Systematic Review and Meta-Analysis

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Is Qi Fu Yin effective in clinical treatment of dementia?

A meta-analysis of 697 patients

Lei Wang, PhD[a,b], Pengli Qiao, BA[b], Lulu Yue, MS[b], Rong Sun, PhD[a,c,d,*]

Abstract

Background: Dementia, a kind of acquired and progressive intelligence-damaging syndrome, is induced by cerebral dysfunction. Ancient records show that Qi Fu Yin (QFY) has the advantages in age-related dementia treatment. This study aims to evaluate therapeutic efficacy of QFY on dementia through meta-analysis.

Methods: We comprehensively reviewed articles from various databases, including China National Knowledge Infrastructure (CNKI), Wanfang, VIP, Chinese Biomedical Literature (CBM), PubMed, and Web of Science published before June 2020, for all randomized controlled trials (RCTs) on dementia treatment with QFY. Then, we selected eligible literatures, extracted related data, and assessed risk of bias. Forest plots of total clinical effective rate, MMSE score, HDS score and ADL score illustrated the difference between the experimental group (treatment with QFY alone or combined with routine western medicine) and the control group (treatment with routine western medicine only). Random effects model and fixed effects model were adopted. Finally, publication bias was further analyzed using funnel plot, sensitivity analysis, Begg and Egger test.

Results: Finally, 9 RCTs, involving 697 patients, were included in this study. The results revealed that the total clinical effective rate of the experimental group was obviously higher than that of the control group (OR = 0.33, 95% CI [0.22, 0.50], $P < .001$). In comparison with the control group, the experimental group showed higher MMSE score (WMD = 2.60, 95% CI [2.16, 3.03], $P < .001$) and HDS score (WMD = 1.51, 95%CI [1.10, 1.92], $P < .001$). Due to few included studies, there were no statistically significance between experimental and control groups (WMD = -9.90, 95%CI [−26.09, 6.30], $P = .231$) regarding ADL score. In addition, there is no publication bias towards clinical effective rate and MMDE score.

Conclusions: QFY only or combined with western medicine therapy can significantly improve cognitive ability compared with only western medicine therapy in dementia. However, multiple samples, RCTs of high quality are still needed to verify our conclusions.

Abbreviations: 95% CIs = 95% confidence intervals, AD = Alzheimer's disease, ADL = activity of daily living scale, CBM = Chinese Biomedical Literature, CNKI = China National Knowledge Infrastructure, FE = fixed effects, HDS = Hasegawa's dementia scale, MD = mean difference, MMSE = mini mental status examination, MoCA = Montreal Cognitive Assessment, NMDR = N-methyl-D-aspartate receptor, ORs = odds ratios, QFY = Qi Fu Yin, RCTs = randomized control trials, RE = random effects, TCM = traditional Chinese medicine, VD = vascular dementia.

Keywords: dementia, meta-analysis, Qi Fu Yin, randomized controlled trial

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Dementia, comprising Alzheimer's disease (AD), vascular dementia (VD), Lewy body dementia, and so on, has become one of major health problems in the world. As many as 50 million people worldwide are attacked by dementia, and the number will triple by 2050.[1–4] Clinical manifestations of dementia are featured with a general, progressive decrease in cognitive function, memory loss and poor execution capacity.[5] Although the pathogenesis of dementia involves the damage of cholinergic paths, synaptic plasticity, excitatory toxicity, oxidative stress, neuroinflammation and genetic mechanism, it remains unclear.[6–8]

So far, effective intervening approaches are still unavailable. The familiar therapeutic medications are routine western medicine, which can ameliorate early clinical symptoms in some way and fail to reverse the progression of disease.[9,10] For instance, Donepezil and Rivastigmine act as representative drugs of acetylcholinesterase inhibitors,[11,12] memantine functions as N-methyl-D-aspartate receptor (NMDAR) antagonists, respectively.[12,13] Since dementia is a multi-factor and multi-target progressive disease,[2,14] in clinical treatment, the multifactorial characteristics of dementia are rarely considered. Current treatments are limited to single-target therapeutic approaches, which cannot effectively improve cognitive function. Fortunately, Traditional Chinese Medicine (TCM) plays unique advantages in curing multifactorial disease.[14,15] Therefore, more and more attention has been focused on TCM for dementia.

Qi Fu Yin (QFY), a canonical and extensively used traditional Chinese herb compound, was recorded in 51st volume of Jingyue Quanshu composed by Jingyue Zhang in the Ming Dynasty.[16] QFY comprises 7 herbs, including 6 g *Panax ginseng* (*Renshen*), 9 g *Rehmannia Glutinosa* (*Shudi*), 9 g *Angelica sinensis* (*Danggui*), 3 g *Glycyrrhiza uralensis* (*Gancao*), 5 g *Atractylodes macrocephala* (*Baizhu*), 5 g *Polygala tenuifolia* (*Yuanzhi*), 6 g *Semen Ziziphi Spinosae* (*Suanzaoren*). In terms of usage and dosage, the above herbs were mixed with 400 ml of water, cooked until 280 ml of residual volume, and divided into 2 equal parts. And then, patients take the warm mixture on an empty stomach, twice a day, once in the morning and once in the evening. Recent studies suggest an effective therapeutic role of QFY in dementia patients. A great number of in vitro and in vivo studies have shown that QFY is nootropic and neuroprotective, good for improving learning and memory capacity,[17,18] and especially suitable for the precaution and cure of AD and VD. Moreover, treating dementia patients with western medicine combined with QFY or Jiajian QFY has better effect.[19–27] However, according to their results, this opinion on the therapeutic role of QFY in dementia is still controversial. It is generally believed that meta-analysis is a powerful data processing tool that could aggregate and analyze multiple studies and overcome the limitation of small sample size in a single study, thereby producing the best estimation. This paper aims to conduct a meta-analysis of all eligible Randomized Control Trials (RCTs) to assess the therapeutic efficacy of QFY in dementia.

2. Methods

2.1. Literature research

This meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Ethical approval and informed consent for this study are not applicable. We reviewed articles through various databases of CNKI, Wanfang, VIP, CBM, PubMed and Web of Science published before June 2020. We retrieved literatures using suitable Medical Subject Headings (MeSH) and keywords, including Qi Fu Yin, Qifu-Yin, Qifuyin, dementia, Alzheimer's disease, vascular dementia in PubMed and Web of Science. Meanwhile, similar keywords in Chinese were also searched in CNKI, Wanfang, VIP and CBM database. Finally, all retrieved articles were managed in Endnote software to exclude repetitive articles.

2.2. Research criteria

2.2.1. Inclusion criteria. ① Type of research: Randomized parallel control trials were included, including both in English and Chinese articles. ② Object of research: Patients were included who diagnosed with dementia according to the textbook of Chinese Internal Medicine,[28] with no specific restriction on age, gender, and course of disease. ③ Intervention measures: The experimental group received QFY or Jiajian QFY alone or combined with routine western medicine, while the control group mainly received treatment with routine western medicine. ④ The outcomes: The clinical total effective rate, mini mental status examination (MMSE) score, activity of daily living scale (ADL) score, Hasegawa's dementia scale (HDS) score, Montreal Cognitive Assessment (MoCA) score, TCM syndrome score, adverse reaction were all adopted to estimate therapeutic efficacy and safety of QFY in the treatment of dementia.

2.2.2. Exclusion criteria. In addition, articles were excluded according to exclusion criteria. ① duplicate publications; ② Animal experiments or component research; ③ reviews; ④ literature analysis; ⑤ non-western medicine intervention in control group.

2.3. Quality assessment

Risk of bias for all included studies in this article were assessed by 2 investigators (Wang L and Qiao PL) independently using Cochrane Collaboration tool.[29] The tool includes 7 items: ① allocation concealment, ② random sequence generation, ③ blinding of outcome assessment, ④ blinding of participants and personnel, ⑤ selective reporting, ⑥ incomplete outcome data, ⑦ other bias. Each study was classified as low risk, high risk, or unclear risk using the tool in Review Manager 5.3 software (The Cochrane Collaboration, Oxford, UK).

2.4. Data extraction and statistical analysis

All candidate literatures were independently extracted by 2 authors (Wang L and Qiao PL). Disagreements were resolved by consensus with a third investigator (Yue LL). For each study, we recorded the following items: title, first author, year of publication, sex, sample size, course of disease, study design, diagnosis criteria, intervention measures, course of treatment, outcomes and adverse reactions.

Odds ratios (ORs), weighted mean difference (WMD) and 95% confidence intervals (CIs) was used as a measure of the therapeutic efficacy. For analyses of effective rate, we calculated ORs. For analyses of MMSE score, ADL score, and HDS score, we calculated WMD. Cochran's Q test and I squared statistic were performed to assess the heterogeneity of included trials. $I^2 \geq 50\%$ or $P < .10$ suggested significant heterogeneity. Random effects (RE) model was adopted if significant heterogeneity existed. Otherwise fixed effects (FE) model was used.[30] In

addition, 8 included studies involved effective rate and MMSE score, towards which publication bias was estimated by funnel plot, sensitivity analysis, Begg and Egger test.[31,32] A 2-sided $P < .05$ was considered statistically significant. All statistical analysis were carried out using STATA 14.0 software (StataCorp, College Station, Texas, USA).

3. Results

3.1. Identification of relevant studies

Literature retrieval was demonstrated in following procedure (Fig. 1). We screened 97 articles and identified 9 studies for further meta-analysis.[19–27]

3.2. Basic information of the included studies

Nine included studies, with a total of 697 patients, are all published in Chinese from 2002 to 2019. The sample size of different studies ranged from 55 to 180. Course of treatment ranged from 1 to 3 months. The intervention measures in the control group were mainly conventional western medicine treatment, such as memantine hydrochloride tablets, nimodipine, donepezil hydrochloride tablets, nicergoline, hydergine tablet, vinpocetine, and Piracetam. Patients in the experimental group received QFY or Jiajian QFY alone or combined with routine western medicine treatment. The total basic information of the final adopted studies was presented in Table 1.

3.3. Quality assessment of the included studies

Only 3 trials adopting random digital table were classified as low risk,[20,22,27] and the remaining trials with unclear randomization procedure were considered as unclear risk. No studies described allocation concealment and blinding clearly, and these were considered as unclear risk and high risk, respectively. All studies had complete outcome data and no selective reporting. It was not clear whether there was any other bias. The details were depicted in Figure 2 and Figure 3.

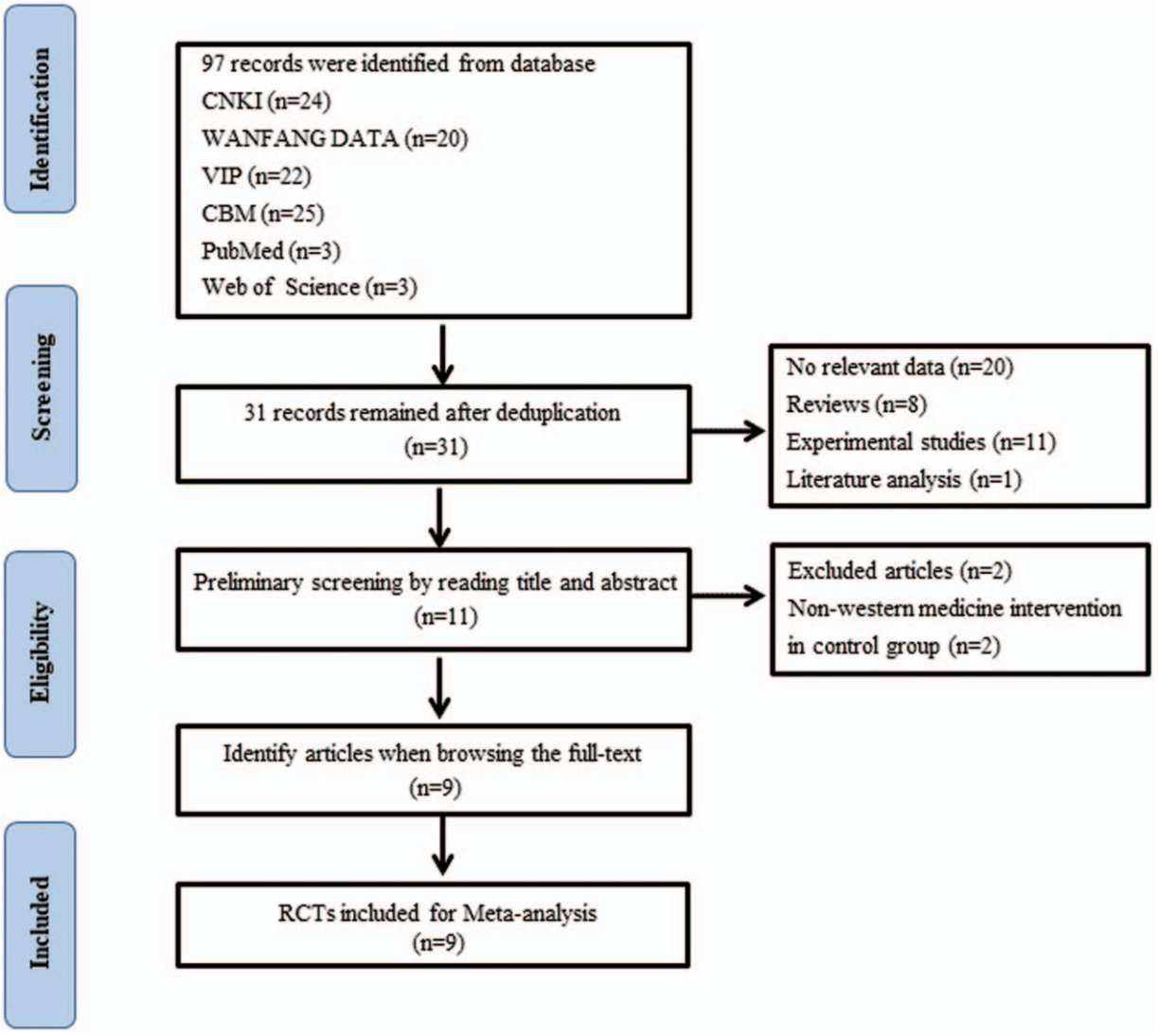

Figure 1. Flow diagram of the included studies. CBM = Chinese Biomedical Literature, CNKI = China National Knowledge Infrastructure, n = numbers, RCTs = randomized control trials.

Table 1

Basic Information of the Included Studies for dementia.

Included Studies	Male/ Female	Number of cases (experimental group/control group)	Course of the disease (year)		Intervention measures		Course of the treatment (month)	Outcome Indicators
			Experimental group	Control group	Experimental group	Control group		
Huifeng Xiao 2019	35/25	60 (30/30)	0.66–1.84	0.67–1.71	Control group + Jiawei QFY	Donepezil Hydrochloride Tablets	3	Total effective rate; MMSE score; MoCA score; ADL score;
Aiguo Wang 2018	47/19	66 (33/33)	0.58–3.5	0.5–4	Control group + Jiawei QFY + thumb-tack needle	Memantine Hydrochloride Tablets	3	Total effective rate; MMSE score;
Xiaobin Chen 2017	*	60 (30/30)	*	*	Control group + QFY	Nimodipine	3	Total effective rate ; MoCA score; MMSE score; ADL score; Scores of TCM syndrome; Safety;
Guiqin Zhao 2014	98/82	180 (90/90)	3–10 (average 5.4)		Control group + Jiajian QFY	Donepezil Hydrochloride Tablets	3	Total effective rate; MMSE score;
Xueping Sun 2014	56/40	96 (64/32)	0.5–4	0.5–3.5	Control group +Jiajian QFY +Rehabilitation Therapy	Nicergoline	2	Total effective rate ; MMSE score; ADL score; Adverse reaction ;
Hailong Jia 2012	36/19	55 (30/25)	2–6	2–5.5	Jiawei QFY	Hydergine	2	MMSE score; Adverse reaction ;
Xueqin Li 2010	39/21	60 (30/30)	0.5–3.1	0.6–2.5	Control group + Jiajian QFY	Nimodipine; Glucose Injection + Citicoline; 0.9% Sodium Chloride Injection + Vinpocetine	1	Total effective rate ; MMSE score; HDS score; ADL score; Adverse reaction;
Huajun Zhu 2009	37/23	60 (30/30)	0.083–2 or 2–5	0.083–2 or 2–5	Control group + Jiajian QFY	Nimodipine	3	Total effective rate; MMSE score; HDS score;
Jianming Wang 2002	41/19	60 (32/28)	0.25–6.5	0.2–6.8	Control group + Jiajian QFY granules	Piracetam	2	Total effective rate; HDS score;

ADL = activity of daily living scale, HDS = Hasegawa's dementia scale rate, MMSE = mini mental status examination, MoCA = Montreal Cognitive Assessment, QFY = Qi Fu Yin, TCM = traditional Chinese medicine.

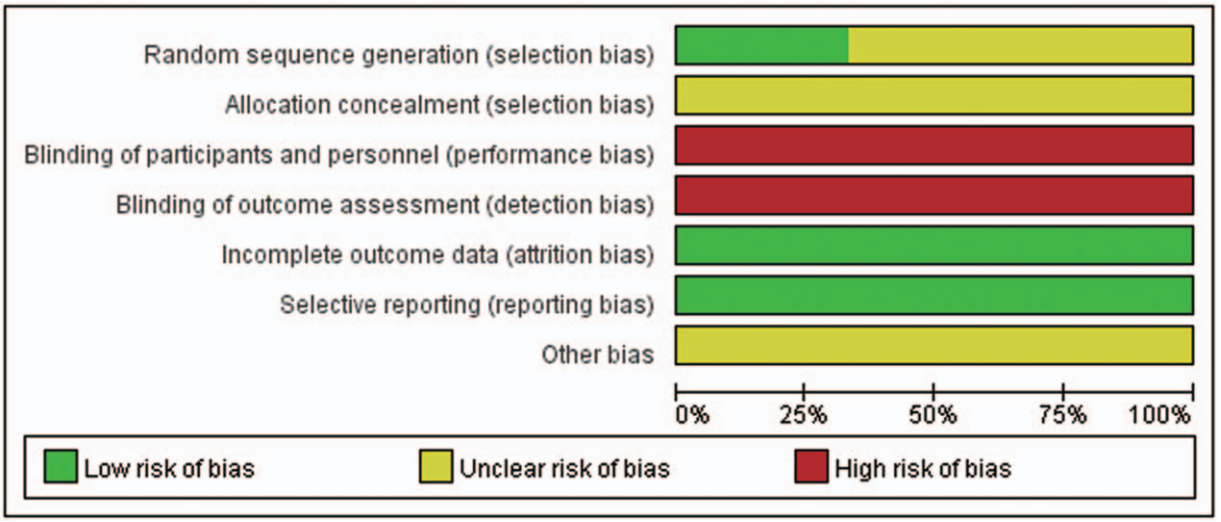

Figure 2. Risk of bias graph.

3.4. Meta-analysis results of dementia treatment with QFY

3.4.1. Total clinical efficiency evaluation. Eight trials were included in the analysis of total clinical efficacy rate.[19–22,24–27] The number of patients receiving effective treatment in the experimental group (n = 339) and the control group (n = 303) were 299 and 215, respectively. Combined data under FE model demonstrated that the total clinical efficiency rate of the experimental groups was significantly higher than that of the control groups (OR = 0.33, 95% CI [0.22, 0.50], $P < .001$, Fig. 4), without statistical heterogeneity ($P = .503$, $I^2 = 0\%$).

3.4.2. MMSE score evaluation. MMSE (Mini-Mental State Examination, MMSE) rating scale, the commonest scales in clinical cognitive examination, is often used to assess people's mental state and degree of cognitive lesion. The lower the score, the more severe the damage. Eight studies with 637 patients (337 cases in the experimental group and 300 cases in the control group) were incorporated into meta-analysis for MMSE score.[19–25,27] No statistical heterogeneity existed among the studies ($P = .128$, $I^2 = 37.8\%$), so FE model was adopted. The results indicated that MMSE score of the experimental groups were significantly higher than that of the control groups (WMD = 2.60, 95% CI [2.16, 3.03], $P < .001$, Fig. 5).

3.4.3. ADL score. ADL (Activities of Daily Living, ADL) rating scale is often used to evaluate patients' life self-care ability in clinical practice. Three trials, totaling 180 patients (90 cases in the experimental group and 90 cases in the control group), report ADL score.[20,24,27] RE model was adopted for data analysis because of statistical heterogeneity among the studies ($P = .000$, $I^2 = 97.7\%$). Our results demonstrated that the ADL score of the experimental group was lower than that of the control group,

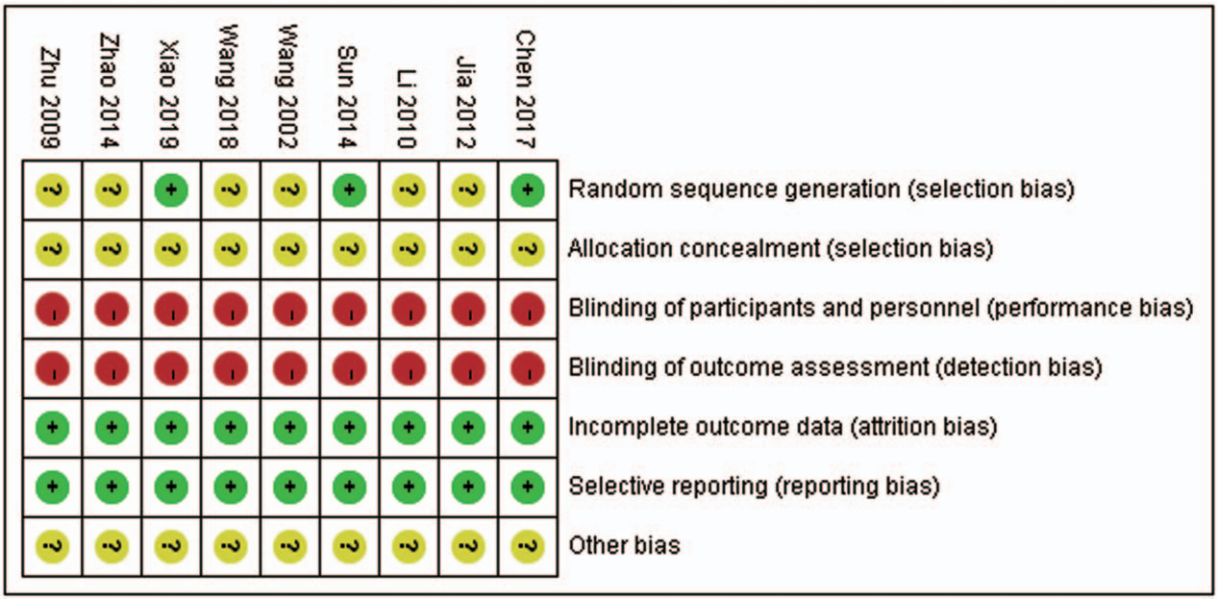

Figure 3. Risk of bias summary.

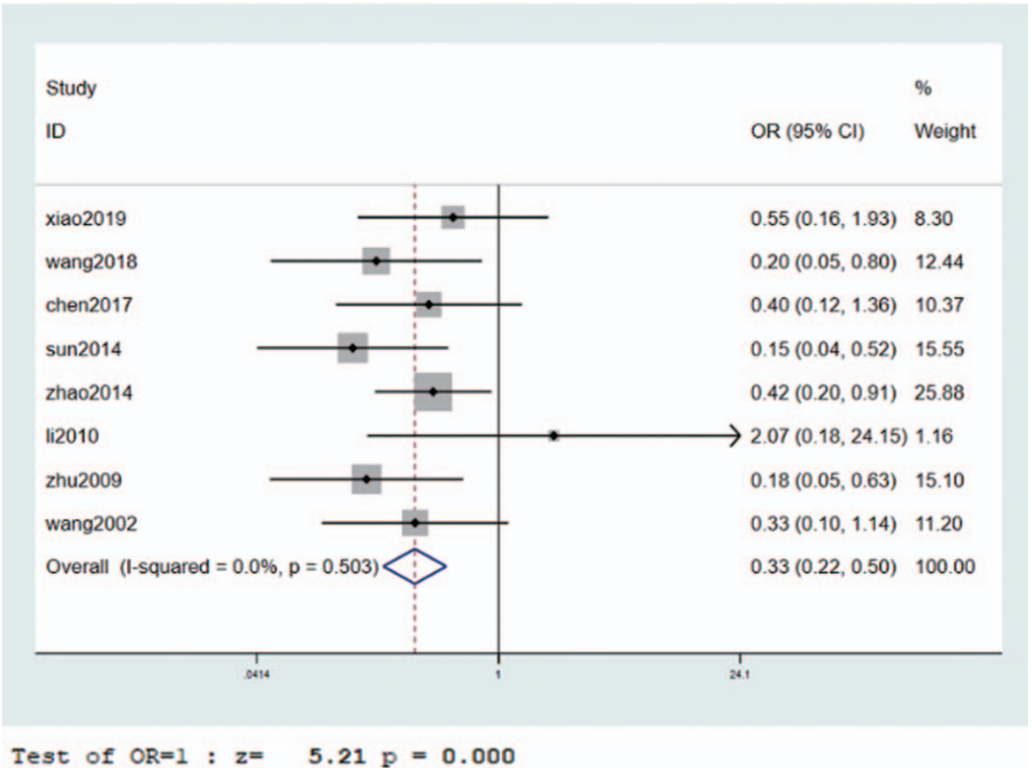

Figure 4. Forest plot of total clinical effective rate.

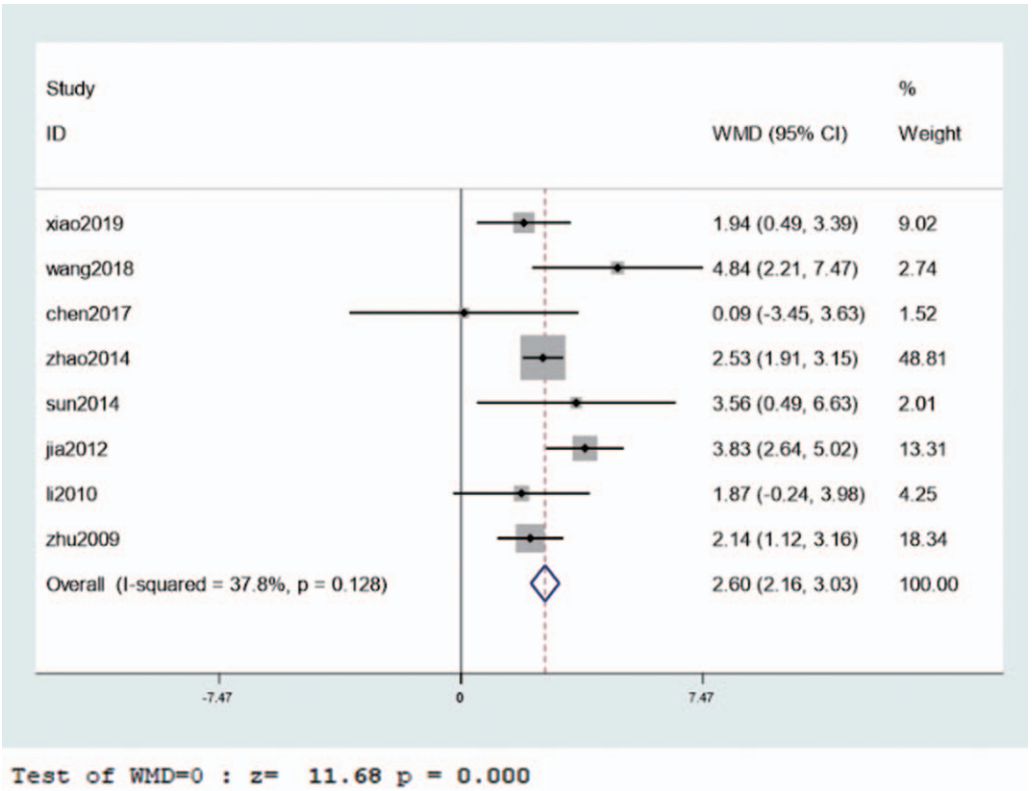

Figure 5. Forest plot of MMSE score. MMSE = mini mental status examination.

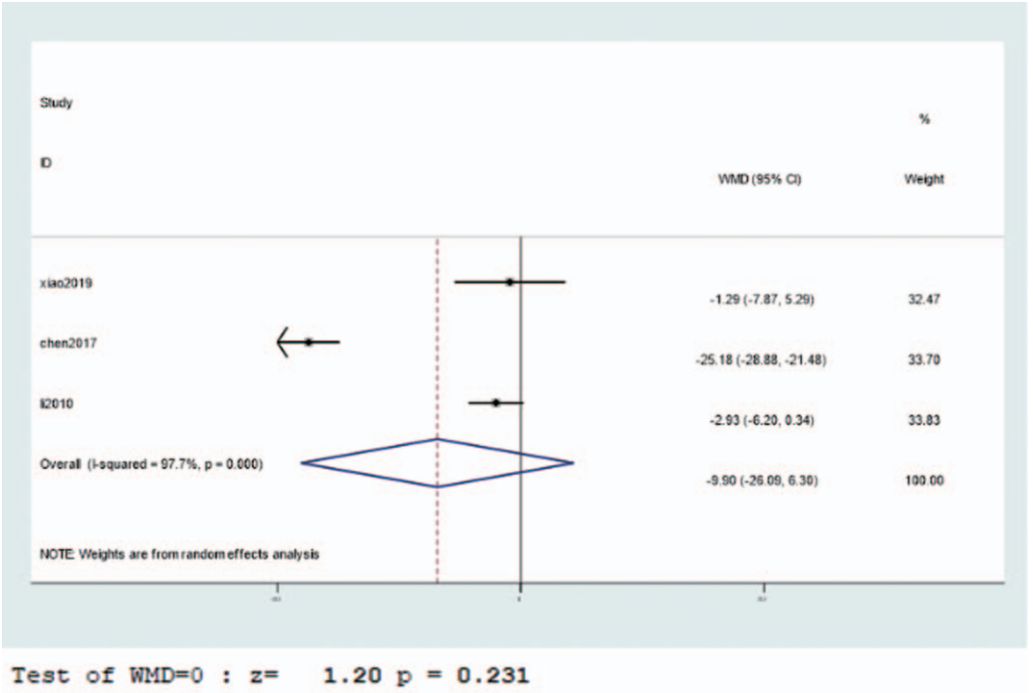

Figure 6. Forest plot of ADL score. ADL = activity of daily living scale.

without statistically significance (WMD = −9.90, 95%CI [−26.09, 6.30], $P = .231$, Fig. 6), due to little included studies. Besides, it should be pointed out that one study showed a contrary tendency.[22]

3.4.4. HDS score. HDS (Hasegawa Dementia Scale, HDS) rating scale clinically acts as one of the best screening tools for senile dementia. The score ranges from 0 to 30. The lower the score, the more severe the dementia. Three trials describe HDS score, including 180 participants (92 cases in the experimental group and 88 cases in the control group).[24–26] In comparison with the control group, HDS score of the experimental groups were significantly higher (WMD = 1.51, 95%CI [1.10, 1.92], $P < .001$, Fig. 7), with no statistical heterogeneity ($P = .194$, $I^2 = 39\%$).

3.4.5. Other outcomes. Among the 9 included trials, only 2 studies[20] reported MoCA (Montreal Cognitive Assessment, MoCA) rating scale and only 1 study reported TCM syndrome score. Compared with the control group, the MoCA score and TCM syndrome score of the experimental group increased slightly and decreased significantly, respectively. Moreover, adverse drug reactions happened in 4 trials.[20,22–24,27] The study of Chen et al revealed 1 case of abnormal liver function, 1 case of nausea and vomiting, 1 case of headache and dizziness in the control group (n = 30).[20] In the experimental group, only 1 case of nausea and vomiting happened (n = 30) during treatment of vascular cognitive impairment of Suihaibuzu with QFY combined with nimodipine, indicating no serious adverse events. Xiao et al[27] reported that only 1 person felt nausea during non-dementia vascular cognitive impairment treatment with QFY combined with donepezil (n = 30). The remaining 3 trials all had no untoward effect during the treatment of dementia with Jiajian QFY only or combined with other medication.[22–24]

3.4.6. Publication bias assessment. In terms of publication bias, significant asymmetry was noted in the funnel plot for total clinical effective rate (Fig. 8). However, funnel plot for MMSE score showed a dispersed distribution (Fig. 9). Thus, further analysis for publication bias was performed through sensitivity analysis, Begg and Egger test. The sensitivity analysis of total clinical effective rate and MMSE score demonstrated that the points were scattered within the 95% confidence interval (Fig. 10 and Fig. 11). Additionally, Begg and Egger test showed no publication bias towards total clinical effective rate ($P = .805$ for Begg test, $P = .203$ for Egger test) and MMSE score ($P = .805$ for Begg test, $P = .899$ for Egger test), suggesting reliable results.

4. Discussion

A great deal of studies have explored the therapeutic efficacy of QFY in dementia patients. However, its role was inconsistent. Therefore, we searched related studies and conducted meta-analysis to reach a more precise evaluation of the therapeutic efficacy of QFY in dementia. The outcomes of 697 dementia patients were combined from 9 included RCTs, demonstrating that QFY only or combined with western medicine significantly increased total clinical efficiency, MMSE score, and HDS score in dementia patients. Besides, among 9 RCTs, 3 studies reported patients with Suihaibuzu, especially suitable for QFY intervention.[19,20,22]

There are few TCM monographs about dementia. The earliest records for dementia appear in The Secret Biography of Hua Tuo in Eastern Han Dynasty.[33] Until the Ming dynasty, a specific chapter named as "Madness and Dementia" in Jingyue Quanshu describes the etiology, syndromes, prognosis and therapy about dementia in detail and suggests to take QFY Chinese herbal compound for treatment.[16,34] QFY, depicted in Volume 51 of Jingyue Quanshu, is comprised of 7 herb ingredients totally,

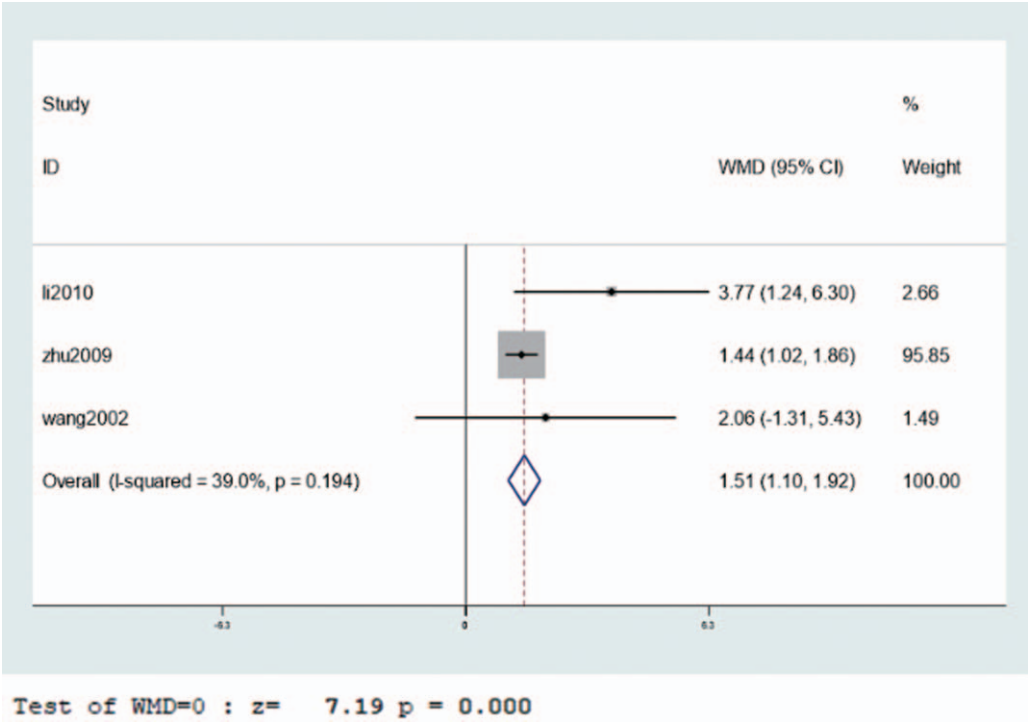

Figure 7. Forest plot of HDS score. HDS = Hasegawa's dementia scale rate.

including 6 g *Panax ginseng* (*Renshen*), 9 g *Rehmannia Glutinosa* (*Shudi*), 9 g *Angelica sinensis* (*Danggui*), 3 g *Glycyrrhiza uralensis* (*Gancao*), 5 g *Atractylodes macrocephala* (*Baizhu*), 5 g *Polygala tenuifolia* (*Yuanzhi*), 6 g *Semen Ziziphi Spinosae* (*Suanzaoren*). The textbook of Chinese Internal Medicine describes that QFY has the advantages of reinforcing qi, nourishing blood, and tonifying kidney. QFY ingeniously associated various organs with qi-blood as a whole to treat senile dementia.[34] Modern pharmacological studies have shown that each compound of QFY prescription exerts neuroprotective effects and enhances learning and memory function.[35–40] Some researchers have established rat models of dementia and found that anti-oxidation,

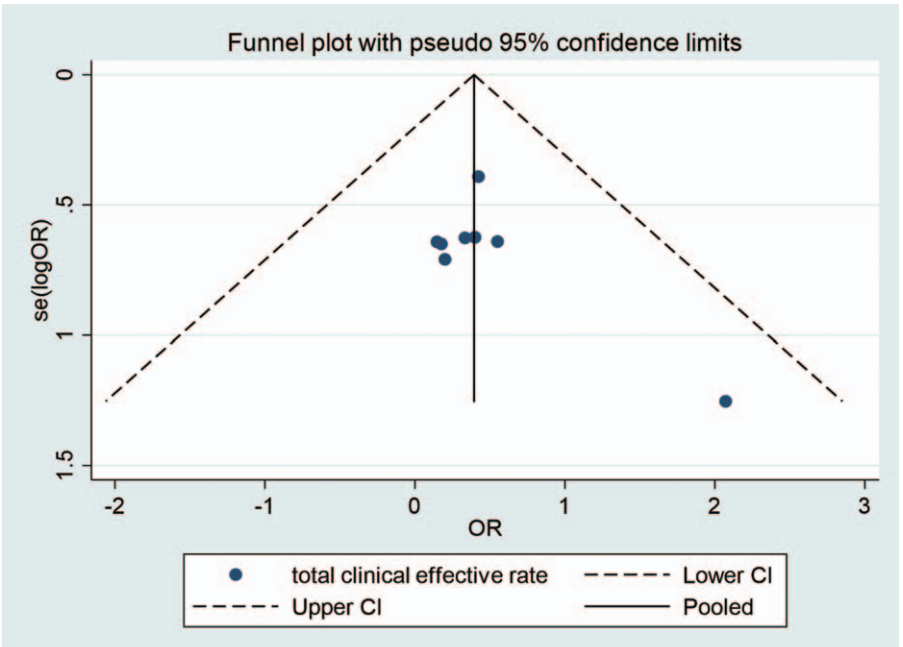

Figure 8. Funnel plot of total clinical effective rate.

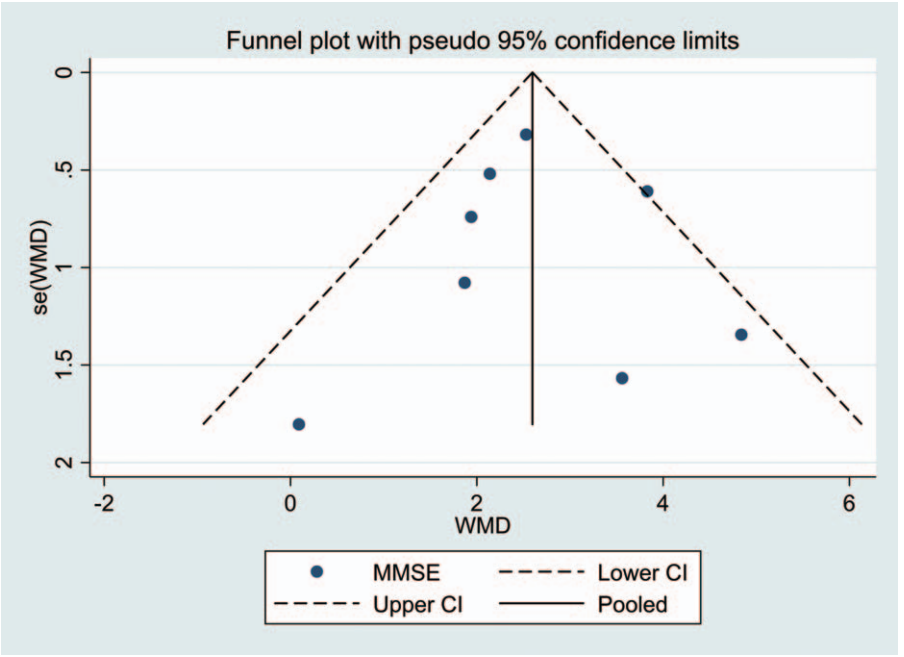

Figure 9. Funnel plot of MMSE score. MMSE = mini mental status examination.

improvement of cholinergic nerve function, reduction of neuronal apoptosis, and inhibition of NF-κB pathway activation are possible mechanisms.[41,42]

We performed funnel plots, sensitivity analysis and Begg and Egger test in order to analyze possible publication bias. The results depicted that there was no publication bias towards outcomes of clinical total effective rate and MMSE score. However, there were some limitations in this study. The included RCTs in WMD for ADL score had significant heterogeneity ($P = .000$, $I^2 = 97.7\%$). Due to few included RCTs regarding ADL score, the origin of heterogeneity could not be traced. Also, it is worth noting that the quality of the included RCTs is not good, and there are many unclear-risk and high-risk data, with only 3 of which adopted random number table. Besides, in terms of therapeutic efficacy, there are relatively small eligible studies. Additionally, all 9 included studies were in Chinese language only. Furthermore, there were limited information on adverse effects and some other outcomes. For example, MoCA score and

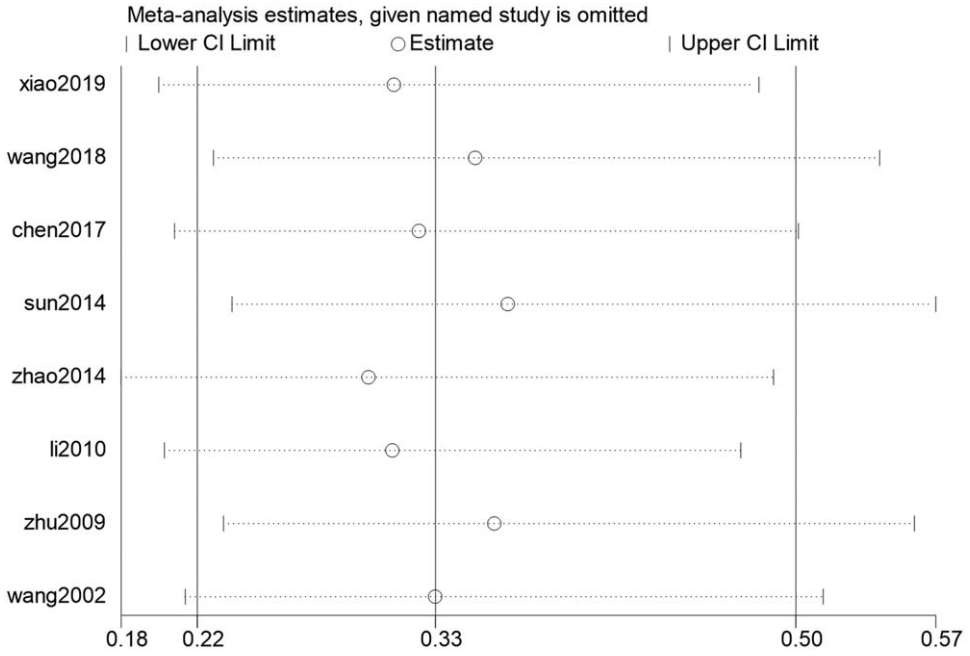

Figure 10. Sensitivity analysis of total clinical effective rate.

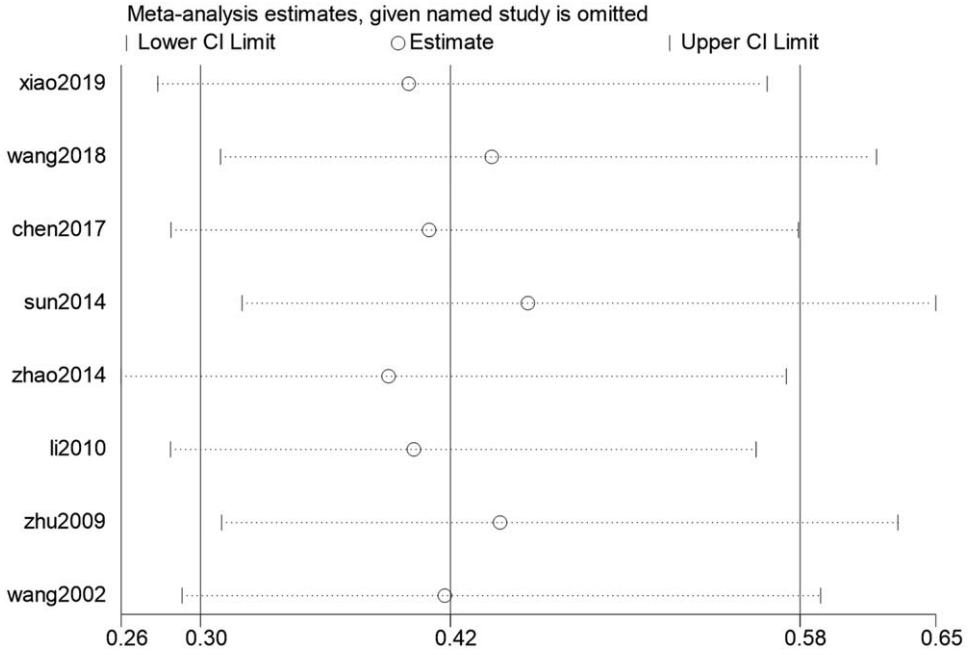

Figure 11. Sensitivity analysis of MMSE score. MMSE = mini mental status examination.

TCM syndrome score were included in only 2 or 1 study, so we could not fully analyze different TCM types of senile dementia due to few related studies and poor quality.

5. Conclusions

In conclusion, the meta-analysis of eligible literatures retrieved from database supports the opinion that QFY is effective and safe in the treatment of dementia, especially for patients suffering from Alzheimer's disease and vascular dementia. However, it is worth mentioning that there are limitations, such as small sample sizes and relatively low quality of included literatures. Therefore, further randomized controlled trials with large sample sizes as well as rigorous design are needed to provide more convincing evidence for the therapeutic efficacy of QFY on dementia.

Author contributions

Conceptualization: Rong Sun.
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Formal analysis: Lei Wang.
Funding acquisition: Rong Sun.
Investigation: Lei Wang.
Methodology: Lei Wang, Pengli Qiao.
Project administration: Lei Wang.
Resources: Rong Sun.
Software: Pengli Qiao.
Supervision: Rong Sun.
Validation: Pengli Qiao, Lulu Yue.
Writing – original draft: Lei Wang.
Writing – review & editing: Lei Wang, Rong Sun.

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