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ORIGINAL ARTICLE

A Randomized, Double-Blind, Positive-Controlled, Multicenter Clinical Trial on the Efficacy and Safety of ShuganJieyu Capsule and St. John's Wort for Major Depressive Disorder with Somatic Complaints

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Abstract

Previous studies have found the effect of ShuganJieyu capsule and St. John's wort on the treatment of depression and explored their potential benefits for somatic symptoms, while the evidence of comparison of them for depression with somatic complaints is lacking. In this multicenter randomized controlled trial, 198 major depressive disorder (MDD) patients with somatic complaints were randomly allocated, 92 in the ShuganJieyu capsule group, and 91 in the St. John's wort group completed 8 weeks treatment. Primary outcome was the change score of the 17-item Hamilton Depression Rating Scale (HDRS-17) at week 8. Secondary outcomes included other indices of depression, somatic symptoms, anxiety, insomnia, quality of life, and adverse events. The change scores of HDRS-17 were not significantly difference between the two groups, but the reduction in HDRS-17 was significantly improved in both the ShuganJieyu capsule (HDRS-17$\Delta = -11.35 \pm 5.38$, $p < 0.001$) and St. John's wort (HDRS-17$\Delta = -11.20 \pm 5.71$, $p < 0.001$) groups. The other outcomes showed similar results. Compared with St. John's wort, the ShuganJieyu capsule induced significantly greater HDRS-17 reductions in male (SMD, −0.55; 95% CI, −1.08 to −0.02) but not in female. Overall, The ShuganJieyu capsule was comparable to St. John's wort as a complementary and alternative intervention for MDD patients with somatic complaints in the acute treatment, especially for male patients.

Keywords Major depressive disorder · Somatic complaints · Randomized controlled trial · ShuganJieyu capsule · St. John's wort

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Major depression disorder (MDD) is a common debilitating mental disease that severely limits an individual's psychosocial functioning and reduces quality of life (Marx et al., 2023). Somatization is one of the most common complaints in patients with MDD, which include insomnia, dizziness, headache, fatigue, and gastrointestinal complaints. Approximately 69% of depressed patients exhibit unexplained somatic symptoms (Vaccarino et al., 2008), which can lead to longer convalescence, higher costs, and fatal consequences due to misdiagnosis. Moreover, patients who could not achieve remission after taking antidepressants experience significantly more somatic symptoms than those who achieved remission (Bekhuis et al., 2016a, 2016b).

Pharmacotherapy is the most frequently used for the treatment of depression and somatic symptoms in primary care (Albus & Geiser, 2019; Collins et al., 2022). Traditional Chinese medicine has become well recognized for its safety and effectiveness in alleviating symptoms of depression (Butler & Pilkington, 2013; Q. Fan et al., 2023). The ShuganJieyu capsule is the only pure herbal pharmaceutical product that has been approved by the China Food and Drug Administration for the treatment of depression (Zhang et al., 2014). St. John's wort is also a herbal product, which is licensed for the treatment of depression according to international guidelines (Qaseem et al., 2016; Ravindran et al., 2016), and the efficacy and safety of St. John's wort for depression with somatic symptoms have also been demonstrated from the published papers (Woelk, 2000). Their main components are both *Hypericum perforatum* (Apaydin et al., 2016; Zhang et al., 2014) and ShuganJieyu capsule that is mixed St. John's wort with *Acanthopanax senticosus* (Zhang et al., 2014). Previous studies showed the effects of *Hypericum perforatum* for the treatment of somatic symptoms, such as insomnia and headaches (M. Fan et al., 2021; Hubner et al., 1994; Murck, 2002). These results indicated that the ShuganJieyu capsule may suit for the major depressive disorder with somatic complaints.

Although the efficacy of the ShuganJieyu capsule and St. John's wort for the treatment of depression has been proved, and their potential benefits for somatic symptoms have also been investigated, there is no report on the comparison of ShuganJieyu Capsule and St. John's wort in the treatment of depression with somatic complaints. This study aimed to evaluate the efficacy and safety of the ShuganJieyu capsule and St. John's wort in the treatment of depression with somatic complaints and provide evidence for clinical practice.

Material and Methods

Study Design and Participants

This randomized controlled trial (RCT) was designed by the Society of Neuropsychological and Affective Disorders, Chinese Neurology Association, Chinese Medical Doctor Association. We conducted an 8-week randomized, double-blind, positive-controlled, multicenter clinical trial across nine clinical centers in China (Xuanwu Hospital of Capital Medical University, The First Hospital of Shanxi Medical University, The Shijiazhuang First Hospital, The Third People's Hospital of Chengdu, The First Hospital of Jilin University, Beijing Tiantan Hospital of Capital Medical University, The First Hospital of Hebei Medical University, Beijing Friendship Hospital of Capital Medical University, and The Second Affiliated Hospital of Harbin Medical University) after approval by the institutional review boards. An independent data and safety monitoring board guarded the study. The protocol was registered in the Chinese Clinical Trial Registry (ChiCTR1800017827). The

study was reported according to the CONSORT guidelines. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by Xuanwu Hospital Capital Medical University (LYS2018018). All subjects provided written informed consent before their participation.

Adults were eligible if they (1) had a diagnosis of MDD with first single episode as determined by the Mini-International Neuropsychiatric Interview (MINI) (Wang et al., 2022), adapted with reference to the Diagnostic and Statistical Manual, fifth edition criteria (Wang et al., 2022); (2) were diagnosed with the syndrome of liver-chi stagnation and spleen deficiency in traditional Chinese medicine (Zheng, 2002); (3) had depressive symptoms defined by a score of ≥ 17 points on the 17-item Hamilton Depression Rating Scale (HDRS-17) (Wang et al., 2022); (4) experienced somatic symptoms, such as insomnia, tension-type headache, migraine, repeated tinnitus, chronic dizziness, fatigue, and chronic pain without explicit organic damage; (5) had a score of ≥ 5 points on the 15-item Patient Health Questionnaire (PHQ-15) (Wang et al., 2020); and (6) aged between 18 and 60 years. Patients were excluded if (1) their depression was caused by psychoactive drugs; (2) their depression was induced by any brain organic diseases; (3) they had secondary depression induced by hypothyroidism, hypothyroidism, or other endocrine disorders; (4) they had schizophrenia, bipolar disorder, somatoform disorder, mania, anorexia, bulimia or any other type of mental illness based on the MINI; (5) they had strong suicidal tendencies (HDRS-17 suicide score of ≥ 4 points); (6) they abused substances; (7) they had received neurosurgery or electroconvulsive therapy in the previous 3 months; (8) they had taken drugs that could interfere with the therapeutic evaluation of the test drug or were contraindicated with the test drug or antidepressants in the previous 4 weeks; (9) they were allergic to the known ingredients of the test drug or had serious side effects after taking the test drug; and (10) they were pregnant and breastfeeding or planning to become pregnant in the following 6 months.

Randomization and Masking

Participants were randomly assigned (1:1) to receive the ShuganJieyu capsule plus the St. John's wort simulant or St. John's wort plus the ShuganJieyu capsule simulant. Random allocation was stratified by clinical center and performed using a computer-generated randomization sequence with randomly block size of 4 within each stratum, which was supervised by an external independent statistician with strict concealment of allocation. Participants, clinicians, and data managers were masked to treatment assignment throughout the study. Treatment was double-blind (masking was achieved by administering tablets with identical appearance); only the database administrator and research pharmacists had knowledge of the treatment allocation.

Procedures

In the 8-week randomization phase, target doses were two capsules (0.72 g) twice a day for the ShuganJieyu capsule and one tablet (0.56 g) twice a day for St. John's wort. Participants attended interviews at screening, baseline, week 4 and week 8 after treatment, during which they completed assessments with clinicians. Visits consisted of laboratory examination, electrocardiogram, assessments of depressive symptoms, somatic symptoms, anxiety

symptoms, sleep quality, quality of life, medication side effects, and routine management of any participant concerns.

Outcomes

Primary outcome was the change of HDRS-17 score (Wang et al., 2022) at week 8. The change was decided by the reduction in HDRS-17 score from baseline to week 8, which provided an interviewer-rated measure of depressive symptom severity. Secondary outcomes were somatic symptoms assessed by the PHQ-15 (Wang et al., 2020); the change of HDRS-17 at week 4, response and reduction rates of HDRS-17, and changes in anxiety symptom severity assessed by the Hamilton Anxiety Scale (HAMA) (Thompson, 2015); response rates of Clinical Global Impression-Improvement (CGI-I) score, changes in the Clinical Global Impression-Severity (CGI-S) (McCall et al., 2019); and others included the Pittsburgh Sleep Quality Index (PSQI) (Wang et al., 2020), the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) (Foa et al., 2022), and adverse events measured by the Treatment Emergent Symptoms Scale (TESS) (NIMH, 1982) at weeks 4 and 8. Response was defined as a 50% or more reduction in HDRS-17 score. Reduction rate was calculated by the percentage change in HDRS-17 score. CGI-I response was defined as a CGI-I score of 1 (very much improved) or 2 (much improved). All outcomes were evaluated from baseline to weeks 4 and 8.

Statistical Analysis

Sample was calculated via two-sample *t*-tests assuming equal variance of PASS 2018. In our pilot study, the mean reduction in HDRS-17 score from baseline to week 8 was 18.60 points (standard deviations [SD] = 4.60) in the ShuganJieyu capsule group and 16.38 point (SD = 3.80) in the St. John's wort group. A difference of 2.22 points between groups was applied to calculate the sample size, assuming a standard deviation of 4.60 points. The analysis revealed that a total of 138 participants (69 per group) would provide a power of approximately 80% at a two-tailed significance level of 5%. The minimum sample size was increased by 20% for the study dropout to 87 participants per group (for a total of 174 participants). The final total sample of 200 was determined based on the funding. Efficacy outcomes were analyzed for intention-to-treat (ITT) and pre-protocol (PP) populations, and safety outcomes were analyzed in a safety set (patient received at least once treatment and had recorded safety data). Baseline demographic and clinical characteristics were compared between the ShuganJieyu capsule and St. John's wort groups. We described continuous variables as means (standard difference [SD]) or medians (interquartile ranges [IQR]) and categorical variables as *n* (%). Binary outcomes were assessed using Pearson's chisquared or Fisher's exact tests and included the response rate and the proportion of participants reporting adverse events. For continuous outcomes, paired-samples *t*-tests and Wilcoxon Mann–Whitney tests were used to compare differences between pre- and post-treatment, and independent-samples *t*-tests and Wilcoxon Mann–Whitney tests for inter-group comparisons. Repeated-measures mixed-effects linear models were used to test for treatment group (ShuganJieyu Capsule or St. John's wort), time point (baseline, week 4, and week 8), and treatment group × time interactions. All statistical analyses were conducted in SAS (version 9.4) using two-tailed tests, and $p < 0.05$ denoted statistical significance.

Results

Recruitment and Baseline Characteristics

We recruited participants from December 2018, and the last interviews were completed by December 2020. Participant recruitment is presented in Fig. 1. Of the 205 patients who completed the screening, five were ineligible and two declined to participate in the study. Thus, a total of 198 participants were randomized into the ShuganJieyu capsule ($n=99$) or St. John's wort group ($n=99$). A total of 183 (92.4%) participants (92 in the ShuganJieyu capsule group and 91 in the St. John's wort group) completed 8-week trial.

Table 1 shows the demographic characteristics of 198 participants at baseline. The median age was 41.52 years (IQR, 30.55–52.91 years), 70.71% were women, and 94.95% were Han nationality. The median body mass index was 22.72 (IQR, 20.75–25.04) kg/m^2, the median HDRS-17 score was 20.00 (IQR, 18.00–23.25), and the median somatic symptoms scores were 13.00 (IQR, 11.00–16.00) on the PHQ-15. There were no significant differences in baseline variables between two arms (all $p>0.05$).

Clinical Outcomes

Table 2 presents the ITT analysis of the primary and secondary outcomes at baseline, week 4, and week 8. At week 8, the HDRS-17 score significantly decreased from baseline in both the ShuganJieyu capsule (HDRS-17$\Delta=-11.35\pm5.38$, $p<0.001$) and St. John's wort (HDRS-17$\Delta=-11.20\pm5.71$, $p<0.001$) groups. The same changes at week 4 were observed in both the ShuganJieyu capsule (HDRS-17$\Delta=-7.63\pm4.41$, $p<0.001$) and St. John's wort (HDRS-17$\Delta=-7.78\pm4.62$, $p<0.001$) groups. But no difference on changes

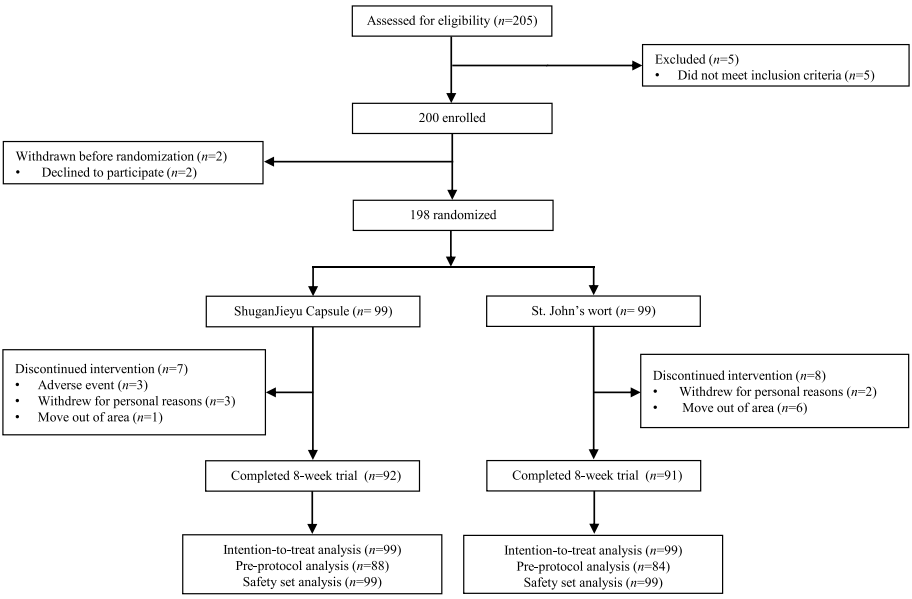

Fig. 1 Consolidated standards of reporting trials flow diagram

Table 1 Baseline demographic and clinical characteristics of participants

Variables	Total ($n=198$)	ShuganJieyu capsule ($n=99$)	St. John's wort ($n=99$)	p value
Mean age, M (Q1, Q3), Y	41.52 (30.55, 52.91)	40.92 (30.40, 54.64)	42.10 (30.60, 52.54)	0.922
Gender, no. (%)				
Male	58 (29.29)	30 (30.30)	28 (28.28)	0.755
Female	140 (70.71)	69 (69.70)	71 (71.72)	
BMI, M (Q1, Q3), kg/m^2	22.72 (20.75, 25.04)	22.72 (20.80, 24.46)	22.72 (20.70, 25.39)	0.615
Ethnicity, no. (%)				
Han nationality	188 (94.95)	93 (93.94)	95 (95.96)	0.516
Minority nationality	10 (5.05)	6 (6.06)	4 (4.04)	
Education, no. (%)				
≤High school	69 (34.85)	39 (39.39)	30 (30.30)	0.299
Junior college	52 (26.26)	23 (23.23)	29 (26.26)	
Bachelor's degree	61 (30.81)	27 (27.27)	34 (34.34)	
Advanced degree	16 (8.08)	10 (10.10)	6 (6.06)	
Marital status, no. (%)				
Married	149 (75.25)	75 (75.76)	74 (74.75)	0.869
Unmarried	49 (24.75)	24 (24.24)	25 (25.25)	
Employment, no. (%)				
Employed	151 (76.26)	75 (75.76)	76 (76.77)	0.867
Unemployed	47 (23.74)	24 (24.24)	23 (23.23)	
Co-prescriptions for other disease, no. (%)	18 (9.09)	8 (8.08)	10 (10.10)	0.621
Yes	180 (90.91)	91 (91.92)	89 (89.90)	
No	20.00 (18.00, 23.25)	20.00 (18.00, 23.00)	20.00 (18.00, 24.00)	0.782
HDRS-17, M (Q1, Q3)	18.00 (14.00, 23.00)	18.00 (15.00, 23.00)	17.00 (13.00, 22.00)	0.258
PHQ-15, M (Q1, Q3)	4.00 (3.00, 4.00)	4.00 (3.00, 4.00)	4.00 (3.00, 4.00)	0.555
HAMA, M (Q1, Q3)	13.00 (11.00, 16.00)	13.00 (11.00, 16.00)	13.00 (11.00, 16.00)	0.585
CGI-S, M (Q1, Q3)	13.00 (10.00, 15.00)	13.00 (10.00, 16.00)	12.00 (10.00, 15.00)	0.168
PSQI, M (Q1, Q3)	41.24 (7.18)	41.12 (7.55)	41.35 (6.83)	0.821
Q-LES-Q-SF, mean (SD)	41.52 (30.55, 52.91)	40.92 (30.40, 54.64)	42.10 (30.60, 52.54)	0.922

Data are means (standard deviations), *n* (%), or medians (interquartile ranges)

BMI body mass index, *HDRS-17* 17-item Hamilton Depression Rating Scale, *PHQ-15* 15-item Patient Health Questionnaire, *HAMA* Hamilton Anxiety Rating Scale, *CGI-S* Clinical Global Impression-Severity, *PSQI* Pittsburgh Sleep Quality Index, *Q-LES-Q-SF* Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form

in HDRS-17 score between the two groups was statistically significant at the post-treatment assessment (week 4, $p=0.953$; week 8, $p=0.814$). For somatic symptoms, both groups demonstrated no significance on changes of PHQ-15 at week 8 and 4 (week 4, $p=0.133$; week 8, $p=0.309$), but both had statistical reductions on PHQ-15 at week 8 in comparison with those at baseline (the ShuganJieyu capsule: PHQ-15$\Delta=-6.26\pm4.34$, $p<0.001$; the St. John's wort: PHQ-15$\Delta=-5.75\pm3.86$, $p<0.001$).

Table 2 Intention-to-treat analysis of primary and secondary outcomes across time

Variables	Assessment time points			Change of pre- and post- treatment		*p* value between groups	
	Baseline	Week 4	Week 8	ΔBaseline and week 4 (*p* value)	ΔBaseline and week 8 (*p* value)	Change of baseline and week 4	Change of baseline and week 8
HDRS-17, mean ± SD							
ShuganJieyu capsule (*n* = 99)	21.14 ± 3.92	13.52 ± 5.20	9.79 ± 5.38	− 7.63 ± 4.41 (< 0.001)	− 11.35 ± 5.38 (< 0.001)	0.953	0.814
St. John's wort (*n* = 99)	21.33 ± 4.03	13.56 ± 5.24	10.13 ± 5.63	− 7.78 ± 4.62 (< 0.001)	− 11.20 ± 5.71 (< 0.001)		
PHQ-15, mean ± SD							
ShuganJieyu Capsule (*n* = 99)	13.85 ± 3.71	9.57 ± 3.81	7.55 ± 4.14	− 4.41 ± 3.75 (< 0.001)	− 6.26 ± 4.34 (< 0.001)	0.133	0.309
St. John's wort (*n* = 99)	13.59 ± 3.72	10.16 ± 3.94	8.07 ± 4.41	− 3.44 ± 3.12 (< 0.001)	− 5.75 ± 3.86 (< 0.001)		
HDRS-17 response, no. (%)							
ShuganJieyu capsule (*n* = 99)	NA	28 (28.28)	64 (64.65)	NA	< 0.001[a]	0.896[b]	0.543[c]
St. John's wort (*n* = 99)	NA	27 (27.27)	61 (61.62)	NA	< 0.001[a]		
HDRS-17 reducing rate, mean ± SD							
ShuganJieyu capsule (*n* = 99)	NA	36.32 ± 20.83	53.71 ± 23.78	NA	< 0.001[a]	0.924[b]	0.826[c]
St. John's wort (*n* = 99)	NA	36.60 ± 20.81	52.47 ± 24.11	NA	< 0.001[a]		
HAMA, mean ± SD							
ShuganJieyu Capsule (*n* = 99)	19.46 ± 6.77	13.41 ± 6.84	9.56 ± 6.80	− 6.23 ± 5.30 (< 0.001)	− 10.10 ± 6.59 (< 0.001)	0.364	0.279
St. John's wort (*n* = 99)	18.71 ± 7.38	13.00 ± 6.25	9.78 ± 5.72	− 5.79 ± 5.14 (< 0.001)	− 9.38 ± 6.11 (< 0.001)		
CGI-I response[d], no. (%)							
ShuganJieyu Capsule (*n* = 99)	NA	44 (44.44)	58 (58.60)	NA	< 0.001[a]	0.616[b]	0.333[c]
St. John's wort (*n* = 99)	NA	41 (41.41)	63 (63.64)	NA	< 0.001[a]		

Table 2 (continued)

Variables	Assessment time points			Change of pre- and post- treatment		*p* value between groups	
	Baseline	Week 4	Week 8	ΔBaseline and week 4 (*p* value)	ΔBaseline and week 8 (*p* value)	Change of baseline and week 4	Change of baseline and week 8
CGI-S, mean ± SD							
ShuganJieyu capsule (*n* = 99)	3.84 ± 0.85	3.12 ± 0.78	2.45 ± 0.97	− 0.73 ± 0.82 (< 0.001)	− 1.37 ± 1.17 (< 0.001)	0.666	0.761
St. John's wort (*n* = 99)	3.94 ± 0.91	3.13 ± 0.86	2.57 ± 1.01	− 0.80 ± 0.92 (< 0.001)	− 1.40 ± 1.17 (< 0.001)		
PSQI, mean ± SD							
ShuganJieyu capsule (*n* = 99)	12.80 ± 3.55	9.51 ± 3.67	6.91 ± 3.60	− 3.36 ± 3.49 (< 0.001)	− 5.97 ± 4.05 (< 0.001)	0.950	0.415
St. John's wort (*n* = 99)	12.25 ± 3.15	8.96 ± 3.41	6.98 ± 3.43	− 3.34 ± 3.06 (< 0.001)	− 5.50 ± 3.86 (< 0.001)		
Q-LES-Q-SF, mean ± SD							
ShuganJieyu capsule (*n* = 99)	41.12 ± 7.55	48.44 ± 7.17	53.14 ± 7.83	7.66 ± 5.98 (< 0.001)	12.15 ± 7.72 (< 0.001)	0.898	0.841
St. John's wort (*n* = 99)	41.35 ± 6.83	49.23 ± 7.71	52.53 ± 8.71	7.92 ± 5.86 (< 0.001)	11.89 ± 7.20 (< 0.001)		

Data are means ± standard deviations or *n* (%)

HDRS-17 17-item Hamilton Depression Rating Scale, *PHQ-15* 15-item Patient Health Questionnaire, *HAMA* Hamilton Anxiety Rating Scale, *CGI-I* Clinical Global Impression-Improvement, *CGI-S* Clinical Global Impression-Severity, *PSQI* Pittsburgh Sleep Quality Index, *Q-LES-Q-SF* Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form, *SD* standard deviation

[a]Between weeks 4 and 8

[b]Difference between intervention groups in week 4

[c]Difference between intervention groups in week 8

[d]CGI-I response was defined as a CGI-I score of 1 (very much improved) or 2 (much improved)

For other secondary outcomes, HDRS-17 response and reduction rates were significant improvements at post-treatment in both the ShuganJieyu capsule and St. John's wort groups (all $p < 0.001$). But there were no significant differences between the ShuganJieyu capsule and St. John's wort groups for response (week 4, $p = 0.896$; week 8, $p = 0.543$) or reduction rate (week 4, $p = 0.924$; week 8, $p = 0.826$) from baseline to post-treatment. At weeks 4 and 8, the two groups showed significant improvements in HAMA, CGI-I response, CGI-S, PSQI, and Q-LES-Q-SF scores from baseline (all $p < 0.001$). Participants in both groups showed improvements in anxiety symptoms, sleep quality, and quality of life after the intervention. However, none of these outcomes was significantly different between the two groups at week 4 or 8 (all $p > 0.05$; Table 2).

Furthermore, the PP population analysis of primary and secondary outcomes showed similar results (eTable 1 in Supplement 1). The eFig. 1 in Supplement 1 shows the changes of all rating scale scores over time, with comparisons between the ShuganJieyu capsule and St. John's wort groups. The mixed-effects models showed no significant time × treatment interactions for any of the rating scale scores at any assessment time point (eTable 2 in Supplement 1).

Non-prespecified and Post Hoc *Outcomes*

Sex significantly modified the effect of the treatment on the HDRS-17 change score at week 8. Compared with St. John's wort, the ShuganJieyu capsule induced significantly greater HDRS-17 reductions in male patients (standard mean difference [SMD], −0.55; 95% CI, −1.08 to −0.02) but not in female patients (SMD, 0.23; 95% CI, −0.12 to 0.57; Fig. 2). No significant differences were found between male and female patients in any of the baseline characteristics, which included age, body mass index, ethnicity, education, marital status, employment, and co-prescriptions, or baseline HDRS-17, PHQ-15, HAMA, CGI-S, PSQI, and Q-LES-Q-SF scores (all $p > 0.05$). Other factors, such as age, ethnicity, education, marital status, employment, co-prescriptions, and baseline HDRS-17 and PHQ-15 scores, did not significantly modify the treatment effect on the change of HDRS-17 score at week 8 (Fig. 2).

Post hoc subgroup analyses were performed separately for HDRS-17 (< 24 vs. ≥ 24) and PHQ-15 (< 15 vs. ≥ 15) scores on HDRS-17, PHQ-15, HAMA, CGI-I, CGI-S, PSQI, and Q-LES-Q-SF change scores, and also the quality and patterns of sleep based on the PSQI, which included seven components: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. For patients who scored higher than 15 on the PHQ-15, the ShuganJieyu capsule group showed a reduction in PSQI sleep latency scores compared with those of the St. John's wort group at week 8 ($p = 0.044$). There were no significant differences on baseline characteristics between patients who scored less than 15 and those who scored higher than 15 on the PHQ-15 (all $p > 0.05$). No other subgroups showed significant differences between the treatments (eTable 3 and eTable 4 in Supplement 1).

Intervention Adherence and Adverse Events

Among the 99 ShuganJieyu capsule group participants, seven (7.1%) did not adhere to the treatment schedule. Of seven, three discontinued treatment due to adverse events (two were related to the study medication), three withdrew for personal reasons, and one moved out of area. Eight of 99 (8.1%) in St. John's wort group did not stand by the treatment schedule.

	ShuganJieyu Capsule group		St. John's Wort group			
	No. of Patients	Mean Change Score (SD)	No. of Patients	Mean Change Score (SD)	8-week Standardised Mean Difference (95% CI)	P Value for Interaction
Gender						
Male	29	−14.24 (4.01)	27	−11.67 (5.17)	−0.55 (−1.08 to −0.02)	.039
Female	65	−10.54 (5.29)	65	−11.80 (5.61)	0.23 (−0.12 to 0.57)	
Age group, y						
18-35	30	−10.60 (6.00)	33	−11.61 (5.56)	0.17 (−0.32 to 0.67)	.365
35-50	31	−12.84 (4.73)	31	−10.26 (6.56)	−0.45 (−0.95 to 0.06)	
≥50	33	−11.58 (4.76)	28	−13.61 (3.13)	0.49 (−0.02 to 1.00)	
Ethnicity						
Han nationality	88	−11.57 (5.22)	88	−11.88 (5.45)	0.06 (−0.24 to 0.35)	.245
Minority nationality	6	−13.33 (5.05)	4	−9.25 (5.91)	−0.68 (−2.01 to 0.64)	
Education						
≤High school	36	−11.08 (4.42)	30	−13.00 (4.44)	0.43 (−0.06 to 0.92)	.416
Junior college	23	−13.35 (6.78)	25	−10.48 (6.12)	−0.44 (−1.01 to 0.14)	
Bachelor's degree	26	−11.35 (4.60)	31	−11.87 (6.12)	0.09 (−0.43 to 0.62)	
Advanced degree	9	−10.78 (5.07)	6	−10.33 (1.86)	−0.10 (−1.14 to 0.93)	
Marital status						
Married	71	−12.07 (5.48)	70	−11.73 (5.11)	−0.06 (−0.39 to 0.27)	.301
Unmarried	23	−10.48 (4.12)	22	−11.86 (6.59)	0.25 (−0.34 to 0.83)	
Employment						
Employed	70	−11.57 (5.49)	69	−11.23 (5.94)	−0.06 (−0.39 to 0.27)	.880
Unemployed	24	−12.00 (4.33)	23	−13.35 (3.26)	0.35 (−0.23 to 0.92)	
Co-prescriptions for other disease						
Yes	86	−11.81 (5.31)	84	−11.65 (4.83)	−0.03 (−0.33 to 0.27)	.117
No	8	−10.25 (3.92)	8	−12.88 (10.48)	0.31 (−0.67 to 1.30)	
HDRS-17 Score						
HDRS-17<24	73	−10.71 (4.94)	65	−10.80 (4.13)	0.02 (−0.31 to 0.35)	.239
HDRS-17≥24	21	−15.05 (4.78)	27	−14.07 (7.38)	−0.15 (−0.72 to 0.42)	
PHQ-15 Score						
PHQ-15<15	57	−10.96 (4.95)	60	−11.80 (4.87)	0.17 (−0.19 to 0.53)	.048
PHQ-15≥15	37	−12.78 (5.46)	32	−11.69 (6.51)	−0.18 (−0.65 to 0.29)	

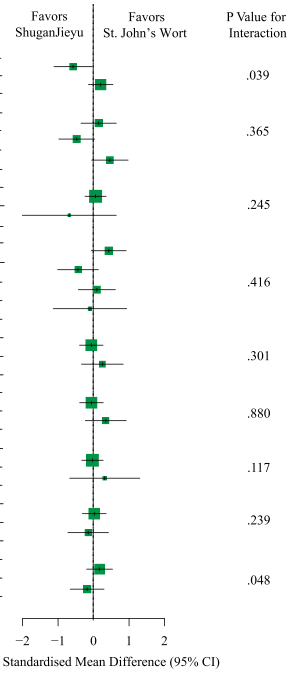

Fig. 2 Non-prespecified and post hoc outcomes for HDRS-17 score at week 8. We calculated the effect sizes and pooled effect estimates across subgroups using a random-effects model. The standardized mean differences (SMD, Cohen's *d*) and 95% confidence intervals (95% CI) are summarized. The *p* values for the interaction terms of the modifier and study group were obtained from the mixed-effects models. SD, standard deviation; 95% CI, 95% confidence intervals; HDRS-17, 17-item Hamilton Depression Rating Scale; PHQ-15, 15-item Patient Health Questionnaire

Of them, six moved into other cities and two withdrew for personal reasons. Fourteen adverse events were reported in 13 (13.1%) patients during the 8-week treatment; of these, eight were in the ShuganJieyu capsule group and six were in the St. John's wort group. Two (1.0%) were related to the study medications and included skin rash and blurred vision, both of which were in ShuganJieyu capsule group. No serious adverse events were reported during the study. All details of adverse events are presented in Table 3, and no significant differences were observed between the two intervention groups (all $p > 0.05$).

Discussion

Depressive disorder in Chinese adults is a leading cause of years lived with disability, with a lifetime prevalence of 6.8% and only 0.5% (12 of 1,007) adequately treatment in the past 12 months (Lu et al., 2021). Somatization symptoms are common yet rarely emphasized complaints in patients with MDD and have been proposed as targets for the treatment of MDD (Bekhuis et al., 2016a, 2016b). To the best of our knowledge, this is the first randomized, double-blind, positive-controlled clinical trial comparing the ShuganJieyu capsule with St. John's wort in MDD patients with somatic symptoms. Our study revealed three

Table 3 Adverse events during the treatment phase

Adverse events	Number of participants reporting each adverse event (%)		*p* value
	ShuganJieyu capsule ($n=99$)	St. John's wort ($n=99$)	
All adverse events	8 (8.08)	6 (6.06)	0.774
AEs related to the study medication	2 (2.02)	0 (0.00)	0.477
AEs leading to discontinuation	3 (3.03)	0 (0.00)	0.245
Severe adverse events	0 (0.00)	0 (0.00)	1.000
Adverse events in detail			
Hyperhomocysteinemia	0 (0.00)	1 (1.01)	0.316
Infectious disease	2 (2.02)	1 (1.01)	0.081
Weight gain	0 (0.00)	1 (1.01)	0.316
Hypnosia	0 (0.00)	1 (1.01)	0.316
Headache	0 (0.00)	1 (1.01)	0.316
Fracture	1 (1.01)	0 (0.00)	0.316
Insomnia	1 (1.01)	0 (0.00)	0.316
Skin rash	1 (1.01)	0 (0.00)	0.316
Nausea	1 (1.01)	0 (0.00)	0.316
Vomiting	1 (1.01)	0 (0.00)	0.316
Stomachache	0 (0.00)	1 (1.01)	0.316
Blurred vision	1 (1.01)	0 (0.00)	0.316

Data are means and *n* (%)

AEs adverse events

main findings. First, the ShuganJieyu Capsule and St. John's wort showed significant effectiveness in improving depressive and somatic symptoms. Second, both of them were also effective for anxiety symptoms, sleep quality and quality of life. Third, male patients and patients who had a score higher than 15 on the PHQ-15 may benefit more from the ShuganJieyu capsule. Taken together, our findings suggested that the ShuganJieyu capsule was comparable to St. John's wort as a complementary and alternative intervention for MDD with somatic symptoms in the acute treatment, especially for male patients.

Our study showed that about two-thirds of patients achieved response after 8 weeks of treatment with the ShuganJieyu capsule (64.7%), which was similar to the published systematic analysis on the response rate of 68.5% for ShuganJieyu capsule in 595 MDD participants across seven double-blind RCTs (Zhang et al., 2014). Also, the study revealed that 61.6% patients in St. John's wort obtained the response, which was lower than that of St. John's wort for depressive patients (81.0%) in the previous RCT (Hansgen et al., 1994). One possible explanation is that the target patients in our study were MDD with somatic complaints, which were more complicated than MDD patients without somatic complaints, such as were associated with more severe depression of longer duration, greater functional impairment, and poorer clinical outcome (Vaccarino et al., 2008). In addition, ethnicity may influence the somatic and psychiatric presentation of depression, for example, Asian patients are more likely to report somatic symptoms than emotional/mood symptoms (Novick et al., 2015). As the Chinese are the world's largest ethnic group (accounting for

18.8% of the global population), a better understanding of treatment of MDD patients with somatic complaints in Chinese has the potential to impact a large number of people.

The ShuganJieyu capsule is composed mainly of extracts of guanye jinsitao (*Hypericum perforatum*) and ciwujia (*Acanthopanax senticosus*) (Feng et al., 2016); the former is also the main component of St. John's wort, which has been used as a herbal remedy for many centuries. The potential mechanisms of antidepressant action of *Hypericum perforatum* include a direct effect on serotonin receptors, monoamine oxidase inhibition, and neuroendocrine and ion channel modulation (Ravindran et al., 2016). This may explain why ShuganJieyu capsule induces similar effects to those induced by St. John's wort. St. John's wort has been shown to be significantly superior to placebo and comparable to other antidepressants, such as fluoxetine, sertraline, and imipramine, in the treatment of MDD (Linde et al., 2005; Woelk, 2000) and is recommended as first-line monotherapy in mild to moderate MDD and second-line adjunctive treatment for moderate to severe MDD (Ravindran et al., 2016). The other potential mechanisms of antidepressant action of ShuganJieyu capsule may include increasing hippocampal neuron production, survival, and neogenesis, reducing the level of caspase-3 protein, and reversing neuronal apoptosis in depression model rats, and ShuganJieyu capsule has been shown to induce similar effects to fluoxetine (Fu et al., 2012). These findings indicate that the ShuganJieyu capsule has potential as a comparable treatment for MDD.

Moreover, patients with more somatic symptoms may benefit more from the ShuganJieyu capsule than with St. John's wort with regard to sleep latency in the study. One possible explanation for this is that *Acanthopanax senticosus* inhibits the synthesis of 5-hydroxytryptamine and the expression of tryptophan hydroxylase and plays a role in antioxidative stress damage, neuroprotection, sedation, calming nerves, and anti-fatigue (Liji et al., 2013). Although multiple hypotheses concerning the biological processes of action exist, such as transmitter transport, neuropeptide endocrine regulation, synaptic growth, and remodeling (Fu et al., 2012, 2014; Liji et al., 2013), the mechanisms by which *Hypericum perforatum* and *Acanthopanax senticosus* cause antidepressant effects are not yet well understood (Zhang et al., 2014).

A novel and unexpected finding of the study was that male patients could benefit more from the ShuganJieyu capsule, even though baseline characteristics and severity of symptoms were not significantly different between males and females. One study demonstrated that the concentrations of testosterone and dehydroepiandrosterone sulfate, as well as the sex hormone-binding globulin, remain largely unchanged in males after treatment with *Hypericum perforatum*, whereas several androgens, such as 5-alpha-reduced steroids, androsterone sulfate (AoS), and epiandrosterone sulfate (epiAoS), significantly decline in males but not in females (Donovan et al., 2005). Indeed, a previous study revealed a relationship between testosterone and depression (Walther et al., 2019); however, there is limited evidence that 5-alpha-reduced steroids, AoS, and epiAoS influence depression. Thus, further studies exploring the potential mechanisms underlying the superior effects of ShuganJieyu over St. John's wort in male patients are warranted.

Study Limitations

This trial has several limitations. First, the study was carried out in China, and the sample size is relatively small and participates included were mostly Han nationality (176/198). Whether our findings generalize to other ethnic groups requires further investigation. Further studies in other ethnic groups are needed before we extend this conclusion to other populations. Second, our assessment was following 8 weeks of acute treatment only, and

we did not evaluate the long-term efficacy of the interventions. Thus, we encourage studies of more than 8 weeks of treatment. Third, the results of the trial were a cumulative effect of the function of medication, and other possible factors, such as living situation, disease characteristics, patient features, and treatment setting (Fava et al., 2017; Wang et al., 2020), need to be examined.

Conclusion

Overall, this study suggested that the ShuganJieyu capsule has similar efficacy and safety to those of St. John's wort, and male patients and patients with more serious somatic symptoms may benefit more from the ShuganJieyu capsule. The ShuganJieyu capsule is comparable to St. John's wort as a complementary and alternative intervention for MDD patients with somatic complaints in the acute treatment, especially for male patients.

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Author Contribution PX and HW contributed to the conception and design of the study; all authors contributed to the acquisition and analysis of data; YX, WS, FD, YZ, YT, LW, PG, CW, LG, HW, and PX contributed to drafting a significant portion of the manuscript or figures. All of the coauthors have approved the submitted version and agreed to publication.

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Data Availability The data that support the findings of this study are available from the corresponding authors, PX and HW, upon reasonable request.

Declarations

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Conflict of Interest The authors declare no competing interests.

Disclaimer The funder of the trial had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

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