalline aluminum chloride (AlCl3 6H2O), maltol, phosphate buffer (pH 7.4), physiological saline, and ethanol (95%) were provided by the biochemical laboratory of Youjiang Medical University for Nationalities. Total protein (TP) test kit, urea nitrogen test kit, triglyceride (TG) test kit, total cholesterol (TC) test kit, acetylcholinesterase (AchE) test kit, β-secretase, α-secretase, γ-secretase enzyme-linked immunosorbent assay (ELISA) kits were purchased from Nanning Juyuan Instrument Co., Ltd.. Traditional Chinese Medicine: Haierfu oral liquid was a patented product donated by Prof. Zhang Shuqiu of Youjiang Medical University for Nationalities. Haierfu is mainly made from star fruit, mung bean, honeysuckle, licorice, and Poria cocos as raw materials, extracted with water, filtered, concentrated by heating, precipitated with alcohol, ethanol recovered,

and sterilized by autoclaving. It has the functions of clearing heat and detoxifying, strengthening the spleen and dispelling dampness, protecting the liver and kidney, excreting heavy metals, and improving immunity. Ziziphus jujuba seeds were purchased from the market and prepared through water boiling and concentration, alcohol extraction after filtration, and autoclaving. And other experimental equipment such as SpectraMax M5 microplate reader, Y-maze stimulator, pipettes (imported), pipette tips (imported), electronic balance, constant temperature water bath, spectrophotometer, high-speed centrifuge, etc.

2.3 Grouping, Modeling, and Treatment

Sixty mice were randomly divided into four groups, each with 15 mice, and housed separately: normal group, model group, treatment group 1, and treatment group 2. The normal group received no treatment. The model group and treatment groups were used to establish a dementia mouse model by intraperitoneal injection of maltol aluminum solution (maltol solution and AlCl3 solution mixed in equal volumes to form maltol aluminum solution with the pH 7.1-7.4, filtered, and stored in a 4℃ incubator). The injection was administered once daily at a dose of 0.30 ml/mouse. This was continued for 6 days, followed by a 1-day cessation, and this cycle was maintained for 9 weeks until the end of the experiment (if unstable vital signs such as a significant decrease in activity, emaciation, or lethargy were observed during the injection process, the injection was temporarily stopped or the injection dose was appropriately reduced). The treatment groups were administered gavage treatment after 5 weeks of intoxication. Treatment group 1 received a diluted jujube seed preparation via gavage, and treatment group 2 received a diluted Hailifu solution via gavage (the gavage treatment solutions were prepared by mixing 0.15 ml of the original drug solution with 0.15 ml of drinking water in equal volumes for dilution). Simultaneously, the normal group and model group received an equal amount of drinking water via gavage until the end of the experiment. Throughout the experiment, the mice were fed standard feed and drinking water, and their basic conditions, such as water intake, food intake, feces, body shape, and activity level, were observed and recorded daily.

2.4 Determination Methods

2.4.1 Learning and Memory Ability Test and Hemoglobin Determination

The learning, cognitive, and memory abilities of mice were assessed using the "Y" maze test before aluminum poisoning modeling, after modeling, and after treatment [6]. The maze was "Y" shaped, with an endpoint platform set on one side level with the water surface. Before aluminum exposure, the mice underwent one week of water maze memory training to guide them to the endpoint platform, familiarize them with the water maze passage, and form a memory. At the formal start of the test, the mice were made to swim from the platform side to the opposite endpoint platform, and the time required, turning around midway, swimming in the wrong direction, and other conditions were recorded with a stopwatch. If the time required to reach the endpoint platform exceeded 10 seconds, it was recorded as timeout; failure was recorded if the endpoint platform was not reached in more than 40 seconds. Each period was tested continuously for three days, and each test involved the mice swimming three times consecutively. At the end of the experiment, the error rate, timeout rate, and failure rate of the mice in the water maze test were calculated for each period. At the same time, whole blood (10 μL) was collected from the tail of the mice before, during, and after the experiment, added to 2.5 mL of conversion solution, and the hemoglobin content was determined using the HiCN method. The relevant measuring instruments were provided by the Research Laboratory of Heavy Metals and Arsenic Toxicants, Youjiang Medical University for

Nationalities, and the operating steps were performed according to the reagent instructions.

2.4.2 Relevant Secretases in Brain Tissue Determination

Following gavage treatment, mice were euthanized, and brain tissue was carefully dissected and extracted. To eliminate residual blood, the tissue was rinsed with ice-cold PBS, then homogenized in physiological saline at a 1:9 volume ratio using an ice bath for 10 minutes. The resulting homogenate was centrifuged at 5000*g for 5 minutes, and the supernatant was immediately collected for enzyme activity assays. β-secretase, α-secretase, and γ-secretase levels in the brain homogenate were quantified via double-antibody sandwich ELISA, adhering strictly to the protocols outlined in the ELISA and AchE kit instructions.

2.4.3 Serum Biochemical Indices Determination

Serum was extracted from blood collected via eyeball puncture in mice prior to sacrifice, followed by centrifugation to isolate the supernatant. Serum alanine aminotransferase (ALT) levels were quantified using the 2,4-dinitrophenylhydrazine method, blood urea nitrogen (BUN) levels were quantified using the urease-Berthelot method, TP levels were quantified using the Coomassie brilliant blue method, TC levels were quantified using the CHOD-PAP method, and TG levels were quantified using the GPO-PAP method. All procedures were performed in accordance with the manufacturer's instructions for each respective kit.

2.5 Statistical Analysis

Data were analyzed using SPSS13.0 statistical software and are presented as ($\bar{x} \pm S$). Statistical comparisons were performed using ANOVA followed by the Q test.

3. Results

3.1 Survival of Mice in Each Group

At the end of the experiment, 14 mice in the normal group, 15 in the model group, 14 in treatment group 1, and 12 in treatment group 2 were survived.

3.2 Brain Secretory Enzyme

Table 1: Comparison of brain β-secretase, brain α-secretase, brain γ-secretase and AchE in each group ($\bar{x} \pm S$)

Groups	β-Secretase	α-Secretase	γ-Secretase	AchE (u/mg.prot)
Normal group	9.54±1.31▲	26.98±5.37▲▲	5.99±1.09	0.08±0.02
Model group	9.79±2.22▲	25.97±3.52	6.22±0.87●●	0.16±0.06▲▲
Treatment group 1	6.92±2.97	48.30±39.06▲▲	8.32±2.75▲▲	0.15±0.07▲▲
Treatment group 2	8.57±2.03	24.10±2.80▲▲	7.54±1.69▲▲●●	0.12±0.05▲

β-Secretase Activity: The model group exhibited higher activity than the normal group. Following treatment, both treatment group 1 and treatment group 2 showed decreased cerebral β-secretase activity, with treatment group 1 demonstrating a more significant reduction. α-Secretase Activity: The model group's activity was slightly lower than that of the normal group. Compared to the model group, treatment group 1 showed a significant increase in activity, while treatment group 2 showed a slight decrease, though the magnitude was not significant. γ-Secretase: The activity of both treatment groups increased. The cerebral AchE of the model group was significantly higher

than that of the normal group, and the activity of both treatment groups decreased after treatment. The measurement results are shown in Table 1.

Analysis of Variance: Brain β-Secretase: F=2.902, P=0.051, compared with treatment group 1, ▲P<0.05, indicating a statistically significant difference. Brain α-Secretase: F=3.973, P=0.013, compared with treatment group 1, ▲▲P<0.01, indicating a statistically significant difference. Brain γ-Secretase: F=4.630, P=0.007, compared with the normal group, ▲P<0.05, indicating a statistically significant difference; compared with treatment group 1, ●●P<0.01, indicating a statistically significant difference. AchE: F=6.833, P=0.001. Compared with the normal group, ▲P<0.05, ▲▲P<0.01, indicating a statistically significant difference.

3.3 Serum Indicators

Analysis of serum urea nitrogen, TP, TC, and TG in mice revealed the following: the normal control group exhibited the highest levels of urea nitrogen and TP, followed by the model group. Treatment groups demonstrated reduced levels of urea nitrogen and TP compared to the model group. Conversely, TC and TG levels were elevated in the treatment groups. Quantitative data are presented in Table 2.

Table 2: Results of AchE, serum urea nitrogen, and total protein in each group ($\bar{x} \pm S$)

Groups	Serum urea nitrogen (mmol/L)	TP (g/L)	TC (mmol/L)	TG (mmol/L)
Normal group	17.28±3.48	65.65±7.89▲	4.03±0.74	1.04±0.24
Model group	14.34±3.49▲	65.34±5.80▲	3.39±0.58	1.35±0.84
Treatment group 1	13.28±2.96▲▲	62.88±5.43	4.20±1.01▲	1.66±0.85▲
Treatment group 2	10.40±2.54▲▲	60.14±6.19	4.01±0.88	1.95±0.90▲▲

Analysis of variance: Urea nitrogen: F=11.559, P=0.000, compared with the normal group, ▲P<0.05, ▲▲P<0.01, the difference was statistically significant. TP: F=2.193, P=0.100, compared with treatment group 2, ▲P<0.05, the difference was statistically significant. Serum TC: F=2.150, P=0.106, compared with the model group, ▲P<0.05, the difference was statistically significant. Serum TG: F=3.730, P=0.017, compared with the normal group, ▲P<0.05, ▲▲P<0.01, the difference was statistically significant. The differences between each group were statistically significant.

3.4 Hemoglobin levels

Hemoglobin levels in mice were measured before exposure, after exposure, and after treatment. The results showed no significant changes in hemoglobin levels in the normal group at all three stages. Hemoglobin levels in the model group and treatment groups decreased after exposure. After treatment, hemoglobin levels in both treatment groups decreased, and the trend of change was consistent with the model group. The measurement results are shown in Table 3.

Table 3: Hemoglobin levels in each group before exposure, after exposure, and after treatment ($\bar{x} \pm S$)

Groups	Before exposure	After exposure	After treatment
Normal group	79.45±4.40	79.68±3.18●●	79.11±11.68●●
Model group	77.61±9.85a	74.20±7.95▲●b	65.65±9.71▲▲●●
Treatment group 1	74.11±7.28a	67.90±6.99▲▲b	57.27±9.29▲▲
Treatment group 2	76.78±6.07a	70.61±6.88▲▲b	53.16±8.42▲▲

Analysis of variance: Comparison of the initial, middle, and late stages within groups: Normal group: F=0.020, P=0.980, P>0.05. There was no statistically significant difference in the

comparison before, during, and after. Model group: F=6.597, P=0.003. Compared with after treatment, aP<0.01, b<0.05, the difference was statistically significant. Treatment group 1: F=16.750, P=0.000. Compared with after treatment, aP<0.01, b<0.05, the difference was statistically significant. Treatment group 2: F=38.816, P=0.000. Compared with after treatment, aP<0.01, b<0.05, the difference was statistically significant.

3.5 Water maze test

The results of the water maze test in mice before exposure, after exposure, and after treatment in each group showed that, except for the normal group, the water maze time was significantly prolonged in the model group and the treatment groups after exposure. After treatment, the water maze time of mice in the model group showed no significant change, while the water maze time in the two treatment groups was significantly shortened. The measurement results are shown in Table 4.

Table 4: Water maze test time (s) in each group before exposure, after exposure, and after treatment ($\bar{x} \pm S$)

Groups	Before exposure	After exposure	After treatment
Normal group	4.27±0.53	4.38±0.94	4.80±1.67▲
Model group	4.15±0.60	6.28±2.16▲▲a	6.04±1.64a
Treatment group 1	4.40±0.58a	6.58±1.90▲▲	4.90±0.72▲a
Treatment group 2	4.41±0.71a	6.58±1.55▲▲	4.71±0.87▲a

Analysis of variance: Comparison of pre-, mid-, and post-exposure within groups: Normal group: F=0.838, P=0.440, P>0.05, the difference in pre-mid-post comparison was not statistically significant; Model group: F=8.141, P=0.001, compared with before exposure, aP<0.01; the difference in pre-mid-post comparison was statistically significant; Treatment group 1: F=12.947, P=0.000, compared with after exposure, aP<0.01, the difference in pre-mid-post comparison was statistically significant; Treatment group 2: F=16.091, P=0.000, compared with after exposure, aP<0.01, the difference in pre-mid-post comparison was statistically significant.

3.6 Measurement results of water maze

The measurement results of water maze error rate (%), timeout rate (%), and failure rate (%) before exposure, after exposure, and after treatment are shown in Table 5.

Table 5: Measurement results of the water maze test for each group before exposure, after exposure, and after treatment

Groups	Before exposure			After exposure			After treatment		
	error rate	timeout rate	failure rate	error rate	timeout rate	failure rate	error rate	timeout rate	failure rate
Normal group	0	0	0	11.85	17.78	1.48	4.76	4.76	0.79
Model group	0	0	0	10.37	16.30	0	0	0.93	0
Treatment group 1	0	0	0	9.36	16.30	1.48	14.07	11.11	0
Treatment group 2	0	0	0	0.75	0.75	0	10.32	4.76	0

4. Discussion

For many years, the amyloid cascade hypothesis has been dominant in academic research on the mechanisms of AD. This hypothesis posits that the primary cause of AD is the excessive deposition

of Aβ peptides in the brain tissue, leading to toxic effects on the brain and consequently, cognitive dysfunction. As one of the main pathological hallmarks of AD, the accumulation of Aβ in the brain is considered the initiating factor for other pathological processes such as neuronal and synaptic dysfunction, Tau protein hyperphosphorylation, and inflammatory responses [7,8]. The precursor of Aβ is amyloid precursor protein (APP). Under normal physiological conditions, only a small portion of APP in the body is continuously cleaved by the synergistic action of β-secretase and γ-secretase to produce Aβ. However, when the human body is affected by certain pathological factors, the physiological metabolic balance of APP in the body is disrupted. Under the continuous cleavage of β-secretase and γ-secretase, several types of Aβ fragments are excessively produced. Aβ40 and Aβ42 fragments, composed of 40 or 42 amino acids, are the two most common types. Among them, Aβ42 is more likely to aggregate in the brain and is more closely related to the toxic effects on neurons, and is regarded as a key factor in the early stage of AD [9,10]. In addition, most of the APP is cleaved through a non-amyloidogenic pathway, in which α-secretase plays a dominant role. APP is cleaved by α-secretase at a certain site within the Aβ peptide sequence into sAPPα and CTFα, the latter is further decomposed by γ-secretase to produce P3, while sAPPα is a molecular fragment with a protective effect on neurons [11,12]. Aluminum is a recognized heavy metal with toxic effects on the nervous system. As an environment-related risk factor, its role in inducing neurodegenerative diseases such as AD has been widely recognized in academia [13]. Numerous studies have shown that excessive aluminum exposure disrupts the balance between the production and clearance of Aβ in brain tissue, leading to its abnormal deposition. At the same time, aluminum also has the hazards of promoting the formation of NFTs, inducing neuronal apoptosis, disrupting the synthesis and decomposition balance of Ach in the body, and inhibiting the effect of neurotransmitters in the learning and memory pathways [14,15].

The Haierfu oral solution used in this experiment has the functions of clearing heat and detoxification, strengthening the spleen, protecting the liver and kidney, and accelerating the transformation and excretion of toxins in the body. It is often used to excrete and remove heavy metals (such as mercury, lead, arsenic, etc.). Suanzaoren (Ziziphus jujuba var. spinosa seed) is a traditional Chinese medicine with a long history. From ancient times to the present, most of the research and use of its pharmacological effects have focused on sedation, hypnosis, and improving sleep quality. With the continuous in-depth exploration by modern scholars, its medicinal value has been extended to anti-anxiety, anti-depression, anti-inflammation, improvement of cognitive function, and enhancement of immunity [16]. In the results of this experiment, β-secretase and γ-secretase in the model group were higher than those in the normal group, and α-secretase was lower than that in the normal group. The water maze test time of mice injected with aluminum maltolate was significantly prolonged, and timeouts and errors occurred, indicating that the model mice had cognitive dysfunction, which may be due to the oxidative stress effect of Al. Al induces dementia in mice by inducing the oxidative stress pathway [17]. The β-secretase activity in treatment group 1 was significantly lower than that in the model group, and the α-secretase activity was higher than that in the model group, suggesting that Suanzaoren preparations inhibited the deposition of Aβ in the brain and enhanced the decomposition of APP through the α-secretase pathway, thereby competitively inhibiting the production of Aβ by APP. The β-secretase activity in treatment group 2 was lower than that in the model group, and the quantitative analysis showed that its inhibitory effect on β-secretase was not as significant as that in treatment group 1, and the α-secretase activity was slightly lower than that in the model group, which may be due to the toxic effects of aluminum.

Dysfunction of the cholinergic system is also considered one of the mechanisms of AD pathogenesis. As a key enzyme in nerve impulse transmission, AChE catalyzes the breakdown of acetylcholine, reducing its expression. Excessive accumulation of AChE in the body can lead to

acetylcholine deficiency, ultimately resulting in cognitive dysfunction [18]. Simultaneously, Li Qian et al. pointed out the relationship between AChE and β-amyloid protein deposition, with AChE activity within and around β-amyloid plaques being higher than in other normal tissues (and the interaction of the two can generate more toxic complexes) [19]. The results of this experiment indicate that AChE activity in the model group mice was significantly higher than that in the normal group. The AChE activity in the brains of mice in treatment group 1 and treatment group 2 decreased compared to the model group, but the difference was not significant. Combined with the Morris water maze data, after treatment, the timeout rate and failure rate of treatment group 1 were reduced, while the error rate increased. In treatment group 2, the error rate and timeout rate increased. From the perspective of water maze time, the swimming time of the two treatment groups was shortened after gavage treatment compared to after modeling, indicating that Semen Ziziphi Spinosae and Hailfu have the effect of improving the disorder of the cholinergic system in the brain, which helps to restore the memory function of dementia mice. The increased error rate and timeout rate in individual mice may be related to the treatment time and gavage dose. Blood urea nitrogen and TP content are important indicators of normal liver function. The blood urea nitrogen and TP content of mice in the model group and treatment groups were lower than those in the normal group, indicating that the liver of the mice was affected by aluminum toxicity and the function was impaired. TG and TC are related to lipid metabolism. After modeling, the TG content of mice was higher than that of the normal group, indicating abnormal blood lipid metabolism, but there was no downward trend after treatment. The TC of the model group was lower than that of the normal group, and the TC content of treatment group 1 and treatment group 2 increased. Whether Hailfu and Semen Ziziphi Spinosae have the effect of improving lipid metabolism and reducing cardiovascular tissue damage needs further investigation.

With the continuous and in-depth exploration of the pathogenesis of AD, the interaction between oxidative stress and AD has received increasing attention. The occurrence of oxidative stress originates from the free radical theory of aging. When certain factors exist, free radicals in the body are excessively produced and cleared improperly, resulting in stress reactions, inflammatory reactions, and other pathological changes related to aging [20]. The effect of oxidative stress on nerve cells is hypothesized to be fundamental to nerve cell death in neurodegenerative diseases. Denaturation and destruction of macromolecules, mitochondrial damage, Aβ, and the induction of AD by metal elements are all based on oxidative stress [21,22]. The interaction between inflammatory response and the pathological changes of AD is multifaceted, such as inducing Aβ accumulation, neuronal damage, and synaptic dysfunction [23]. Relevant experiments have demonstrated that Hailfu oral solution has an extremely high scavenging effect on free radicals (hydroxyl radicals and superoxide anion free radicals) in the body, and there is a linear correlation between the increase in concentration and the scavenging efficiency [24,25]. Long Qinghua et al. confirmed through experiments that Semen Ziziphi Spinosae has practical efficacy in inhibiting neuroinflammation and improving the imbalance between oxidation and antioxidation in the body [26,27].

5. Conclusion

This study found that Ziziphi Spinosae preparations and Haierfu possess medicinal value in reducing β-secretase activity in the brains of demented mice and improving memory impairment and dementia symptoms. Traditional Chinese medicine preparations are rich in various natural and effective pharmacological ingredients, giving them a unique medicinal value advantage in treating age-related chronic diseases such as Alzheimer's disease. Future research is still needed to find more evidence for in-depth analysis, continuously explore its specific pharmacological mechanisms and

medicinal value, and provide more directions and clinical basis for the diagnosis and treatment of AD.

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