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REVIEW

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The efficacy and safety of donepezil plus ginkgo biloba for Alzheimer's disease: a systematic review and meta-analysis

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Highlights

Donepezil and ginkgo biloba for Alzheimer's disease can improve the clinical efficacy, and enhance cognitive function comparing donepezil alone based on the study. And the Grading of Recommendations Assessment, Development and Evaluation was applied to rate the quality of evidence. Hence, the systematic review and meta-analysis of donepezil and ginkgo biloba for Alzheimer's disease can provide the reference in the clinical application and further studies.

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Abstract

Background: To evaluate the efficacy and safety of donepezil and ginkgo biloba for Alzheimer's disease. **Methods:** A systematic literature retrieval was carried out for eligible studies in PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Wanfang and China Science and Technology Journal Database from the establishment of database to 1 February 2020. Nine randomized controlled trials were included in our study in the Review Manager 5.3. **Results:** Our meta-analysis found that compared with donepezil alone, ginkgo biloba and donepezil could improve clinical efficacy and enhance cognitive function measured by the mini-mental state examination score. No significant difference in the total adverse reaction, the digestive symptoms and the neurological symptoms between two groups was observed. **Conclusion:** The combination of donepezil plus ginkgo biloba could provide more benefits for Alzheimer's disease patients than donepezil alone.
Key words: Alzheimer's disease, Donepezil, Ginkgo biloba, Meta-analysis

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Abbreviations:

AD, Alzheimer's disease; Aβ, amyloid-β; GB, ginkgo biloba; MMSE, mini-mental state examination; RR, risk ratio; MD, mean difference; CI, confidence interval.

***Competing interests*:**

The authors declare that they have no conflict of interest.

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Background

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by impaired cognitive function, mental symptoms and behavioral decline. According to World Alzheimer Report 2018, about 50 million dementia patients live in the world and this number will be more than 152 million by 2050. Furthermore, the total cost of dementia is estimated to be US$1 trillion in 2018 and will rise to US$2 trillion by 2030 [1]. AD is the most common cause of dementia, which accounts for about 60% to 80% of all cases [2]. Besides, AD is one of the major causes of death in dementia patients [3]. AD brought much pain to patients and their families, caused heavy damage to the society. Unfortunately, the neuropathology mechanism remains unclear and there is a lack of effective treatment for AD. Researchers indicated that extracellular amyloid-β (Aβ) deposition as senile plaques in brain parenchyma and hyper-phosphorylation of Tau protein as neurofifibrillary tangles were the hallmark of AD [4, 5]. In addition, the accumulation of Aβ activated N-methyl-D-aspartate receptors and influx of Ca^{2+}, which led to synaptic dysfunction, neuron losing and cognition impairment [6, 7]. Meanwhile, Aβ could stimulate microglia to release cytokine: interleukin-1β, NO and tumor necrosis factor-α, which induced neuroinflammatory response and neuron death [8].

The loss of cholinergic neurons accounted for the majority of neuron death, with decreasing of acetylcholine levels, which was the primary reason of cognition dysfunction in AD [9, 10]. Therefore, promoting the levels of acetylcholine is an effective treatment for AD. Donepezil, a Food and Drug Administration-approved drug for the treatment of AD, is a selective, potent, noncompetitive and rapidly reversible acetylcholinesterase inhibitors [11]. A cluster of studies suggested that donepezil could increase acetylcholine levels and improve cognitive function of AD patients [12, 13]. However, the progressive trend of AD still exists [14]. Some studies showed that the treatment of AD focused on increasing cerebral blood flow perfusion and improving the circulation of brain tissue [15]. Ginkgo biloba (GB) could increase cerebral blood flow perfusion, combined with donepezil could significantly improve patients' mental state, ability of daily life and cognitive function [14]. GB have been wildly used in the treatment of cognition dysfunction for decades now [16, 17, 18]. However, there is very limited evidence to estimate the effectiveness of combining donepezil and GB for AD patients. Therefore, we conducted this meta-analysis to demonstrate whether donepezil and GB could be effective and safe for AD patients.

Materials and methods

Search strategy

We conducted a systematic literature retrieval in PubMed, Embase, Cochrane library, Web of Science, China National Knowledge Infrastructure, Wanfang and China Science and Technology Journal Database from the establishment of database to 1 February 2020. Key words were the following: ginkgo biloba, donepezil and Alzheimer disease. The review was conducted in accordance with the guidelines for preferred reporting items for systematic reviews and meta-analyses [19]. The retrieval strategy (PubMed) was as follows:

#1 "donepezil" [mesh terms] OR "donepezil" [title/abstract]
#2 "ginkgo biloba"[mesh terms] OR "ginkgo biloba" [title/abstract]
#3 "Alzheimer disease" [mesh terms] OR "Alzheimer disease" [title/abstract]
#4 #1 AND #2 AND #3

Inclusion criteria

Study type. We included randomized controlled trials associated with the AD using GB and donepezil as the therapy.
Participants. Participants with a definitive diagnosis of AD were included in our study.
Intervention. GB and donepezil were used in the treatment group and donepezil or placebo was applied in the control group.
Outcome. We included the efficacy criteria, which involved the clinical efficacy and the mini-mental state examination (MMSE) score. If there were any symptoms during the treatment which did not meet the propose of drug use, the adverse reactions would be adopted in the safety criteria. The standard of clinical efficacy was based on the MMSE score, MMSE score ≥ 1 was effective, and MMSE score unchanged or reduced was noneffective.

Exclusion criteria

The exclusion criteria were duplicated literature and irrelevant study; non-randomized controlled trials, such as traditional review, systematic review and meta-analysis, theoretical study, retrospective study and consensus; non-clinical trials, such as animal studies; and articles in which interventions other than GB, donepezil and conventional therapy were used in the treatment group and the control group; studies which were inconsistent outcome.

Quality assessment

The quality of included studies was assessed by two researchers (H-Y and T-CY) dependently by the Cochrane collaboration's tool [20]. If there were any disagreements between the researchers regarding each study, a third researcher (J-XJ) would help them to resolve it. This evaluation tool consists of random

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sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The quality of studies was classified as being at of high, unclear or low risk of bias. Besides, the Grading of Recommendations Assessment, Development and Evaluation was applied to rate the quality of evidence by the consensus of two authors (H-Y and T-CY).

Data extraction and statistical analysis

Data extraction was carried out in a standard excel sheet independently by two researchers (H-Y and Y-L). Any disagreements were discussed with the third researcher (L-HH) and resolved. The following information for each study was extracted: the first author, publication year, sample size, age, diagnosis standard, interventions, course of treatment and outcomes.

The statistics analysis was carried out in the Review Manager 5.3 (Cochrane collaboration's information management system). The risk ratio (RR) was used for dichotomous data, and the mean difference (MD) was used for continuous variables; for both, the corresponding 95% confidence interval (CI) and forest plots were applied. The heterogeneity between studies was assessed by the chi-squared test and the I^2 statistic. If there was no heterogeneity ($P > 0.10$ or $I^2 < 50\%$), the fixed-effect model was adopted. Otherwise, random-effect model was used. Sensitivity analysis was aimed to assess the stability of the pooling results.

Results

Study selection

A total of 142 studies were identified by database retrieval. And there were 100 records left after removing duplicated articles. Eighty records were excluded by scanning titles and abstracts. Eleven studies were selected for full text review carefully. Nine studies [21–29] were finally included in the qualitative and quantitative synthesis. The flow chart of study selection was presented in Figure 1.

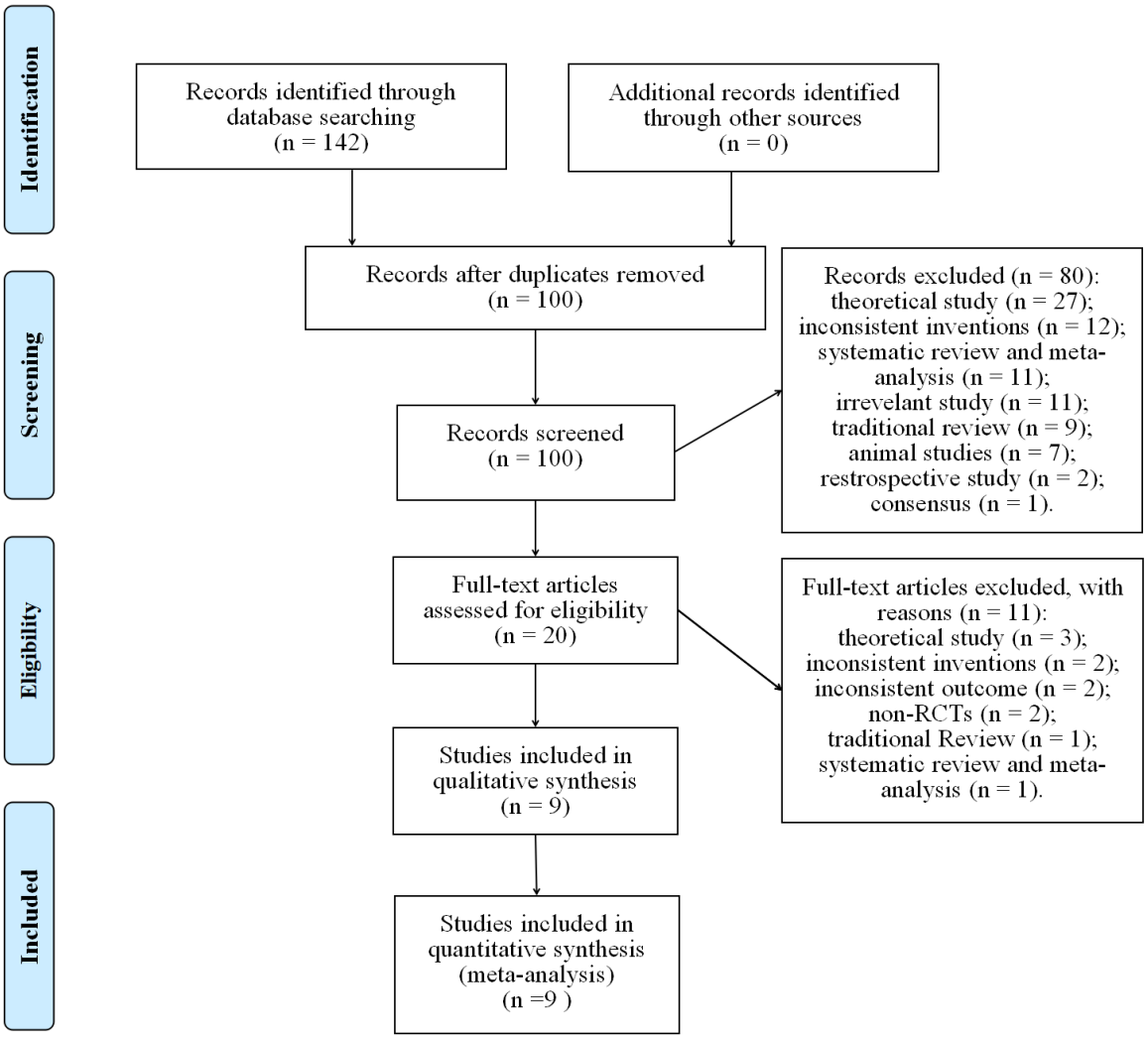

Figure 1 The flow chart of study selection. RCTs, randomized controlled trials.

Study characteristics

All included studies [21–29] were published from 2013 to 2019. These studies [21–29] contained 611 AD patients. Experimental and control groups were comprised of 308 and 303 patients respectively. Five diagnosis standards were applied, which included National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, Diagnostic and Statistical Manual of Mental Disorders, National Institute of Aging-Alzheimer's Association, Classification and Diagnostic Criteria of Mental Disorders in China-third-edition. The treatment course of three studies [26, 27, 29] was 3 months, and three studies [23–25] were 4 months, and 3 trials [22, 28, 21] were 1 month, 6months and 12months, respectively. Five studies [21, 22, 25, 28, 29] evaluated clinical efficacy. Nine [21–29] studies assessed the MMSE score and 3 studies [21, 24, 26] estimated adverse reactions. The characteristics of included studies were presented in Table 1.

Quality of the included studies

Nine studies mentioned randomization, which were rated as low risk of bias. Three studies [22, 24, 26] using random number table method were rated as high risk of bias when assessing the risk of allocation concealment. Nine studies did not mention blindness and were rated as unclear risk of bias. As for incomplete outcome data and selective reporting, nine studies were rated as low risk of bias. As to other bias, the baseline of four studies [21, 23, 25, 28] was unclear, rating as unclear risk of bias. The quality of the included studies was reflected in Figure 2. Summary of Findings table was shown in Table 2.

Table 1 The characteristics of included studies

Studies	Sample size		Age (year)		Diagnosis standard	Intervention		Course of treatment (month)	Outcomes
	Experimental	Control	Experimental	Control		Experimental	Control		
Di et al. 2017 [21]	33	33	71.4 ± 8.8	70.8 ± 8.4	NINCDS-ADRDA	Ginkgo 19.2 mg, tid+ donepezil 5 mg, qd	Donepezil 5 mg, qd	12	①②③
Long et al. 2016 [22]	32	30	-	-	NINCDS-ADRDA	Ginkgolide injection 6 ml, qd + donepezil 5 mg, qd	Donepezil 5 mg, qd	1	①②
Wu et al. 2013 [23]	29	28	64.0 ± 7.9	63.4 ± 8.3	NINCDS-ADRDA	Ginkgo bilobate dropping pill 40–50 mg, tid + donepezil 5 mg, qd	Donepezil 5 mg, qd	4	②③
Zhang et al. 2015 [24]	30	30	68.5 ± 5.3	68.2 ± 5.6	DSM-IV-R	Ginkgo bilobate dispersible tablets 150 mg, tid + donepezil 5 mg, qd	Donepezil 5 mg, qd	4	②③
Qu et al. 2019 [25]	45	45	73.42 ± 11.21	73.34 ± 10.2	-	Ginkgo biloba 12 mg, tid + donepezil 5 mg, qd	Donepezil 5 mg, qd	4	①②
Jiang et al. 2013 [26]	31	29	65.90 ± 5.29	66.38 ± 5.16	DSM-IV-R	Ginkgo 12 mg, tid + donepezil 5 mg, qd	Donepezil 5 mg, qd	3	②
Huang et al. 2016 [27]	40	40	66.9 ± 4.1	66.1 ± 3.9	CCMD-3	Ginkgo biloba extract injection 5 ml, qd + donepezil 10 mg, qd	Donepezil 10 mg, qd	3	②
Xu et al. 2018 [28]	38	38	74.15 ± 4.93	72.85 ± 4.83	-	Ginkgo biloba extract tablets 80 mg, tid + donepezil 5 mg, QD	Donepezil 5 mg, qd	6	①②
Cheng et al. 2016 [29]	30	30	74.13 ± 4.93	72.87 ± 4.83	CCMD-3	Ginkgo biloba extract tablets 80 mg, tid + donepezil 5 mg, qd	Donepezil 5 mg, qd	3	①②

NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; DSM-IV-R, Diagnostic and Statistical Manual of Mental Disorders; NIA-AA, National Institute of Aging-Alzheimer's Association; CCMD-3, Classification and Diagnostic Criteria of Mental Disorders in China-third-edition.
①, Clinical efficacy; ②, Mini-mental state examination (MMSE); ③, Adverse reactions; -, not mention.

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Meta-analysis of outcome criteria

Clinical efficacy. A total of five studies [21, 22, 25, 28, 29] involving 354 patients reported the clinical efficacy. Among the 354 patients, 178 patients were used GB and donepezil for experimental therapy, and 176 patients were treated by donepezil. There was no significant heterogeneity (I^2 = 0%, P = 0.55); Thus, fixed-effect model was used. Significant differences in the clinical efficacy were observed between the experimental group and the control group (RR = 1.24, 95% CI: 1.13–1.36, P < 0.0001) (Figure 3).

The MMSE score. A total of nine studies [21–29] totaling 611 patients evaluated the MMSE score. Among the 611 patients, 308 patients were used GB and donepezil for experimental therapy, and 303 patients were treated by donepezil. There was significant heterogeneity (I^2 = 89%, P < 0.00001); thus, random-effect model was used. Experimental group showed significant difference in the MMSE score compared to the control group (MD = 2.96, 95% CI: 1.91–4.02, P < 0.00001) (Figure 4). By removing one study at a time to reduce heterogeneity, sensitivity analysis indicated that the results remained similar to those before the exclusion of the study, which showed that the pooled results were stable.

Adverse reaction. Three studies [21, 23, 24] demonstrated adverse reaction in the treatment, which included 183 patients, 92 of them used GB and donepezil for therapy, and 91 patients were treated by donepezil. There was no significant heterogeneity (I^2 = 0%, P = 0.49; I^2 = 40%, P = 0.19; I^2 = 0%, P = 0.78; respectively); thus, fixed-effect model was used. There was no significant difference in the total adverse reaction (RR = 1.10, 95% CI: 0.72–1.70, P = 0.65), the digestive symptoms (RR = 1.40, 95% CI: 0.60–3.26, P = 0.44) and the neurological symptoms (RR = 0.67, 95% CI: 0.26–1.71, P = 0.40) between the experimental group and the control group (Figure 5).

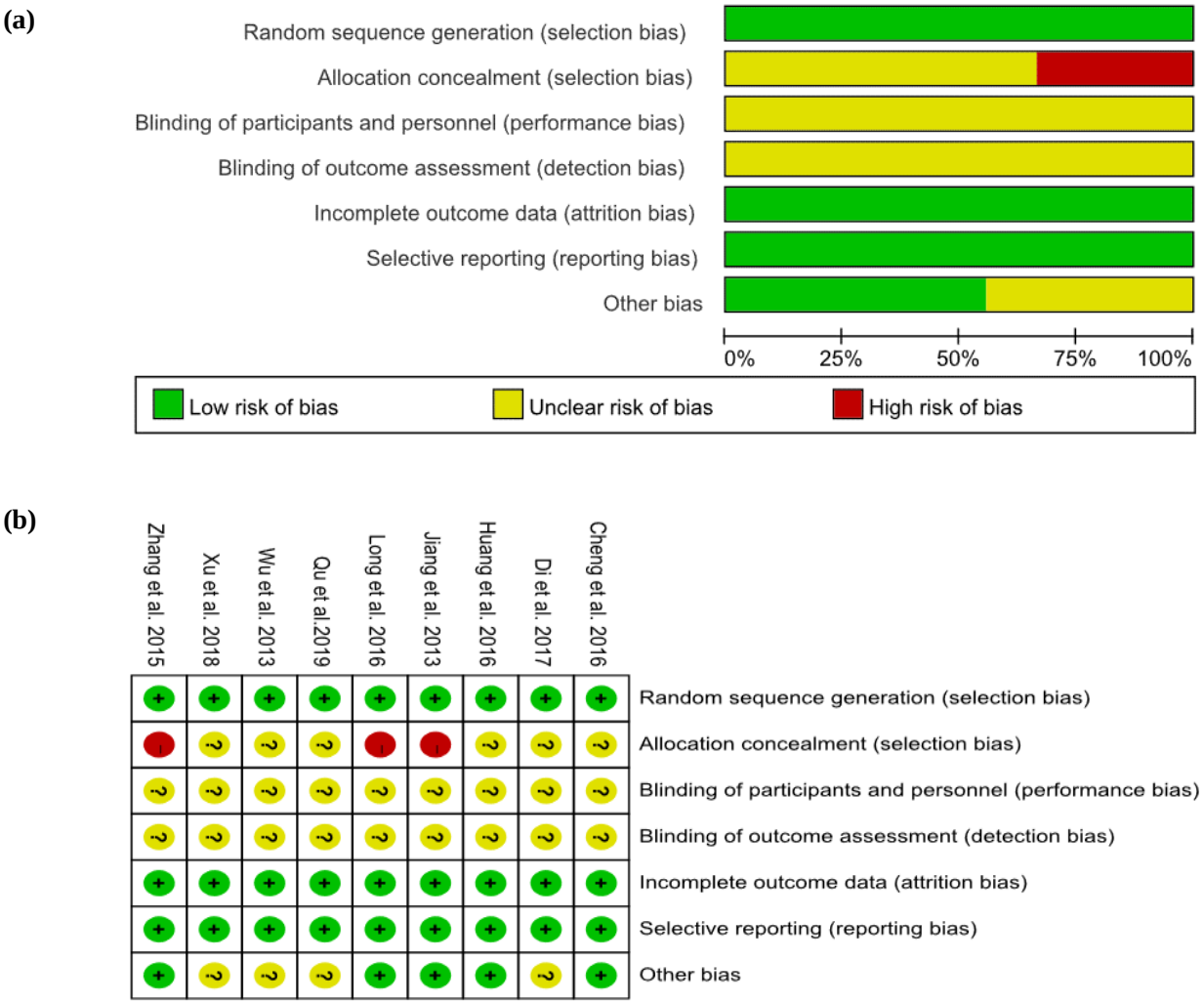

Figure 2 The quality of the included studies. (a) risk of bias summary; **(b)** risk of bias graph.

Table 2 Summary of findings table

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	***Ginkgo biloba* and donepezil vs donepezil**			
Clinical efficacy	**Study population**		**RR 1.24** (1.13 to 1.36)	354 (5 studies)	⊕⊕⊖⊖ **Low**
	744 per 1000	**923 per 1000** (841 to 1000)			
	Medium risk population				
	733 per 1000	**909 per 1000** (828 to 997)			
MMSE		The mean MMSE in the intervention groups was **2.96 higher** (1.91 to 4.02 higher)		611 (9 studies)	⊕⊖⊖⊖ **Very low**
Adverse reaction-digestive symptoms	**Study population**		**RR 1.4** (0.6 to 3.26)	126 (2 studies)	⊕⊖⊖⊖ **Very low**
	111 per 1000	**155 per 1000** (67 to 362)			
	Medium risk population				
	117 per 1000	**164 per 1000** (70 to 381)			
Adverse reaction-total adverse reaction	**Study population**		**RR 1.1** (0.72 to 1.7)	183 (3 studies)	⊕⊖⊖⊖ **Very low**
	275 per 1000	**302 per 1000** (198 to 468)			
	Medium risk population				
	321 per 1000	**353 per 1000** (231 to 546)			
Adverse reaction-neurological symptoms	**Study population**		**RR 0.67** (0.26 to 1.71)	126 (2 studies)	⊕⊕⊕⊖ **Moderate**
	143 per 1000	**96 per 1000** (37 to 245)			
	Medium risk population				
	147 per 1000	**98 per 1000** (38 to 251)			

Patient or population: patients with Alzheimer; settings: inpatients or out patients; intervention: ginkgo biloba and donepezil vs donepezil. *The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence. High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate.

MMSE, mini-mental state examination; CI, confidence interval; RR, risk ratio; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Discussion

The study systematically reviewed the results of nine studies comparing GB and donepezil with donepezil alone for AD. Our meta-analysis demonstrated that: for AD patients, significant differences for clinical efficacy were found between the experimental group and the control group, which meant GB and donepezil could improve clinical efficacy than donepezil alone; experimental group showed significant difference in the MMSE score compared to the control group, which indicated that compared with donepezil alone, donepezil combined with GB could improve cognitive function of AD patients such as the improvements of

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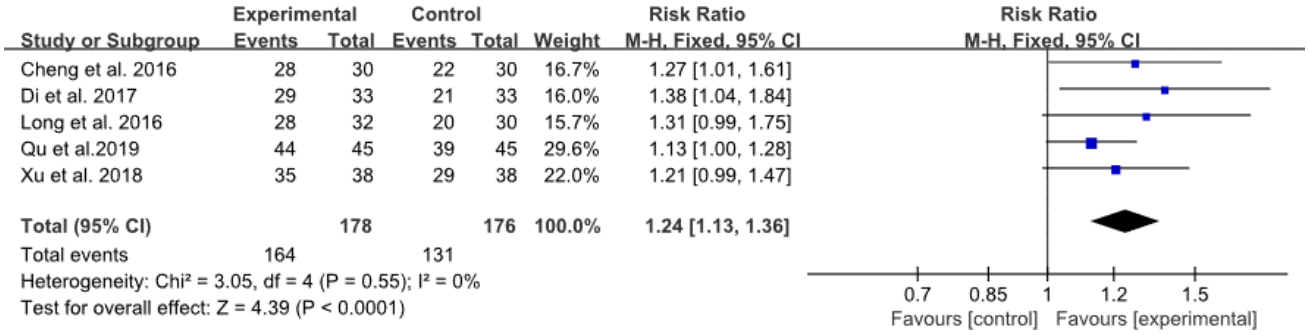

Figure 3 Forest plot of the meta-analysis of clinical efficacy. CI, confidence interval.

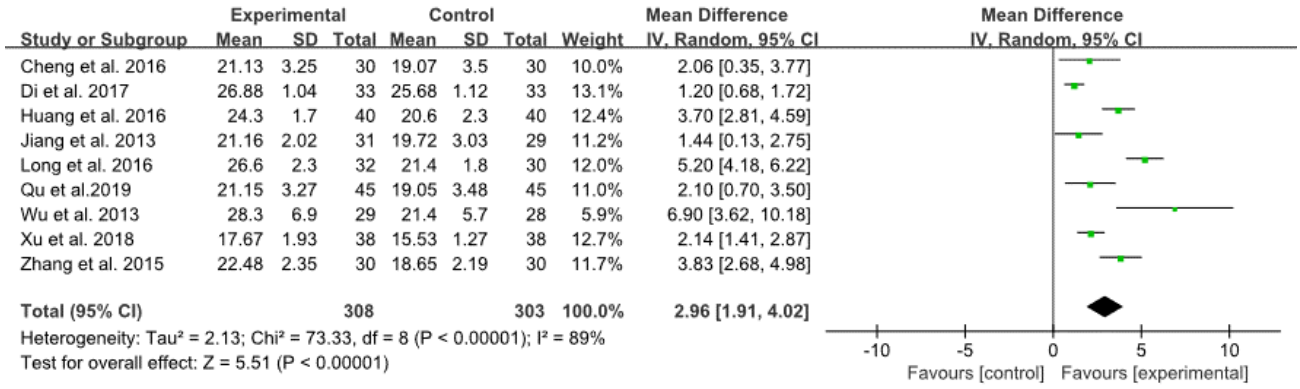

Figure 4 Forest plot of the meta-analysis of the MMSE score. MMSE, mini-mental state examination; CI, confidence interval.

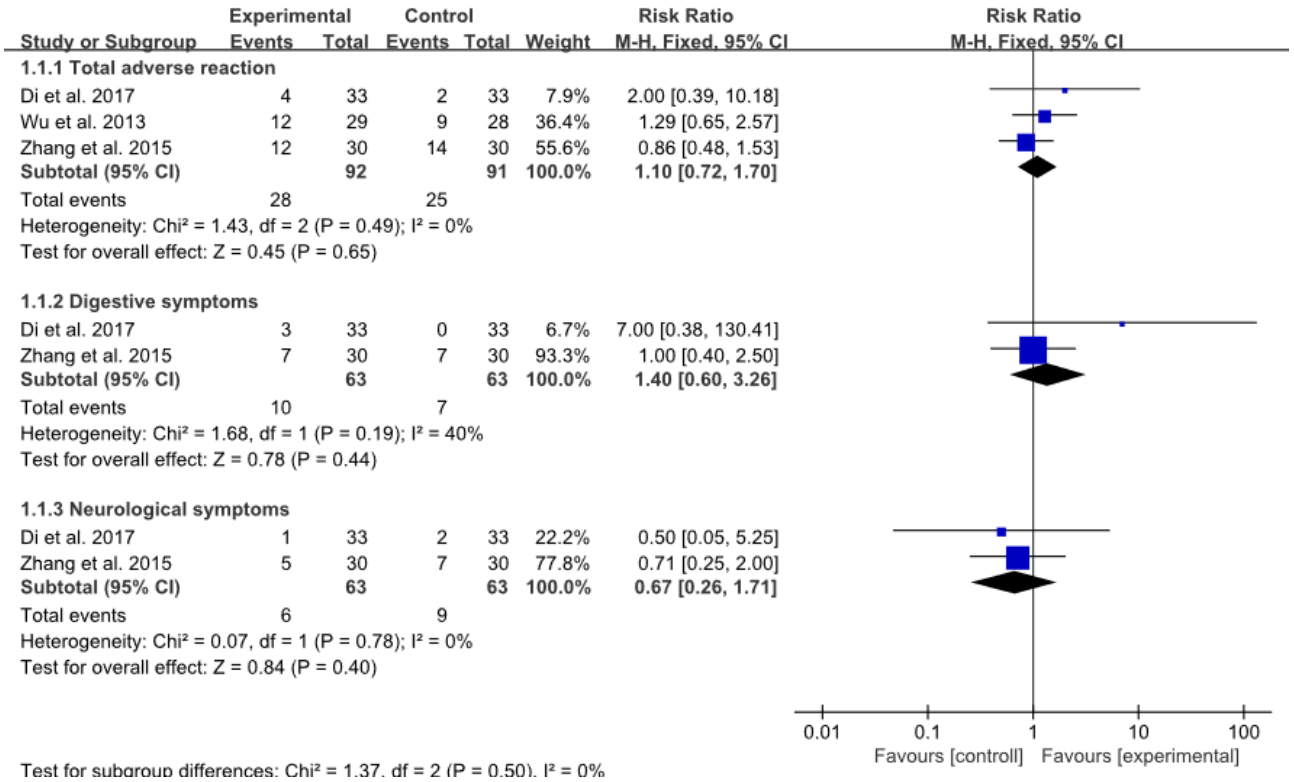

Figure 5 Forest plot of the meta-analysis of adverse reaction. CI, confidence interval.

the main symptoms, memory and comprehension; no significant difference in the total adverse reaction, the digestive symptoms and the neurological symptoms between two groups was observed, indicating that there was no evidence for major differences in the adverse reactions between combination therapy and monotherapy.

The mechanisms by which the combination of donepezil and GB improved the clinical efficacy and the MMSE score are unclear. The most obvious explanation is that donepezil and GB alone enhance the improvement of individual symptoms. Donepezil, the most prevalent type of medicine for AD patients approved by Food and Drug Administration, is an acetylcholinesterase inhibitor [30]. It suppresses cholinesterase and decreases the degradation of choline, which induces a generation of acetylcholine in the brain and improves the cognitive function of AD patients. Importantly, donepezil is the least toxic and can cross the blood-brain barrier [31]. There are different components in the ginkgo leaf. Ginkgolides is an antagonist of platelet-activating factor, which cause platelet activation and aggregation, produce pro-inflammatory effects and increase vascular permeability [32, 33]. Moreover, plate-activating factor has a direct effect on neuronal function and long-term enhancement [34, 35]. Flavonoid, a major component of GB, contributes to the functions of antioxidation and scavenging free radicals [36]. Dozens of studies showed that GB could protect brain neurons fromoxidative stress caused by peroxidation [37, 38, 39], reduce the damage of neurons after ischemia [40] and inhibit caspase-3 activation and Aβ aggregation [41]. GB have been widely used in Europe and the United States to treat memory disorders including AD [42].

Although this meta-analysis showed that donepezil and GB were effective for AD patients, there were a few limitations associated with it. Firstly, the sample size for included studies was small, leading to a low precision. Secondly, there were of low methodological quality. All studies did not report the use of blindness, which may exaggerate curative effect observed. Besides, rating results of the Grading of Recommendations Assessment, Development and Evaluation tool showed that the level of evidence for the three outcomes were very low; Two outcomes were low and moderate, respectively. Thus, more carefully designed and large sample size studies is necessary. Thirdly, there were no uniform GB extracts used for included studies, which influenced the comparison of different experimental results, making the results more difficult to explain. Finally, we did not carry out subgroup analysis because of the small number of studies included.

Conclusions

In conclusion, we demonstrated that the combination of donepezil and GB could provide more benefits for AD patients than donepezil alone. The further large scale and high quality studies are needed to corroborate the findings, due to the small sample size and low methodological quality.

Data availability

All data used to support the findings of this study are included within the article.

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