SPECIAL ARTICLE

Efficacy and safety of *Morinda officinalis* oligosaccharide capsules for depressive disorder: a systematic review and meta-analysis

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Objective: To evaluate the efficacy and safety of *Morinda officinalis* oligosaccharide (MOO) capsules for depressive disorder.

Methods: Eight electronic databases were searched for relevant studies from inception to April 19, 2020. Randomized controlled trials comparing MOO capsules with antidepressants were included. Data analysis was conducted using Review Manager 5.3 software. The risk of bias was assessed using the Cochrane Risk of Bias Tool, and the quality of the studies was evaluated by two researchers using the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) software.

Results: Seven studies involving 1,384 participants were included in this study. The effect of MOO capsules for moderate depressive disorder was not different from that of antidepressants (risk ratio [RR] = 0.99, 95%CI 0.92-1.06). Regarding adverse events, no significant difference was found between MOO capsules and antidepressants (RR = 0.84, 95%CI 0.65-1.07). In addition, the quality of evidence related to these adverse events was rated as low.

Conclusion: This systematic review suggests that the efficacy of MOO capsules in the treatment of mild to moderate depression is not inferior to that of conventional antidepressants, which may provide a new direction for clinical alternative selection of antidepressants. However, more high-quality research and detailed assessments are needed.

Keywords: *Morinda officinalis* oligosaccharide capsules; depressive disorder; systematic review; meta-analysis

Introduction

Depressive disorder has become a medical and social issue that has attracted extensive attention and demands urgent resolution.[1] A cross-sectional study showed that the prevalence of depressive disorder is as high as 17% in the United States and reaches 4% in China.[2] Depressive disorder can result in serious dysfunction during social and family activities for patients; accordingly, it has been ranked as the largest contributor to non-fatal health loss by the World Health Organization.[3] At present, the mainstream form of antidepressant treatment is still pharmacotherapy; however, the overall effectiveness rate of antidepressants is less than 70%.[4] Moreover, the undesirable side effects of antidepressants result in poor compliance with treatment.[5] Furthermore, discontinuation of medications may cause withdrawal reactions and

relapse of depressive disorder, consequently leading to increased medication cycles.[6] In this context, traditional Chinese medicine (TCM) has gradually been highlighted by a large number of researchers dedicated to identifying new therapies with greater efficacy and safety.

The root of *Morinda officinalis* F.C.How., known as "Bajitian" in China, is commonly prescribed to improve the symptoms of depressive disorder and sexual dysfunction.[7-10] Capsules of *Morinda officinalis* oligosaccharide (MOO) mainly contain inulin-type oligosaccharides extracted from the roots of *M. officinalis* and have been approved for sale by the Chinese Food and Drug Administration (CFDA) since 2012. Pharmacological studies have shown that MOO can increase 5-hydroxytryptamine in the brains of mice and enhance the expression of brain-derived neurotrophic factor in naive rats,[11-13] thereby improving the symptoms of depressive disorder, including

anhedonia, fatigue, weakness, and decreased libido. According to previous experimental studies, MOO can promote the regeneration of neurons in the hippocampal dentate gyrus of depressive rats and regulate the neurotrophic pathway in the hippocampus, thus improving the depressive behaviors of rats, similar to the effects of fluoxetine.[10] A series of clinical trials have been conducted to further reveal the effects of MOO on depressive disorder. However, most published studies vary in research quality; some have limited sample sizes, and some recruited patients with primary depressive disorder, while others have involved patients with depressive disorder secondary to somatic diseases. Consequently, the overall efficacy and safety of MOO capsules remain unclear. Therefore, a systematic review of published randomized controlled trials (RCTs) is crucial. This study aimed to provide a comprehensive, accurate. and objective evaluation of the efficacy and safety of MOO capsules for the treatment of depressive disorder.

Methods

Search strategy

The PubMed, MEDLINE (Ovid), Cochrane Library, Chinese National Knowledge Infrastructure, Wan Fang Data, VIP Data, SinoMed, and Embase databases were searched. The retrieval query consisted of multiple combinations of the keywords "*Morinda officinalis* oligosaccharides/*Morinda officinalis* oligosaccharide capsules," "depression/depressive disorder/mood disorder" and "control study/randomized trial."

The results of the search included all articles published in Chinese or English before April 19, 2020. The references of the included studies were manually reviewed to identify additional relevant articles.

Selection criteria

RCTs of MOO capsules for depressive disorder that met the following inclusion criteria were included in the analysis:

1) The patients were diagnosed with depressive disorder, and the diagnostic criteria included but were not limited to the DSM-5, the ICD-10 diagnostic criteria for depressive disorder, and the Chinese Classification and Diagnostic Criteria of Mental Disorders (CCMD); individuals with depressive disorder secondary to somatic diseases were not excluded.
2) The intervention group received MOO capsules with no limit on dosage, while the control group received antidepressants or placebo. If the clinical trials included multiple control groups, only the desired clinical control groups were selected.
3) The outcome measures were as follows: clinically rated depression scales, self-rated depression scales, or "clinical remission" events, which were often defined as experiencing some improvement in depressive disorder; the secondary outcome was adverse events.

4) Non-randomized controlled studies, single case reports, theoretical studies, and non-human studies were excluded.

Trial inclusion and data extraction

After excluding repeated articles, two authors (YD & QZ) independently read titles and abstracts for initial screening and then screened the full texts according to the predefined inclusion and exclusion criteria, eventually cross-checking the included articles. In case of disagreement, the third author (MQ) made the decision regarding inclusion.

Published data (first author, publication time, title of the trial) and research characteristics (patient demographics, research design, sample size, depressive disorder diagnostic criteria, experimental and control group details, durations of interventions), as well as the outcomes and adverse events, were extracted. The main outcome of the systemic evaluation was "clinical remission" events based on reductions in depressive disorder-related scale scores. The evaluation of side effects was based on the incidence rate or scales of adverse reactions in the trial; again, in case of disagreement, the third author (MQ) assessed the adverse events that were controversial.

Quality assessment

Each included article was assessed for the risk of bias using the Cochrane Risk of Bias (RoB) Tool.[14] Each of the included studies was evaluated according to seven items, and each item had three levels of risk: low risk, high risk, and unclear/undecidable risk. The assessment criteria for the overall risk of bias based on a previous study[15] were as follows: a, if all seven items of the RoB tool were evaluated as low, then the overall risk of bias was judged as a "low risk of bias"; b, if at least one item was evaluated as unclear and other items were all evaluated as low, then the study was judged to have an "uncertain risk of bias"; and c, if any item was evaluated as high, then the study was judged to have a "high risk of bias."

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) software was used to assess the quality of the articles and evaluate the level of evidence.[16] We classified the overall quality of evidence as high, moderate, low, or very low.

The risk of bias assessment and the quality of evidence evaluation were performed independently by two authors (YD & QZ). According to the original data, another author (MQ) independently reviewed and ultimately assessed these data.

Statistical analysis

Kappa statistics were used to test the consistency of individual studies and assess the overall evaluations of the two independent authors.[17] Review Manager (RevMan 5.3) software was used for meta-analysis. When the

outcomes of the included articles were the same continuous variable, the mean difference (MD) was estimated; when the outcomes were different continuous variables, the standardized mean difference was estimated; and when the outcomes were categorical variables, the risk ratio (RR) was estimated, and the heterogeneity was measured using I^2. When $I^2 < 50\%$ and $p > 0.10$, the included studies were considered homogeneous, and a fixed effect model was used; when $50\% \leqslant I^2 < 75\%$, the included studies were considered to have obvious heterogeneity, and a random effect model was used; when $I^2 \geqslant 75\%$, sensitivity analysis was carried out to identify the potential factors affecting heterogeneity; if $I^2 \geqslant 75\%$ after removing outliers, the results of the study were only described, and an integration analysis was deemed unnecessary; finally, when more than 10 studies were involved, a funnel chart was used to evaluate the publication bias of the included articles.

Results

Study selection

After the initial electronic search, 197 articles were found, 70 of which were repeated or irrelevant and were excluded. Moreover, 101 articles were excluded after reading the titles and abstracts, and 19 articles were excluded after reading the full texts based on the predetermined inclusion and exclusion criteria. Finally, seven articles[18-24] were selected for the meta-analysis (Figure 1), which were all RCTs with a non-inferiority trial design.

A total of 1,384 Chinese outpatients/inpatients with mild or moderate depressive disorder were included. The subjects in these seven studies were all adults (age over 18 years).

The specific characteristics of the seven included studies are shown in Table 1. The inclusion and exclusion criteria varied among them. Five[18-20,22,24] studies used the ICD-10, and two[21,23] studies used the CCMD-3 diagnostic criteria for depressive disorder. Moreover, scores on the Hamilton Depression Scale 17-items (HAMD-17) were required to be greater than 17 in six[18-23] studies. The doses of the MOO capsules in seven studies ranged from 300-800 mg/d, and Zhang[19] established high- and low-dose MOO groups. Regarding the control groups, one study[21] used duloxetine capsules, three studies[18-20] used fluoxetine hydrochloride, one[24] used agomelatine, two[22,23] used escitalopram oxalate, and two[18,20] used a placebo. The reduction rate in HAMD-17 score was used as a criterion for increasing the dosages of MOO or control drugs in four studies,[18-20,22] where patients were treated with an increased dose after 2 weeks of treatment
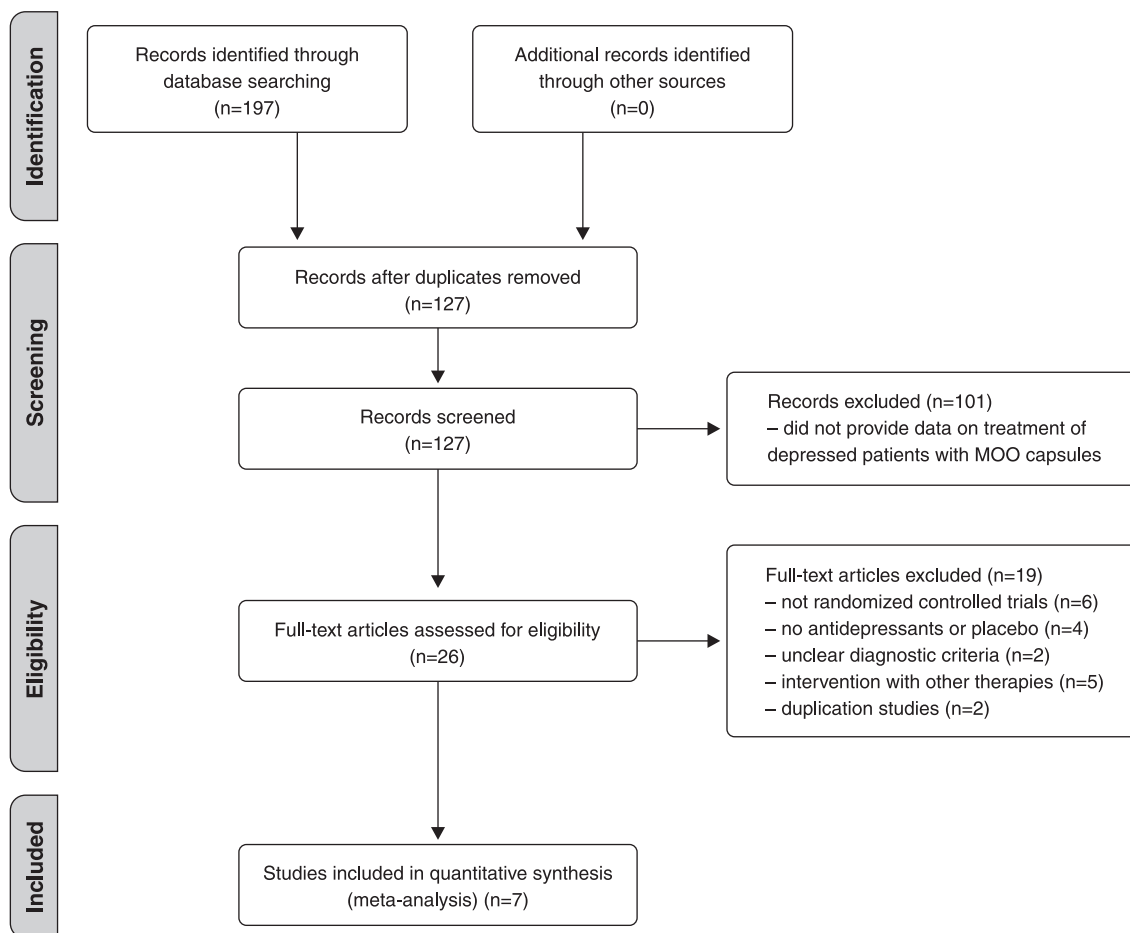
Figure 1 Flow diagram of the study search and selection process. MOO = *Morinda officinalis* oligosaccharide.

Table 1 Overview of included studies

Study	Diagnostic criteria for depressive disorder	Experimental drug (mg/d) Intervention group/control group/placebo group	Sample size	Duration (weeks)	Scales (percentage of achieving study-specific criteria of "clinical remission")	Dose escalation?
Kong[18]	ICD-10	MOO capsules 300→600	351	6	HAMD-17 (50%↓)	Yes End of 2 weeks SR < 30%
	HAMD score ≥ 18	Fluoxetine hydrochloride tablets 20→30	117			
		Placebo: MOO capsule simulant 300→600 Fluoxetine tablet simulant 20→30	119			
Zhang[19]	ICD-10	MOO capsules 300→600/ 400→800	119/119	6	HAMD-17 (50%↓)	Yes End of 2 weeks SR < 30%
	HAMD score: 18-24	Fluoxetine hydrochloride tablets 20→30	118			
Chen[20]	ICD-10	MOO capsules 300→600	30	8	HAMD-17 (30%↓)	Yes End of 2 weeks SR < 30%
	HAMD score: 18-24	Fluoxetine hydrochloride tablets 20→40	30			
		Placebo 2→4 pills	30			
Wu[21]	CCMD-3	MOO capsules 300	36	8	HAMD-17 (50%↓) TESS	No
	HAMD score > 17	Duloxetine capsules 120	36			
Li[23]	CCMD-3	MOO capsules 600	43	6	HAMD-17 (50%↓)	Yes Increase the dosage of control groups after one week
	HAMD score > 18	Escitalopram oxalate tablets 10→20	43			
Chen[22]	ICD-10	MOO capsules 300→600	35	6	HAMD-17 (50%↓)	Yes End of 2 weeks
	HAMD score: 17-24	Escitalopram oxalate tablets 10→20	34			
He[24]	ICD-10	MOO capsules 600	62	6	HAMD-17	No
		Agomelatine tablets 25	62			

→ increasing dosage to
CCMD-3 = The Chinese Classification and Diagnostic Criteria of Mental Disorder, third edition; HAMD = Hamilton Depression Scale; HAMD-17 = Hamilton Depression Scale 17-items; MOO = *Morinda officinalis* F.C.How oligosaccharides; SR = Score reduction; TESS = Treatment Emergent Symptom Scale.

if their score reduction (SR) was less than 30%. The durations of the trials were 8 weeks in two studies[20,21] and 6 weeks in the other five studies.

Outcome evaluation

All seven studies used the HAMD-17 to evaluate efficacy. The Treatment Emergent Symptom Scale (TESS) was applied to observe side effects only in Wu's study,[21] while no evaluation method was mentioned in the remaining studies.

Risk of bias and quality evaluation

The risk of bias assessment results for the 7 studies are shown in Figure S1, available as online-only supplementary material. Li XJ and Chen JY did not describe any details of the RCT method in their articles. The random grouping method was described only in He's and Wu's studies.[21,24] The double-blind method was reported in Kong's,[18] Zhang's,[19] and Chen's[20] articles, and Chen's[22] article clarified that no blinding method was applied during the research.

Overall, Chen's[22] study was judged to have a high risk of bias, the other six studies were judged as having an uncertain risk of bias, and no study was judged to have a low risk of bias. The weighted kappa value was used to test the consistency of the two evaluators (YD & QZ), and the result was kappa = 0.8. The funnel plot of efficiency was asymmetrical (Figure S2, available as online-only supplementary material). Publication bias detection was not possible as the number of included studies was fewer than 10.

According to the GRADE scoring principles, the overall quality of evidence for efficacy was assessed as moderate; however, the quality of evidence for side effects was assessed as low. These results are shown in Table 2.

Efficacy assessment

MOO capsules vs. antidepressants

All analyses are shown in Figure 2. Six[18-23] studies evaluated the therapeutic effect of MOO capsules based on the SR on the HAMD and set criteria for clinical remission. According to the different antidepressants used in the control groups, subgroup analysis was performed as follows: MOO capsules vs. fluoxetine hydrochloride, MOO capsules vs. escitalopram oxalate, MOO capsules vs. duloxetine, and MOO capsules vs. agomelatine.

Three studies[18-20] used fluoxetine hydrochloride tablets in the control groups. The fixed effect model was adopted with no overt heterogeneity (I^2 = 0% and p = 0.95). The results revealed no significant difference in efficacy between MOO capsules and fluoxetine hydrochloride (RR = 0.97, 95%CI 0.89-1.07). Two studies[22,23] used escitalopram oxalate tablets in the control groups. After the heterogeneity test (I^2 = 0% and p = 0.41), the fixed effect model was adopted for meta-analysis. The results suggested that the efficacy of escitalopram was not greater than that of MOO capsules (RR = 1.06, 95% CI 0.89-1.26). One[21] study compared efficacy between MOO capsules and duloxetine capsules, and the results showed no significant difference in efficacy between the two drugs (RR = 1.00, 95%CI 0.68-1.48). One[24] study compared efficacy between MOO capsules and agomelatine, and the results also showed no significant difference in efficacy between these two drugs (RR = 0.98, 95%CI 0.84-1.14).

Based on the meta-analysis of MOO capsules and antidepressants, the overall result (RR = 0.99, 95%CI 0.92-1.06) suggested no significant difference in efficacy between MOO capsules and antidepressants.

MOO capsules vs. placebo

Two studies[18,20] involving 530 patients used a placebo for the control groups. Because the heterogeneity was 92% ($>$ 75%), meta-analysis was not applied for these two studies. The results of comparative efficacy between MOO capsules and placebo are described in Table 3. Chen's study showed no difference between the two groups, while Kong's study showed a better outcome for MOO capsules than for the placebo.

Adverse events

Among the seven studies, the incidence of side effects was recorded in six. Based on the control type (placebo or antidepressants), two analyses were performed. As shown in Figure 3A, we found no significant difference in

Table 2 Summary of meta-analysis of different outcome indicators and GRADE ratings of evidence

Outcome	No. studies (sample size)	Heterogeneity test		Analysis model	Estimate	95%CI for estimate	GRADE rating
		I^2	p-value				
Efficacy							
MOO capsule vs. antidepressants	7 (1,111)	0%	0.92	Fixed	RR = 0.99	0.91-1.07	Moderate
MOO capsule vs. placebo	2 (530)	92%	0.00004	-	-	-	Moderate
Adverse reactions							
MOO capsule vs. antidepressants	6 (1,115)	0%	0.70	Fixed	RR = 0.84	0.65-1.07	Low
MOO capsule vs. placebo	2 (530)	0%	0.47	Fixed	RR = 0.86	0.57-1.29	Low

95%CI = 95% confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; MOO = *Morinda officinalis* oligosaccharides; RR = risk ratio.
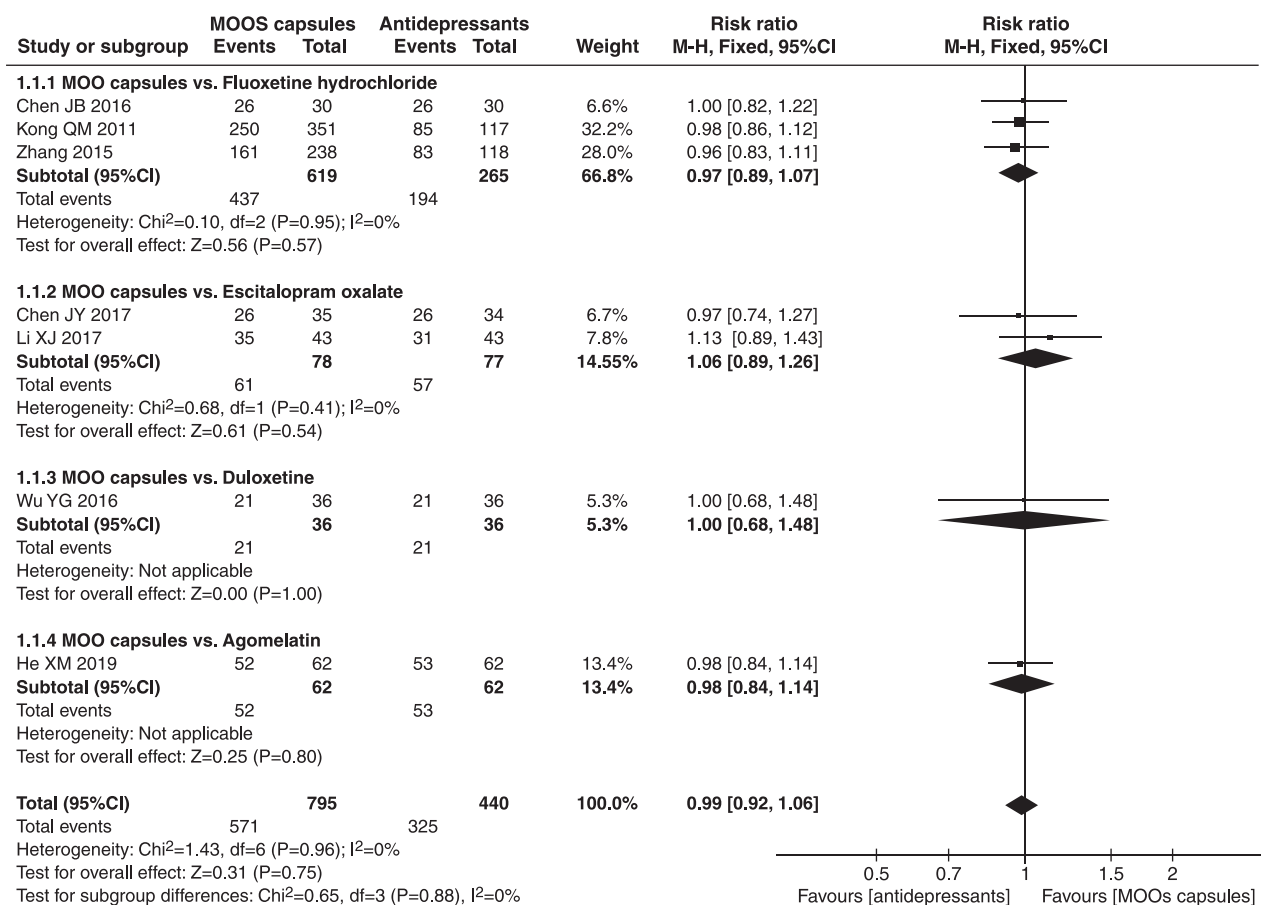
Figure 2 Forest plot of the efficacy of MOO capsules vs. antidepressants. 95%CI = 95% confidence interval; MOO = *Morinda officinalis* oligosaccharide.

adverse events between MOO capsules and placebo (RR = 0.86, 95%CI 0.57-1.29, I^2 = 0%). With respect to the difference in side effects between MOO capsules and antidepressants, the results showed no significant difference (RR = 0.84, 95%CI 0.65-1.07, I^2 = 0%). These results are shown in Figure 3B.

Discussion

This systematic review included seven studies, three[18-20] of which were multicenter clinical trials. All studies focused on moderate depressive disorder. The overall quality of these seven studies met the inclusion criteria of the Cochrane RoB Tool.

Non-inferiority trials are performed to observe whether one drug is not inferior to another drug, and are often used in clinical studies which employ definitively effective drugs as controls.[25] When the experimental drug is not inferior to the positive drug, the effectiveness of the experimental drug is shown. The articles included in this study were all RCTs with a non-inferiority trial design, using fluoxetine hydrochloride, duloxetine, escitalopram oxalate, or agomelatine as the positive control.

This study confirmed the efficacy of MOO in the treatment of depressive disorder. The overall effect value

was RR = 0.99 (95%CI 0.92-1.06). In addition, the GRADE rating of the quality of evidence for the efficacy of MOO was assessed as moderate, indicating that the results of the meta-analysis of this outcome were relatively credible. The results of the meta-analysis showed that the effect of MOO capsules was not different from that of antidepressant drugs, and Kong et al.[18] showed an effect significantly superior to that of placebo.

The incidence of adverse reactions to MOO capsules was not different from that of antidepressants (RR = 0.84, 95%CI 0.65-1.07). The results also showed no significant difference in adverse events between MOO capsules and placebo, which seems somewhat contradictory to clinical practice and is probably due to the lack of available literature, especially regarding comparisons of adverse reactions between MOO capsules and placebos. Analysis of the side effects of MOO capsules did not fully explain the problem, and showed only that the side effects of MOO capsules were not more obvious than those of antidepressants.

Thus, MOOs clearly had a positive effect on moderate depressive disorder, offering a new direction for the choice of clinical antidepressants and supporting the novel hypothesis of using a single TCM extract for the treatment of depressive disorder.

Table 3 Efficacy of MOO capsules vs. placebo

| Study | MOO capsules | | Placebo | | Risk ratio (95%CI) |
	Events	Total	Events	Total	
Chen[20]	26	30	23	30	1.13 (0.89-1.44)
Kong[18]	250	351	44	119	1.93 (1.51-2.46)

95%CI = 95% confidence interval; MOO = *Morinda officinalis* oligosaccharide.

A

| Study or subgroup | Experimental | | Control | | Weight | Risk ratio M-H, Fixed, 95%CI | Risk ratio M-H, Fixed, 95%CI |
	Events	Total	Events	Total			
Chen JB 2016	2	30	1	30	2.6%	2.00 [0.19, 20.90]	
Kong QM 2011	61	351	25	119	97.4%	0.83 [0.55, 1.25]	
Total (95%CI)		381		149	100.0%	**0.86 [0.57, 1.29]**	
Total events	63		26				

Heterogeneity: Chi^2=0.53, df=1 (P=0.47); I^2=0%
Test for overall effect: Z=0.73 (P=0.46)

Favours [MOO capsule]   Favours [placebo]

B

| Study or subgroup | MOO capsule | | Antidepressants | | Weight | Risk ratio M-H, Fixed, 95%CI | Risk ratio M-H, Fixed, 95%CI |
	Events	Total	Events	Total			
Chen JB 2016	2	30	3	30	2.8%	0.67 [0.12, 3.71]	
Chen JY 2017	9	35	9	34	8.5%	0.97 [0.44, 2.15]	
Kong QM 2011	61	351	27	117	37.7%	0.75 [0.50, 1.13]	
Li XJ 2017	7	43	10	43	9.3%	0.70 [0.29, 1.67]	
Wu YG 2016	2	36	6	36	5.6%	0.33 [0.07, 1.54]	
Zhang J 2015	59	240	29	120	36.0%	1.02 [0.69, 1.50]	
Total (95%CI)		735		380	100.0%	**0.84 [0.65, 1.07]**	
Total events	140		84				

Heterogeneity: Chi^2=3.00, df=5 (P=0.70); I^2=0%
Test for overall effect: Z=1.43 (P=0.15)
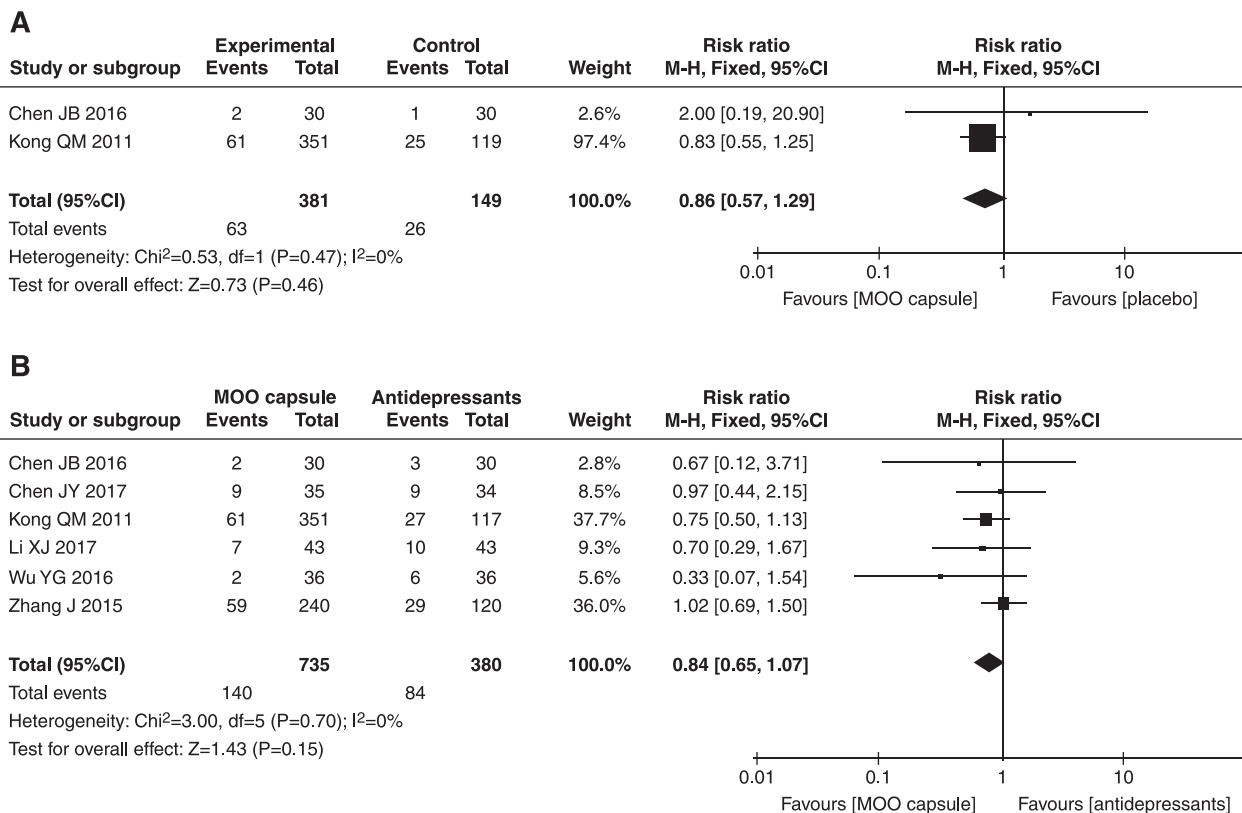
Favours [MOO capsule]   Favours [antidepressants]

Figure 3 A) Forest plot of adverse events of MOO capsules vs. placebo; B) Forest plot of adverse events of MOO capsules vs. antidepressants. 95%CI = 95% confidence interval; MOO = *Morinda officinalis* oligosaccharide.

Regarding safety, our results showed no significant difference in adverse reactions between MOO capsules and antidepressants. In the conventional view, natural products such as herbal extracts are expected to be safer; nevertheless, the results of our study could not be used to technically support this idea. The GRADE method assessed the quality of evidence for side effects as low. Thus, using these results to represent the overall side-effect profile of MOO capsules would be inappropriate. Furthermore, side effects in these studies were evaluated by only the number of incidents, and their severity was not evaluated; the articles simply mentioned that the degree of side effects from MOO capsules was lower than that from antidepressants. Therefore, further clinical trials are needed to thoroughly assess the safety of MOO. An accurate and detailed assessment scale should be used to evaluate the incidence and severity of side effects and then provide a more comprehensive and valid evaluation.

Other limitations exist. First, problems in the clinical research methods of currently published papers include unscientific randomization methods, poor allocation concealment, and imperfect quality control measures. In addition, high-quality RCTs of MOO capsules for depressive disorder are still very scarce. Second, the current studies lack clinical evaluations of sexual desire and improvement in sexual dysfunction. MOO is the extract of the TCM component Bajitian (the root of *M. officinalis*). As a representative drug used for tonifying the kidneys and strengthening *yang*, Bajitian is effective for treating sexual dysfunction, infertility and reproductive diseases, and a Raman spectroscopy analysis of MOO also showed that MOO can protect human sperm DNA.[26] Sexual dysfunction is also one of the main clinical symptoms of depressive disorder[27]; thus, the effect of MOO capsules on improving libido should have been assessed in trials on depressive disorder. From the results of these published articles, the clinical advantages of MOO have not been fully demonstrated. Third, all included participants were Chinese. Our conclusions are based on clinical trials in Chinese populations; thus, caution should be exercised in extending the results to other ethnic groups.

Therefore, additional high-quality, multicenter, randomized controlled studies with larger samples, use of detailed scales to assess side effects, and evaluation of sexual function are urgently needed to further clarify and explore the efficacy, safety, and potential unique advantages of MOO in the treatment of depressive disorder.

In conclusion, this systematic review suggests that the efficacy of MOO capsules in the treatment of mild to moderate depression is not inferior to that of conventional antidepressants, which may provide a new direction for clinical alternative selection of antidepressants. However, additional high-quality studies with detailed assessments are needed.

Acknowledgements

Disclosure

The authors report no conflicts of interest.

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