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Meta-analysis of the Efficacy of Traditional Chinese Medicine in the Treatment of Alzheimer's Disease

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Abstract: *In order to systematically evaluate the efficacy of traditional Chinese medicine in the treatment of Alzheimer's disease. We collected randomized controlled (RCT) clinical trials of traditional Chinese medicine in the treatment of Alzheimer's disease published from the establishment of the database to December 2022. The databases included CNKI, WanFang Data, VIP, Pubmed, Embase, Cochrane Library. Researchers with different research processes independently completed the meta-analysis of the extracted data using RevMan5.3 literature management software. Resultly, a total of 1973 articles were retrieved by searching various databases, and 29 articles were finally included. The total sample size was 2418 cases, 1140 cases in the Chinese medicine treatment group and 1278 cases in the western medicine control group. Compared with the western medicine control group, the MMSE score [MD=1.43 95%CI (0.79, 2.07), P<0.05], HDS score [MD=2.79 95%CI (1.23, 4.34), P=0.0004] and effective rate [RR=1.25 95%CI (1.10, 1.40), P<0.05] in the Chinese medicine treatment group were increased. The ADAS-Cog score of the Chinese medicine treatment group [MD=-2.38 95%CI (-4.44, -0.31), P<0.05] was lower than that of the western medicine control group; the adverse reactions in the Chinese medicine treatment group were lower than those in the western medicine control group [RR=0.21 95%CI (0.07, 0.64), P<0.05]. The ADL score of the Chinese medicine treatment group [MD=-3.99 95%CI (-8.38, 0.41), P=0.08] was not statistically significant compared with the western medicine control group. In conclusion, according to the results of the analysis, the treatment with traditional Chinese medicine can improve the symptoms of patients with Alzheimer's disease and improve the clinical efficacy of patients. The therapeutic effect is better than that of western medicine. No obvious adverse reactions were observed, and the safety was significantly higher than that of western medicine. However, due to the limited number of documents and the limited retrieval process, the quality of methodology is generally low when researchers analyze the data. Therefore, researchers also need large-scale, high-quality research to further verify these results.*

Keywords: *Traditional Chinese medicine; Alzheimer's disease; senile dementia; meta-analysis; randomized control*

1. Introduction

Alzheimer's disease (Alzheimer Diseases, AD): it is a hereditary and sporadic neurodegenerative disease mainly characterized by amnesia cognitive impairment, and a small part of it is characterized by non-amnesia cognitive impairment [1]. In addition to cognitive impairment, it also includes other symptoms such as mood swings, sleep disorders and behavior changes. In the late stage of the disease, there will be more serious complications such as malnutrition, multiple organ failure caused by neuronal necrosis, and even brain death. AD significantly shortens life expectancy, seriously affects the physical and mental health of the elderly, and reduces the quality of life of the elderly, which is the fifth leading cause of death in the elderly. At present, more than 25 million people in the world suffer from dementia, most of them Alzheimer's disease, with about 5 million new cases each year [2]. The study found that about 50% to 70% of dementia patients in the elderly are associated with AD [3]. The prevalence rate is closely related to age. On average, every 6.1 years of age increases, the prevalence rate doubles. The disease not only brings heavy pressure to the family, but also brings great economic burden to the society; therefore, the effective prevention and treatment of AD is the most important problem at this stage.

There are several theories about the pathogenesis of AD about the pathogenesis of AD. The

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dominant theory is the amyloid hypothesis, which holds that Alzheimer's disease is caused by the accumulation of amyloid β (A β) in the brain. There are several theories about the pathogenesis of AD. The dominant theory is the amyloid hypothesis, which holds that Alzheimer's disease is caused by the accumulation of amyloid β (A β) in the brain. It leads to neurotoxicity in the central nervous system, which suggests that the imbalance between A β production and clearance is the main cause of the disease [4]. Another important theory is the tau protein theory. Tau protein is mainly found in nerve cells, and its function is to stabilize tubulin. According to the theory, excessive phosphorylation of tau protein will lead to tubulin instability, resulting in some neurofibrillary tangles that damage the function of neurons and synapses, and then form the disease [5]. In recent years, some scientists have also put forward a new hypothesis that cerebrovascular dysfunction is the main cause of neuronal dysfunction. They believe that the dysfunction of cerebral vessels will affect the activity of neurons and lead to changes in the function of neurons. At the same time, cyclin regulation disorder, oxidative stress, inflammation. Some hypotheses such as disease mechanism and mitochondrial dysfunction have also been proposed.

At present, clinical trials and approved drugs for AD are based on the regulation of excitatory neurotransmitter transmission pathway. They are agonists or antagonists of neurotransmitter production or neurotransmitter receptors. These drugs have varying degrees of side effects in clinical use and are single-target drugs [6]. Such as acetylcholinase inhibitors (Donepezil, cabaladine, etc.), NMDA receptor antagonists (memantine), brain metabolic agents (oxiracetam), etc., can only alleviate the symptoms of patients, the effect is single, the effect is limited. However, traditional Chinese herbal medicine has many ingredients, which can improve and prevent neurodegenerative diseases in multiple ways and targets at the same time. Therefore, this study uses the method of Meta-analysis to systematically evaluate the efficacy and safety of traditional Chinese medicine in the treatment of Alzheimer's disease, so as to provide evidence-based basis for the rational use of traditional Chinese medicine in clinic.

2. Materials and methods

2.1. Inclusion of literature standards

(1) Subjects: patients who were clearly diagnosed as Alzheimer's disease and whose diagnostic criteria met the diagnostic criteria of DSM-IV's AD dementia. (2) types of study: a randomized controlled trial of all traditional Chinese medicines in the treatment of Alzheimer's disease (Randomized Controlled Trial, RCT). (3) Intervention: the treatment group was given oral administration of any form of traditional Chinese medicine (traditional Chinese medicine and proprietary Chinese medicine), and the control group was treated with oral conventional western medicine. (4) Outcome indicators: the main outcome indicators include Mini Mental State examination (Mini-Mental State Examination, MMSE) and effective rate, while the secondary outcome indicators include internationally recognized dementia assessment scales such as AD Assessment scale-Cognition scale (Alzheimer's Disease Assessment Scale-Cognitive Section, ADAS-Cog), Hasegawa dementia scale (Hastgawa Dementia Scale, HDS) and activity of Daily living scale (Activity of Daily Living Scale, ADL). The adverse reaction was the safety index.

2.2. Exclusion criteria

(1) Non-Chinese and English literature was excluded. (2) non-RCT study, case report, medical record summary, review and etc. were excluded. (3) literature with unclear diagnostic criteria was excluded. And literature involving vascular dementia and other types of dementia caused by other causes was excluded. (4) Republished literature was excluded. (5) Literature with incomplete information was excluded.

2.3. Strategies and methods of document Retrieval

We searched from multiple databases for randomized controlled clinical trials (RCT) of traditional Chinese medicine in the treatment of Alzheimer's disease from the establishment of the database to the publication on the 1st of 2022. The database included CNKI, WanFang Data, VIP, Pubmed, Embase, Cochrane Library. Chinese search words include: Alzheimer's disease, dementia, traditional Chinese medicine, proprietary Chinese medicine, randomized controlled trial, clinical efficacy, curative effect observation. English search words included: Alzheimer Diseases, Alzheimer Syndrome, Alzheimer-Type Dementia, Dementia, Alzheimer, Dementia, Senile Senile Dementia, Traditional

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Chinese Medicine, Chinese Medicine, Traditional, Chinese Herbal Drugs, Chinese Plant Extracts, Extracts, Chinese Plant, Randomized controlled trial, Randomized. In the process of retrieval, subject words and free words were used. In the process of retrieval, the search method of combining subject words with free words were used.

2.4. Literature screening and data extraction

Literature screening and data extraction were carried out independently by two researchers. If there was a difference of opinion between the two researchers, we asked the third researcher to judge whether to include it or not. And if the required information was insufficient, we contacted the author as much as possible to supplement it. In the process of retrieval, the input articles are retrieved by using Endnote software, and repetitive articles are excluded. For the existing papers, firstly we interpreted the title and abstracts, eliminated the papers that did not conform to the study. And then we read the full text in detail to determine the final included papers. The main contents of data extraction are as follows: (1) the basic situation of the included research, including research topics, authors and published journals, etc.; (2) the basic characteristics and intervention methods of the subjects; (3) the main factors affecting the deviation of factors; (4) statistical analysis of the end point measurement and end point measurement concerned in the study.

2.5. Quality evaluation

The two researchers independently evaluated the quality of the items such as whether the Cochrane manual was in random order, whether it was hidden for distribution, whether the subjects, interveners and results evaluators used blind method, whether the index data were complete, the possibility of selectively reporting the research results and the sources of bias in other aspects, and so on. If there are differences between the two sides, the team will discuss and assist in the judgment.

2.6. Statistical analysis

Statistical analysis data processing was based on RevMan5.3. We used mean difference (Mean-Difference, MD) analysis for continuity variables. The two classified variables were analyzed by relative risk (Relative Risk, RR). Their point values and 95% confidence intervals are given for each effect. On this basis, the heterogeneity was evaluated by X2 test (α=0.05) and I2 quantification. When there is no statistical difference, the fixed effect model is used; if there is statistical difference, the random effect model is used for data analysis.

3. Results

3.1. The basic situation of literature retrieval and inclusion

A total of 1973 articles were searched in 6 databases, repetitive, irrelevant and substandard literatures were removed, and 29 articles were included, with a total of 2418 patients. The specific screening process is shown in Figure 1.

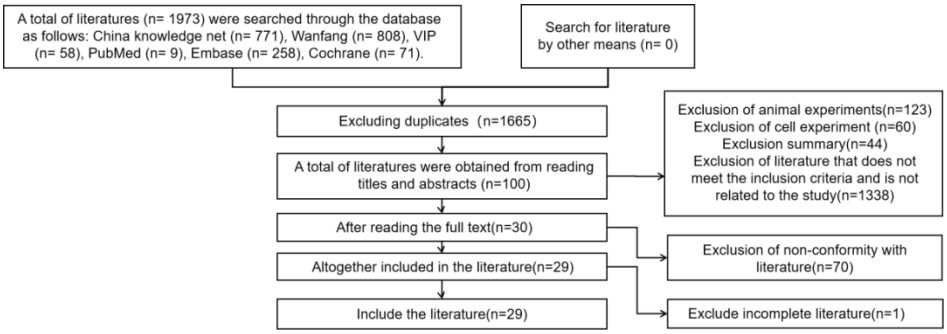

Figure 1: Flow chart of literature screening

3.2. The Basic characteristics of articles

A total of 29 articles were included, the intervention measures were treated with traditional Chinese

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medicine to treat Alzheimer's disease, and the control group was treated with conventional western medicine, as shown in Table 1.

Table 1: Basic characteristics of the included study

Reference	Sample size	Gender (example)		Age (years)		Intervention measures		Course of treatment	Outcome index
	T/C	Male	Female	T	C	T	C		
[7]	31/15	21	25	65.77±6.17		Nourishing heart and strengthening brain liquid	Naofukang (Piracetam)	3 months	
[8]	34/31	47	18	73.2	72.8	Yucong decoction	Chloroester, γ-aminocaseic acid, folicacid	1 month	
[9]	140/70	162	48	71.62±7.45	72.53±7.62	Anti-senile dementia capsule	Naofukang (Piracetam)	3 months	①②③⑥
[10]	20/15	12	23	74.7±7.7	71.52±7.53	Laozhifu oral liquid	Shuangyi plain film	2 months	⑥
[11]	68/34	43	59	-	-	Tiaoxin recipe / Bushen recipe	Donepezil	3 months	
[12]	53/51	62	42	75.20±5.15	74.50±5.15	Tongqiao Yizhi decoction	Naofukang (Piracetam)	4 months	⑥
[13]	20/15	12	23	74.7±7.7	6.05±4.65	Smart soup	Shuangyi plain film	2 months	⑥
[14]	28/26	-	-	-	-	Fuzhisan	Alison (Donaipiazi)	40 days	④⑤
[15]	50/46	76	20	67.5		Yinao Tongmai decoction	Almitrine and Raubasine Tablets	2 months	②③⑥
[16]	30/26	45	11	66.5±12.3	67.6±10.8	Addition and subtraction of Dihuang Yinzi decoction	Pyritinol Hydrochloride Tablets	2 months	②③⑥
[17]	18/15	18	15	70.94±8.49	72.13±9.47	Jianpi Yizhi decoction	Naofukang (Piracetam)	2 months	②③⑥
[18]	24/24	27	21	62.3±3.56	61.25±4.45	Ginseng Rong Yizhi drink	Donepezil	4 months	
[19]	120/89	110	99	66.78±4.27	67.12±5.3/68.29±3.16	Compound Polygonum multiflorum extract	Naofukang (Piracetam)	3 months	②③
[20]	14/13	13	14	72.36±7.27	74.38±8.58	Compound prescription for tonifying kidney, removing phlegm and removing blood stasis	Naofukang (Piracetam)	84 days	②③④
[21]	32/28	32	28	65.18±6.45	64.65±6.53	Modified Danggui Shaoyao Powder	Donepezil hydrochloride	1 months	②④
[22]	30/30	27	33	67.1±5.2	66.3±4.8	Traditional Chinese medicine decoction	Aniracetam	6 months	②③④
[23]	66/65	-	-	-	-	Tiaoxin recipe or Bushen recipe	Donepezil hydrochloride	15months	⑤
[24]	30/30	35	25	74.97±7.26	75.07±8.61	Yiqi Mingming decoction	Piracetam	3 months	②
[25]	35/35	35	35	66.47±7.31	67.07±9.13	Buyang Huanwu decoction	Donepezil hydrochloride	1 months	③
[26]	52/52	-	-	-	-	Rong Jia Yi Zhi tablet	Donepezil hydrochloride	6 months	③④⑤
[27]	34/34	25	43	72.82 ± 7.04	72.29 ±6.80	Decoction-free granules of Bushen Yisui recipe and its simulant	Anlisin (Donepezil) and its simulator	6 months	③
[28]	72/72	55	89	72.79±6.76	72.97±6.59	Bushen prescription non-decoction granule	Donepezil hydrochloride	6 months	③④⑤
[29]	72/72	-	-	-	-	Decoction-free granule of Yishen Huazhuo recipe; combined with Donepezil Hydrochloride tablet simulator	Yishen Huazhuo Fang granule Simulator + Donepezil Hydrochloride tablets	6 months	
[30]	31/32	25	38	74.82±7.96	75.06±7.83	Add and subtract Dioscorea Pill concentrated decoction	Donepezil hydrochloride	3 months	①②③④⑤
[31]	31/28	32	27	72.66±15.98	73.12±17.65	Tiaoxinfang granule	Donepezil hydrochloride	3 months	②
[32]	27/24	8	43	65.48±7.329 □□	60.88±8.93□□	Jiannao Yizhi Fang granule / Donepezil Hydrochloride mimic	Donepezil Hydrochloride / Jiannao Yizhi Formula Simulator	6 months	①②③④⑤
[33]	25/25	21	29	67.84±8.28	68.08±9.26	Addition and subtraction of Rehmannia root drink	Donepezil hydrochloride	3 months	③
[34]	42/42	48	36	71.83±7.98	70.75±7.23	Return Shaodan	Donepezil hydrochloride	6 months	①②③④⑤
[35]	76/74	82	78	70.3±9.3	70.6±9.1	Fuyuan Huoxue decoction	Piracetam tablet	3 months	②⑤⑥

Note:-unreported T-test group C-control group ①Total efficacy ②MMSE ③ADL ④ADAS-cog ⑤Adverse reaction event ⑥HDS

3.3. Quality evaluation

All the 29 articles included were randomly assigned, of which 10 were rated as low risk by random number method, computer random number table or drawing method. 18 articles were only marked randomly and did not describe specific methods, and were rated as medium risk, while 1 article was classified as high risk according to the order of medical treatment. Among the included literatures, 5

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articles indicated double-blind and single-blind use, 24 articles only indicated the blind method, but did not describe the specific method; as to whether the allocation was hidden, 5 articles were clearly put forward, and 25 articles were not sure whether the allocation was hidden; about the integrity of the data, 4 articles were not sure whether the data were complete, and the other 25 articles had complete data; the bias risk map is shown in Figure 2.

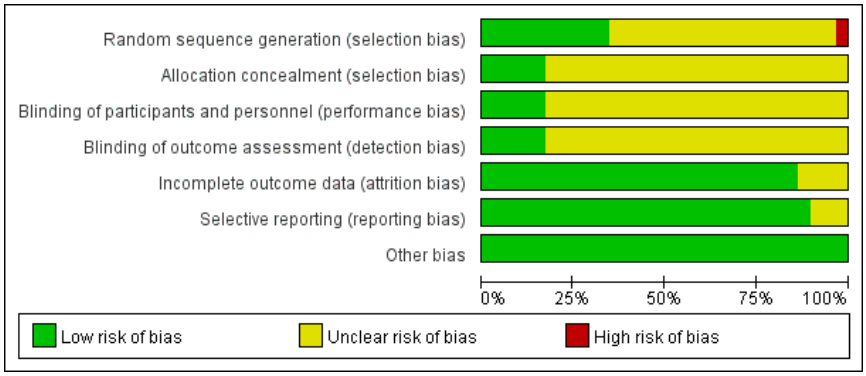

Figure 2: Bias risk assessment chart

3.4. Results

3.4.1. Efficient comparison

A total of 21 studies [7-10,12,13,15-22,24,26,27,30-32,35] reported overall symptom improvement in the treatment, including 1581 patients. Based on the heterogeneity test results of I2: 67% Personality 0.05, the random effect model was used to analyze the included literature. The results showed that the treatment group could significantly improve the patients' symptoms compared with the control group, and the difference between the groups was statistically significant. See Figure 3 for details.

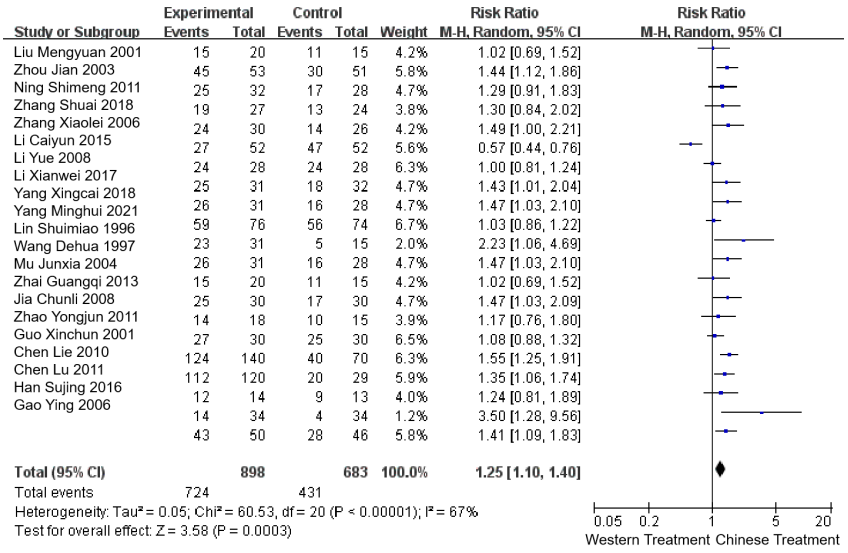

Figure 3: Meta analysis of the effective rate of traditional Chinese medicine and proprietary Chinese medicine treatment compared with the control group

3.4.2. MMSE score comparison

The outcome index of 19 studies [9,11,14-17,19-25,28,30-32,34,35] was MMSE, and a total of 1597 patients participated in the study. According to the heterogeneity test results of I2B76% Personality 0.05, the random effect model was used for statistical analysis. The results showed that the difference between the groups was statistically significant [MD=1.43 95%CI (0.79, 2.07), pamphltter0.05]. Compared with the control group, the MMSE score of the treatment group was significantly higher, as shown in Figure 4.

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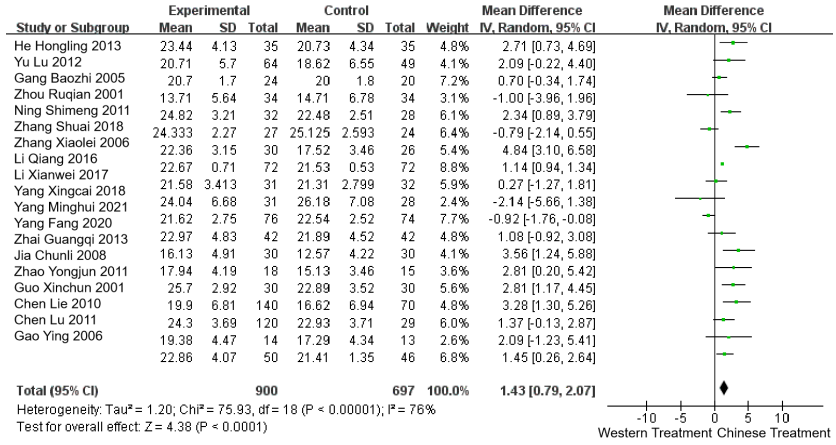

Figure 4: Meta-analysis of the improvement of MMSE in AD patients treated with traditional Chinese medicine and proprietary Chinese medicine compared with the control group

3.4.3. ADL score comparison

The outcome index of 13 studies [9,15-17,19,20,22,25,26,28,30,32,34] was ADL. A total of 1147 patients participated in the study. The heterogeneity results showed that the ADL scores of the traditional Chinese medicine treatment group and the western medicine control group were statistically analyzed by random effect model. The results showed that there was no statistical significance in the difference of the MD=-3.99 95%CI score between the traditional Chinese medicine treatment group and the western medicine control group [MD=-3.99 95%CI (- 8.38) 0.41], as shown in Figure 5.

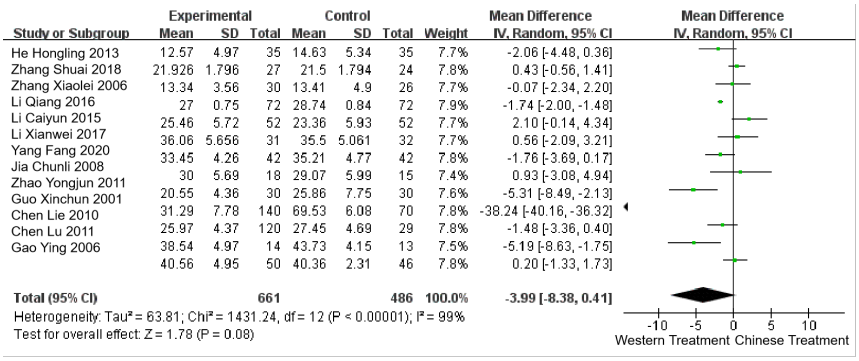

Figure 5: Meta-analysis of the improvement of ADL in AD patients treated with traditional Chinese medicine and proprietary Chinese medicine compared with the control group

3.4.4. ADAS-cog score comparison

The outcome index of 9 studies [14,20-22,26,28,30,32,34] was ADAS-cog, and there were 637 patients. According to the heterogeneity result I2q95% Prunltter0.05, the random effect model was used for analysis. According to the forest map, the diamond fell on the left side of the baseline and did not intersect, indicating that the treatment score was significantly lower than that of the control group. The difference between the groups was statistically significant [MD=-2.38 95%CI (- 4.4jue 0.31), Prun0.02], as shown in Figure 6.

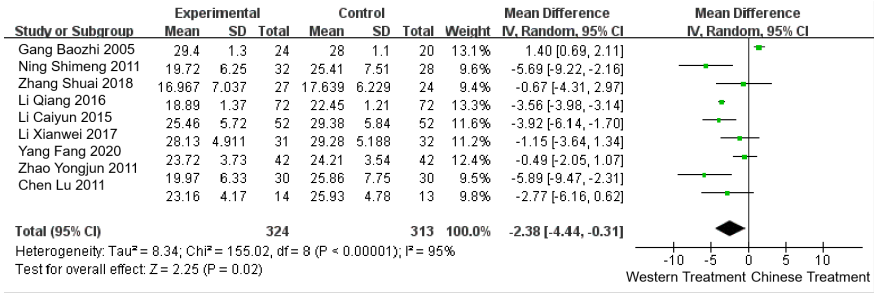

Figure 6: Meta-analysis of the improvement of ADAS-cog in AD patients treated with traditional Chinese medicine and proprietary Chinese medicine compared with the control group

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3.4.5. HDS score comparison

Eight of the included studies [9,10,12,13,15-17,35] took HDS as the outcome indicator, with a total of 719 patients. According to the forest map results show that I2q80% quotient 0.05, you can see the different quality of the included research, using the random effect model for data analysis, the analysis results [MD=2.79 95%CI (1.234.34), 0.0004], it can be seen that the score of the traditional Chinese medicine treatment group is significantly higher than that of the control group, and the difference between the groups is statistically significant. See Figure 7 for details.

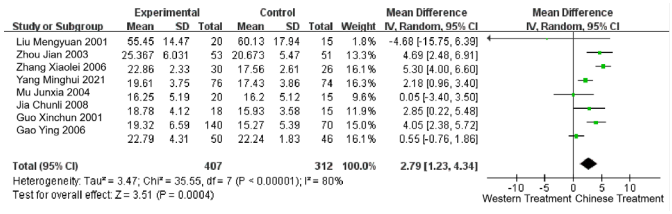

Figure 7: Meta-analysis of the improvement of HDS in AD patients treated with traditional Chinese medicine and proprietary Chinese medicine compared with the control group

3.4.6. Comparison of adverse reactions

A total of 7 [14,23,26,28,30,32,35] studies reported adverse drug reactions in patients. The result of forest map shows that the research included is different in quality, and the random effect model is used to analyze the results [RR=0.21 95%CI (0.07 ~ 0.64), pantomime (0.05)]. It can be seen that the adverse reaction in the traditional Chinese medicine treatment group is significantly lower than that in the control group, and the difference between the groups is statistically significant. See Figure 8 for details.

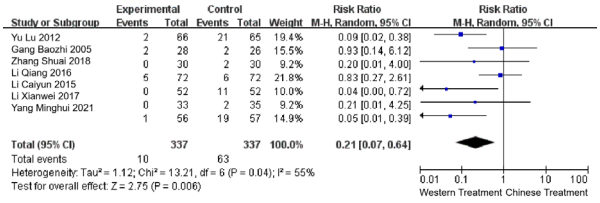

Figure 8: Meta-analysis of adverse reactions between traditional Chinese medicine and proprietary Chinese medicine treatment and control group

3.5. Publication bias test and sensitivity analysis

The funnel chart is drawn with the total efficiency of the included literature as the outcome index. according to the following figure, we can see that the left and right distribution of the research points is uneven, and there may be publication bias in this study. (Figure 9) excluding individual studies one by one, it is found that there is no significant change in the results, and the results of meta-analysis are stable.

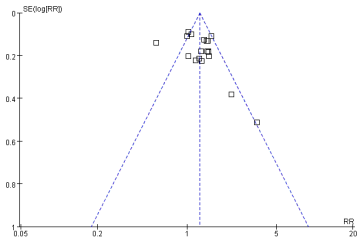

Figure 9: Funnel chart of literature screening

4. Discussion

The purpose of this study is to analyze the clinical efficacy of traditional Chinese medicine in the treatment of AD. A total of 29 studies were included, involving 2418 cases. This study shows that, compared with western medicine treatment, the effect of traditional Chinese medicine treatment is obvious. 21 trials showed that the total curative effect of traditional Chinese medicine was better than

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that of the control group. 19 trials showed that the MMSE scores of patients treated with traditional Chinese medicine were significantly improved. 9 trials showed that the ADAS-cog score of patients treated with traditional Chinese medicine decreased significantly. 8 trials showed that the HDS scores of patients treated with traditional Chinese medicine were significantly improved. 7 experiments showed that the toxicity and side effects of taking traditional Chinese medicine were significantly lower than those in the control group. 13 studies showed that there was no significant difference in ADL score between the traditional Chinese medicine treatment group and the western medicine control group. There are still some limitations in this meta-analysis, as follows: (1) The main results are as follows: 1 the included literature is mainly in Chinese, and there are few foreign literature , which affects the external authenticity of the study, and the results still need to be confirmed by multicenter and large sample randomized controlled trials. (2) Although the literature has been strictly screened according to the exclusion criteria to ensure the homogeneity of the literature, the control groups of different literatures are not exactly the same in terms of drug dose and time, which makes some heterogeneity in the included literature. In order to make the research results more reliable, the inclusion and exclusion criteria should be more strict in the future. (3) There are many defects in the included literature. Most of the literature only explains the random distribution, but the allocation method is not explained, which leads to the low quality of the article. (4) Bias analysis funnel diagram may have publication bias.

To sum up, through the above meta-analysis, this study proved that the curative effect of traditional Chinese medicine in the treatment of AD was better than that of conventional western medicine in the control group of AD. However, this study still has some shortcomings in many aspects, which makes the quality of the included literature on the low side. Therefore, in the future clinical research, the design should be improved as much as possible, and the use of blind method and the screening of research objects should be carried out in strict accordance with the standard, so as to provide higher quality evidence for clinical decision-making.

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