ORIGINAL RESEARCH

A meta-analysis on the efficacy and safety of St John's wort extract in depression therapy in comparison with selective serotonin reuptake inhibitors in adults

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Objective: The aim of the study was to investigate the efficacy and safety of St John's wort extract and selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression.

Methods: Databases were searched for studies comparing efficacy and/or safety of St John's wort extract with SSRIs in depression from 1966 to April 2015. Stata software was used for statistical analysis.

Results: Twenty-seven studies met the study entry criteria. A total of 3,126 patients with depression were included. St John's wort extract did not differ from SSRIs in clinical response, remission, and mean reduction in Hamilton Rating Scale for Depression score. St John's wort extract had a significantly lower rate of adverse events compared to SSRIs (summary relative risk: 0.77; 95% confidence interval: 0.70, 0.84, P=0.00) and had fewer withdrawals due to adverse events. St John's wort extract had superior safety in the management of patients with depression.

Conclusion: Both St John's wort extract and SSRIs are effective in treating mild-to-moderate depression. St John's wort extract is safer than SSRIs.

Keywords: St John's wort, selective serotonin reuptake inhibitors, depression, meta-analysis

Introduction

According to "the World Health Report 2001" by the World Health Organization, approximately one in ten persons suffer from depression globally, and depression is expected to become the second most common disease after coronary heart disease in 2020. The incidence of depression in the People's Republic of China is estimated at 5%–6% of the population[1] compared to 15.4% in the US[2] and 27% in European countries.[3] The total number of depression patients in the People's Republic of China has reached 90 million[1] and continues to rise, compromising the health of the general population. Depression has a long treatment cycle period, slow efficacy of medications, and high recurrence rate.

Fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and fluvoxamine are the most commonly used selective serotonin reuptake inhibitors (SSRIs) for treatment of major depression. However, these antidepressants may cause multiple side effects, such as nausea, insomnia, and sexual dysfunction.[4] Thirty-eight percent of patients with long-term use of SSRIs have experienced at least one side effect, with sexual dysfunction, sleepiness, and weight gain being the most common.[5]

Well-defined extracts from St John's wort (*Hypericum perforatum*), namely, St John's wort extract (Neurostan), have been used to treat depression for more than a 100 years

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in Germany. Significant efficacy and safety have been demonstrated in animal studies and clinical trials.[6,7] St John's wort has better antidepressant efficacy than placebo[8–10] and lower rates of side effects than conventional antidepressants.[11,12] The use of St John's wort extract for patients with depression, however, remains somewhat controversial, since some studies showed no significant difference in efficacy and safety between St John's wort extract and conventional SSRIs.[11–15] Given that depression often requires rapid, timely, and prolonged treatment, we should consider not only the effectiveness but also safety of the treatment. Therefore, based on the meta-analysis by Rahimi et al,[16] which covers literature from 1966 to June 2008, we collected published randomized, controlled clinical trials comparing the efficacy and safety of St John's wort extract and SSRIs from June 2008 to April 2015. In addition, we included similar studies that have been published since 1966 in the People's Republic of China to conduct a comprehensive and objective update on the use of St John's wort extract as an alternative to SSRIs.

Materials and methods
Data sources
The search terms were "St John's wort" or "hypericum" or "Neurostan" and "fluoxetine" or "paroxetine" or "citalopram" or "sertraline" or "escitalopram" or "fluvoxamine" and "depression." PubMed, Cochrane Central Register of Controlled Trials, and Ovid Technologies were searched from June 2008 to April 2015, and China Biology Medicine disc, WanFang Data, and China National Knowledge Infrastructure were searched from 1966 to April 2015.

Study selection
We searched for studies of treatment of depression with St John's wort extract with no language restriction. All studies were required to meet the following inclusion criteria: 1) randomized controlled trials, 2) depressive patients, 3) at least 4 weeks of treatment, 4) SSRI-controlled, 5) available efficacy or safety indicators, and 6) outcome measures for depression or clinical diagnosis. Exclusion criteria were as follows: 1) lack of data on efficacy and safety, 2) combination with other antidepressants, and 3) single-blind and uncontrolled trials. Data from selected studies were extracted in tabular form, including basic information on the study, study design, study time, intervention measures, and specific outcomes.

Measures of efficacy and safety
The primary outcome measure for treatment efficacy and safety was change in total Hamilton Rating Scale for Depression (HAMD) score between baseline and end point. Responder rates (reduction in HAMD score >50%), remission rate (reduction in HAMD score >75%), mean reduction in HAMD score, the incidence of adverse events, total withdrawal rate, and withdrawals due to adverse events were the key outcomes of interest.

Formula conversion
Some of the data in this study were not directly usable for statistical analysis, and therefore, converted into a form available for analysis. The main formulas used were 1) calculation of mean and standard deviation (SD) for change according to the known mean and SD before and after treatment: mean $(b - a)$ = mean $(b) - (a)$, variance $(b - a)$ = variance (b) + variance (a), taking the square root to obtain SD: $(b - a)$ and 2) calculation of SD: $(CI_{max} - CI_{min})/(1.96 \times 2)$ by using the confidence intervals.

Statistical analysis
All included studies were analyzed using Stata/SE (11.2) (StataCorp LP, College Station, TX, USA). For each meta-analysis, heterogeneity of treatment effects was tested before the data were pooled; if $P > 0.05$ or $I^2 < 50\%$, we considered the data to be homogeneous and used a fixed-effects model. Otherwise, we applied a random-effects model. Relative risk (RR) and 95% confidence intervals (95% CI) were calculated, and effect size (weighted mean difference) meta-analysis was performed. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using the chi-square test, and the results were expressed as an odds ratio (OR) and P-values.

Results
A total of 27 articles were retrieved.[11–15,17–24] The basic data of all studies are shown in Table 1. A total of 3,126 patients were included in the analysis, with 1,177 patients from the People's Republic of China.

Efficacy
Summary RR for all included studies for clinical response was 1.02 (95% CI: 0.96, 1.09, $P=0.51$, Figure 1). Furthermore, the combined summary RR of all studies for remission by St John's wort extract versus SSRIs therapy was 1.07 (95% CI: 0.94, 1.22, $P=0.308$, Figure 2). Effect size (standard mean difference) for mean reduction in HAMD score from baseline with St John's wort extract versus SSRIs therapy among all the studies was −0.06 (95% CI: −0.13, 0.02, $P=0.15$, Figure 3).

Table 1 Characteristics of studies included in the meta-analysis

Study	Setting	Original country	Participants	Hypericum preparation	SSRI	Diagnosis criteria	Depression severity	Indicators	N	Jadad score
Harrer et al[17]	Randomized double-blind comparative trial	Germany	Psychiatric disorders	LoHyp-57 (800 mg/d for 6 weeks)	Fluoxetine (20 mg/d for 6 weeks)	ICD-10	Mild to moderate	Clinical response, HAMD, AD	161	3
Brenner et al[18]	Randomized, controlled, blinded	USA	Depressive disorder	LI-160 (600–900 mg/d for 7 weeks)	Sertraline (50–75 mg/d for 7 weeks)	DSM-IV	Mild to moderate	HAMD, Clinical Global Impression	30	3
Schrader[19]	Randomized, controlled, double-blind	Germany	Depressive disorder	Ze117 (500 mg/d for 6 weeks)	Fluoxetine (20 mg for 6 weeks)	ICD-10	Mild to moderate	HAMD, Clinical Global Impression	240	4
Behnke et al[20]	Randomized, controlled, double-blind	Denmark	Depressive disorder	Calmigen (300 mg/d for 6 weeks)	Fluoxetine (40 mg/d for 6 weeks)	ICD-10	Mild to moderate	HAMD, Clinical Global Impression	70	3
Hypericum Depression Trial Study Group[21]	Double-blind, randomized	USA	Major depression disorder	LI-160 (900–1,500 mg/d for 8 weeks)	Sertraline (50–100 mg/d for 8 weeks)	DSM-IV	Moderate to severe	HAMD, adverse effect	428	5
van Gurp et al[22]	Double-blind, randomized	Canada	Major depression	SJW (900–1,800 mg/d for 12 weeks)	Sertraline (50–100 mg/d for 12 weeks)	DSM-IV	Mild to severe	HAMD, self-reported side effects	90	4
Bjerkenstedt et al[23]	Randomized, placebo-controlled multicenter	Germany	Major depression disorder	LI-160 (900 mg/d for 4 weeks)	Fluoxetine (20 mg/d for 4 weeks)	DSM-IV	Mild or moderate	HAMD, safety and tolerability	174	3
Gastpar et al[13]	Randomized, double-blind	Germany	Moderate depression	STW3 (612 mg/d for 12 weeks)	Sertraline (50 mg/d for 12 weeks)	ICD-10	Moderate	HAMD, adverse events	241	4
Fava et al[11]	Randomized, parallel-group, double-blind study	Germany	Major depressive disorder	LI-160 (900 mg/d for 12 weeks)	Fluoxetine (20 mg/d for 12 weeks)	DSM-IV	Mild to severe	HAMD, CGI-I, adverse events	135	4
Szegedi et al[12]	Randomized, double-blind	Germany	Acute major depression	WS 5570 (900–1,800 mg/d for 6 weeks)	Paroxetine (20–40 mg/d for 6 weeks)	DSM-IV	Moderate	HAMD, adverse events	301	5
Gastpar et al[14]	Randomized, double-blind	Germany	Moderate depression	STW3-VI (900 mg/d for 6 weeks)	Citalopram (20 mg/d for 6 weeks)	ICD-10	Moderate	HAMD, responders, adverse events	388	5
Moreno et al[15]	Randomized, double-blind	Brazil	Affective disorders of psychiatry	Iperisan (900 mg/d for 8 weeks)	Fluoxetine (20 mg/d for 8 weeks)	DSM-IV	Mild to moderate	HAMD, Clinical Global Impression	72	3

(Continued)

Table I (*Continued*)

Study	Setting	Original country	Participants	Hypericum preparation	SSRI	Diagnosis criteria	Depression severity	Indicators	N	Jadad score
Papakostas et al[24]	Randomized, parallel-group, double-blind study	USA	Major depressive disorder	LI-160 (20 mg/d for 12 weeks)	Fluoxetine (20 mg/d for 12 weeks)	DSM-IV	Mild to severe	Response, remission, HDRS-17 scores	135	2
Rapaport et al[44]	Three-arm, randomized clinical trial	USA	Minor depression	SJW (810 mg/d for 12 weeks)	Citalopram (20 mg/d for 12 weeks)	DSM-IV	Mild	HAMD, adverse events	169	3
Gu et al[32]	Randomized, double-blind, multicenter	People's Republic of China	Depressive disorder	SJW (900 mg/d for 6 weeks)	Fluoxetine (20 mg/d for 6 weeks)	CCMD-2-R	Mild to moderate	HAMD, HAMA, adverse events	135	4
Mo et al[33]	Randomized, double-blind	People's Republic of China	Post-stroke depression	SJW (1,350 mg/d for 7 weeks)	Fluoxetine (20 mg/d for 6 weeks)	CCMD-2-R(3)	HAMD total score 18–24	HAMD, clinical response, adverse events	65	3
Wang et al[34]	Randomized, open	People's Republic of China	Depressive disorder	SJW (900 mg/d for 6 weeks)	Fluoxetine (20 mg/d for 6 weeks)	CCMD-3	HAMD total score 18–24	HAMD, HAMA, adverse events	40	2
Zhang et al[35]	Randomized, controlled	People's Republic of China	Depressive disorder	SJW (900 mg/d for 6 weeks)	Paroxetine (20 mg/d for 6 weeks)	CCMD-3	HAMD total score $\geq$18	HAMD, HAMA, clinical response, adverse events	56	2
Gao[36]	Controlled	People's Republic of China	Post-stroke depression	SJW (600 mg/d for 4 weeks)	Paroxetine (20 mg/d for 4 weeks)	Unknown	HAMD total score $\geq$18	HAMD, HAMA, clinical response, adverse events	68	1
Lou et al[37]	Randomized, open, controlled	People's Republic of China	Depressive disorder	SJW (900 mg/d for 7 weeks)	Fluoxetine (20 mg/d for 7 weeks)	CCMD-3	HAMD total score $\geq$18	HAMD, HAMA, clinical response, adverse events	81	2
Hu et al[38]	Randomized, open, controlled	People's Republic of China	Depressive disorder	SJW (900 mg/d for 6 weeks)	Paroxetine (20 mg/d for 6 weeks)	CCMD-3	HAMD total score $\geq$18	HAMD, HAMA, clinical response, adverse events	70	2
Hu and Yang[39]	Randomized, open, controlled	People's Republic of China	Depressive disorder	SJW (900 mg/d for 6 weeks)	Citalopram (20 mg/d for 6 weeks)	CCMD-3	HAMD total score $\geq$18	HAMD, HAMA, clinical response, adverse events	60	2
Li and Wei[40]	Randomized, controlled	People's Republic of China	Post-stroke depression	SJW (600 mg/d for 6 weeks)	Citalopram (20 mg/d for 6 weeks)	Unknown	HAMD total score $\geq$18	HAMD, HAMA, clinical response, adverse events	60	2
Li[41]	Randomized, controlled	People's Republic of China	Post-stroke depression	SJW (900 mg/d for 12 weeks)	Fluoxetine (20 mg/d for 12 weeks)	CCMD-3	Unknown	HAMD, HAMA, clinical response, adverse events	158	2
Tang et al[42]	Randomized, controlled	People's Republic of China	Depressive disorder	SJW (600–900 mg/d for 8 weeks)	Sertraline (50–100 mg/d for 8 weeks)	CCMD-3	Unknown	HAMD, HAMA, clinical response, adverse events	64	2

Study	Design	Country	Condition	Intervention	Comparator	Diagnostic criteria	Inclusion	Outcomes	Sample size	
Tan et al[43]	Randomized, controlled	People's Republic of China	Post-stroke depression	SJW (900 mg/d for 4 weeks)	Paroxetine (20 mg/d for 4 weeks)	CCMD	Unknown	Clinical response, adverse events	120	2
Wang and Chen[45]	Randomized, controlled	People's Republic of China	Hypertension with depression	SJW (900 mg/d for 12 weeks)	Paroxetine (30 mg/d for 12 weeks)	Unknown	HAMD total score ≥18	HAMD, clinical response, adverse events	200	3

Abbreviations: AD, adverse events; CCMD, Chinese classification of mental disorders; CGI-I, clinical global impression-improvement; DSM, diagnostic and statistical manual of mental disorders; HAMA, Hamilton anxiety scale; HAMD, Hamilton rating scale for depression; HDRS-17, 17-item Hamilton depression scale; ICD, international classification of diseases; SJW, St John's Wort; SSRIs, selective serotonin reuptake inhibitors.

Safety

The number of patients reporting adverse events and withdrawal due to adverse events were evaluated in 19 and 12 trials, respectively. The summary RR for adverse events of St John's wort extract versus SSRI therapy among all included trials was 0.77 (95% CI: 0.70, 0.84, P=0.00) (Figure 4). Twelve trials investigated withdrawals and withdrawal due to adverse events of St John's wort extract and SSRI therapy. The total withdrawal rate and withdrawal rate due to adverse events were 18.2% (167/916) and 4.1% (38/916) in the St John's wort extract group, and 20.3% (183/901) and 6.7% (61/901) in the SSRI group, respectively. There was no significant difference in the total withdrawal rate of the two groups (chi-square test; OR =0.88, 95% CI: 0.69, 1.11, P=0.28). Withdrawal due to adverse events in the St John's wort extract group was significantly less than that in the SSRI group (OR =0.60, 95% CI: 0.39, 0.90, P=0.02).

Publication bias

We did not observe a skewed distribution and the data substantially met a normal distribution, and the publication bias was also small.

Sensitivity analysis

We excluded trials one by one to perform sensitivity analysis. There was no significant difference between the statistical results before and after each exclusion, indicating that the study was stable and reliable.

Discussion

Although St John's wort extract has been used to treat depression for >100 years and its efficacy[8–10] and safety[11,12] have been proven in several clinical studies, its use in depression still remains somewhat controversial. A meta-analysis by Rahimi et al[16] of 13 eligible randomized, placebo-controlled clinical trials published between 1966 and 2008 showed that St John's wort extract was comparable to SSRIs in efficacy and safety. Our current meta-analysis included additional studies as of 2008 with a total of 27 eligible studies and 3,126 depression patients. We found that consistent with the findings of Rahimi et al,[16] St John's wort extract was comparable to SSRIs in efficacy, including clinical response, remission, and mean reduction in HAMD score. Unlike the study by Rahimi et al,[16] we further demonstrated that St John's wort extract had a lower incidence of adverse events than SSRIs. These findings indicate that, compared to SSRIs, St John's wort extract is equally effective, but has superior safety in the management of depression patients.
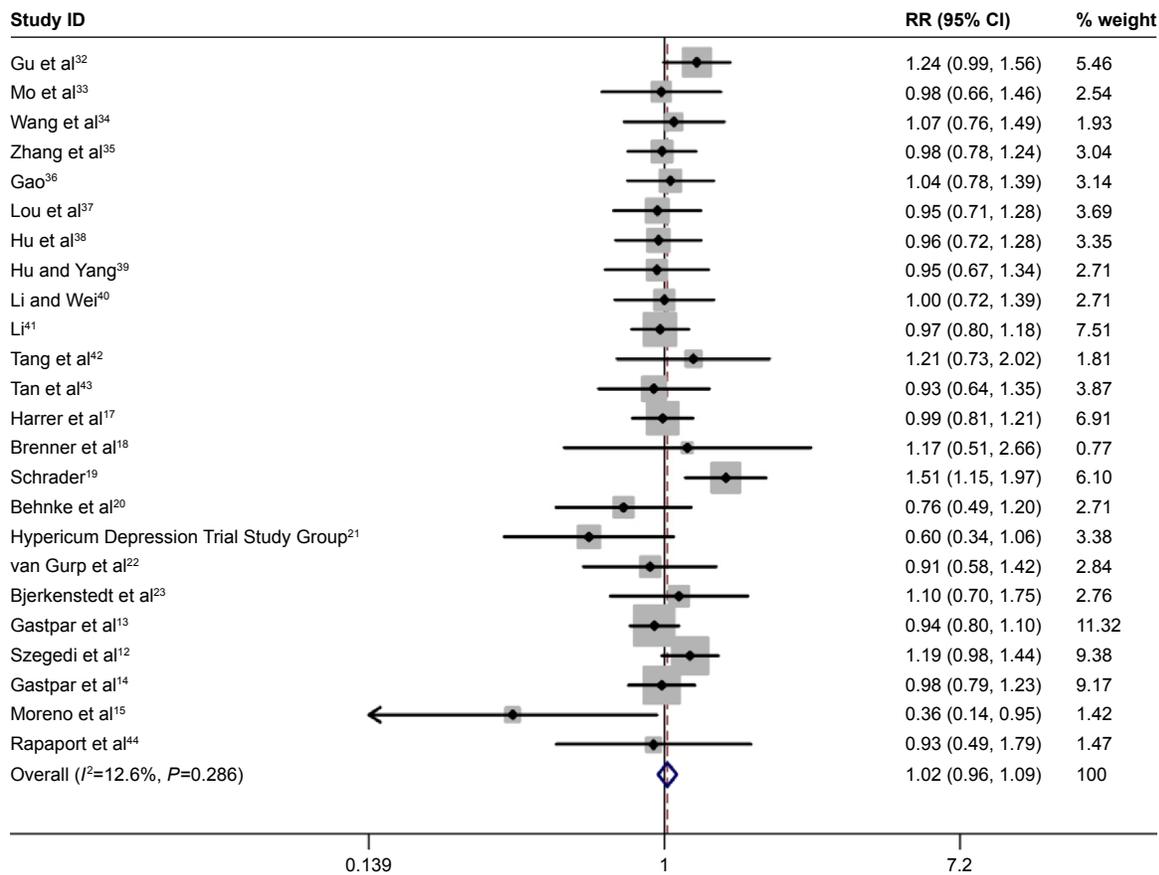
Study ID		RR (95% CI)	% weight
Gu et al[32]		1.24 (0.99, 1.56)	5.46
Mo et al[33]		0.98 (0.66, 1.46)	2.54
Wang et al[34]		1.07 (0.76, 1.49)	1.93
Zhang et al[35]		0.98 (0.78, 1.24)	3.04
Gao[36]		1.04 (0.78, 1.39)	3.14
Lou et al[37]		0.95 (0.71, 1.28)	3.69
Hu et al[38]		0.96 (0.72, 1.28)	3.35
Hu and Yang[39]		0.95 (0.67, 1.34)	2.71
Li and Wei[40]		1.00 (0.72, 1.39)	2.71
Li[41]		0.97 (0.80, 1.18)	7.51
Tang et al[42]		1.21 (0.73, 2.02)	1.81
Tan et al[43]		0.93 (0.64, 1.35)	3.87
Harrer et al[17]		0.99 (0.81, 1.21)	6.91
Brenner et al[18]		1.17 (0.51, 2.66)	0.77
Schrader[19]		1.51 (1.15, 1.97)	6.10
Behnke et al[20]		0.76 (0.49, 1.20)	2.71
Hypericum Depression Trial Study Group[21]		0.60 (0.34, 1.06)	3.38
van Gurp et al[22]		0.91 (0.58, 1.42)	2.84
Bjerkenstedt et al[23]		1.10 (0.70, 1.75)	2.76
Gastpar et al[13]		0.94 (0.80, 1.10)	11.32
Szegedi et al[12]		1.19 (0.98, 1.44)	9.38
Gastpar et al[14]		0.98 (0.79, 1.23)	9.17
Moreno et al[15]		0.36 (0.14, 0.95)	1.42
Rapaport et al[44]		0.93 (0.49, 1.79)	1.47
Overall (I^2=12.6%, P=0.286)		1.02 (0.96, 1.09)	100

0.139   1   7.2

Figure 1 Pooled relative risk of the outcome of "clinical response" in the studies comparing St John's wort extract versus SSRIs therapy.
Abbreviations: CI, confidence interval; RR, relative risk; SSRIs, selective serotonin reuptake inhibitors.
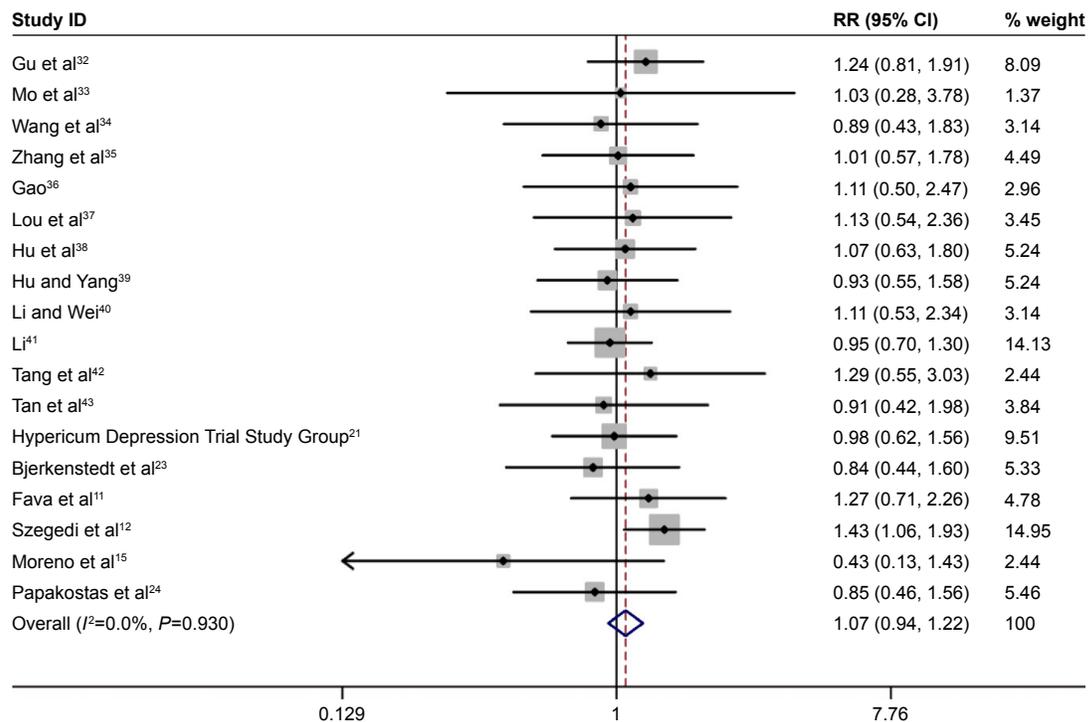
Study ID		RR (95% CI)	% weight
Gu et al[32]		1.24 (0.81, 1.91)	8.09
Mo et al[33]		1.03 (0.28, 3.78)	1.37
Wang et al[34]		0.89 (0.43, 1.83)	3.14
Zhang et al[35]		1.01 (0.57, 1.78)	4.49
Gao[36]		1.11 (0.50, 2.47)	2.96
Lou et al[37]		1.13 (0.54, 2.36)	3.45
Hu et al[38]		1.07 (0.63, 1.80)	5.24
Hu and Yang[39]		0.93 (0.55, 1.58)	5.24
Li and Wei[40]		1.11 (0.53, 2.34)	3.14
Li[41]		0.95 (0.70, 1.30)	14.13
Tang et al[42]		1.29 (0.55, 3.03)	2.44
Tan et al[43]		0.91 (0.42, 1.98)	3.84
Hypericum Depression Trial Study Group[21]		0.98 (0.62, 1.56)	9.51
Bjerkenstedt et al[23]		0.84 (0.44, 1.60)	5.33
Fava et al[11]		1.27 (0.71, 2.26)	4.78
Szegedi et al[12]		1.43 (1.06, 1.93)	14.95
Moreno et al[15]		0.43 (0.13, 1.43)	2.44
Papakostas et al[24]		0.85 (0.46, 1.56)	5.46
Overall (I^2=0.0%, P=0.930)		1.07 (0.94, 1.22)	100

0.129   1   7.76

Figure 2 Pooled relative risk of the outcome of "remission" in the studies comparing St John's wort extract versus SSRI therapy.
Abbreviations: CI, confidence interval; RR, relative risk; SSRIs, selective serotonin reuptake inhibitors.
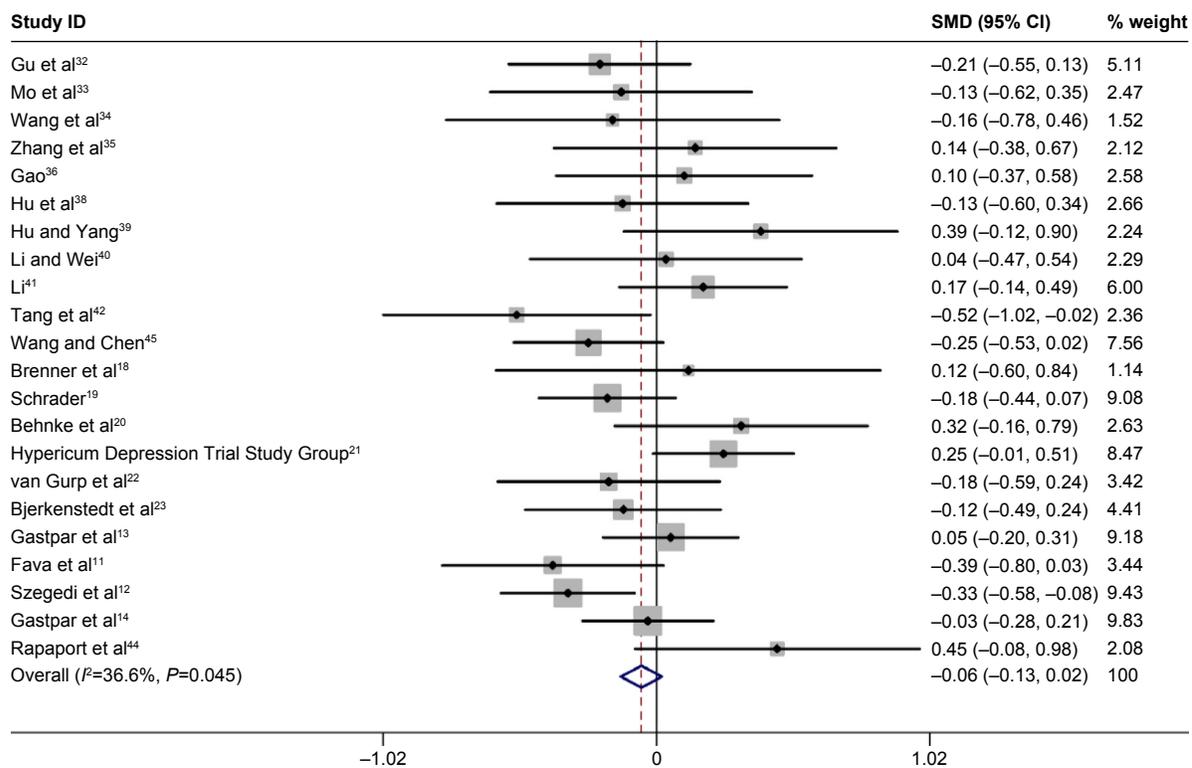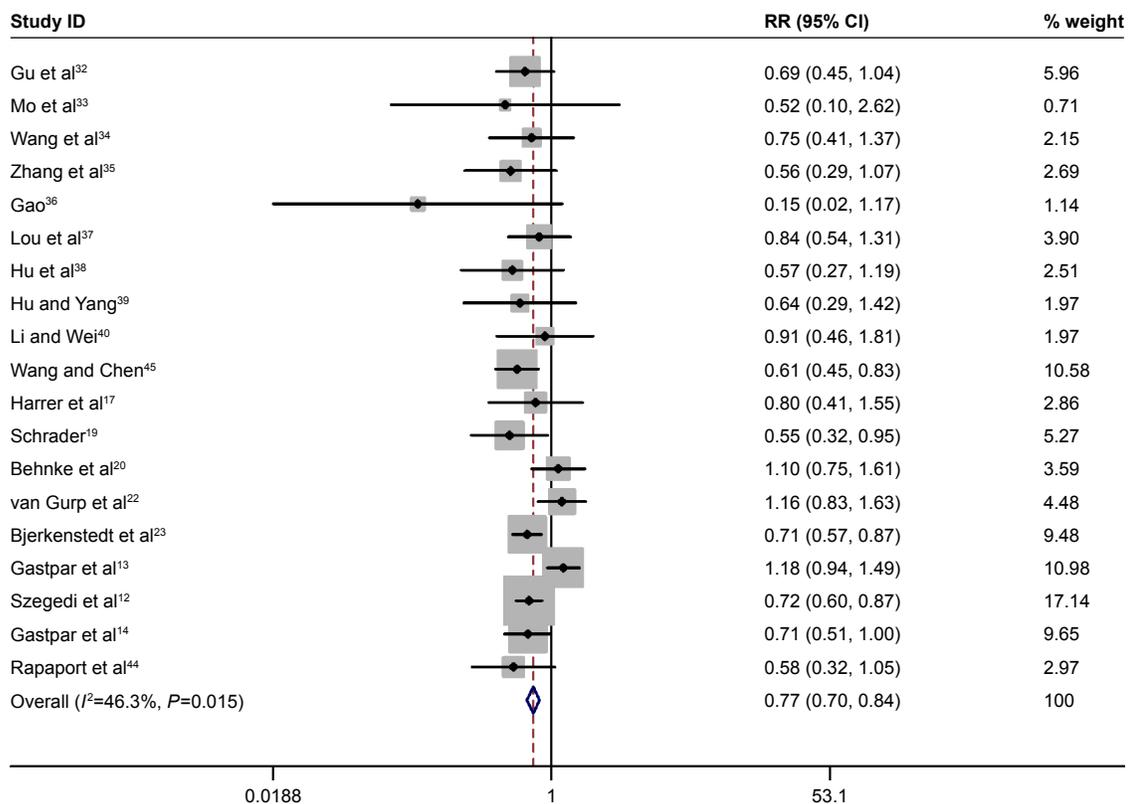
Study ID		SMD (95% CI)	% weight
Gu et al[32]		−0.21 (−0.55, 0.13)	5.11
Mo et al[33]		−0.13 (−0.62, 0.35)	2.47
Wang et al[34]		−0.16 (−0.78, 0.46)	1.52
Zhang et al[35]		0.14 (−0.38, 0.67)	2.12
Gao[36]		0.10 (−0.37, 0.58)	2.58
Hu et al[38]		−0.13 (−0.60, 0.34)	2.66
Hu and Yang[39]		0.39 (−0.12, 0.90)	2.24
Li and Wei[40]		0.04 (−0.47, 0.54)	2.29
Li[41]		0.17 (−0.14, 0.49)	6.00
Tang et al[42]		−0.52 (−1.02, −0.02)	2.36
Wang and Chen[45]		−0.25 (−0.53, 0.02)	7.56
Brenner et al[18]		0.12 (−0.60, 0.84)	1.14
Schrader[19]		−0.18 (−0.44, 0.07)	9.08
Behnke et al[20]		0.32 (−0.16, 0.79)	2.63
Hypericum Depression Trial Study Group[21]		0.25 (−0.01, 0.51)	8.47
van Gurp et al[22]		−0.18 (−0.59, 0.24)	3.42
Bjerkenstedt et al[23]		−0.12 (−0.49, 0.24)	4.41
Gastpar et al[13]		0.05 (−0.20, 0.31)	9.18
Fava et al[11]		−0.39 (−0.80, 0.03)	3.44
Szegedi et al[12]		−0.33 (−0.58, −0.08)	9.43
Gastpar et al[14]		−0.03 (−0.28, 0.21)	9.83
Rapaport et al[44]		0.45 (−0.08, 0.98)	2.08
Overall (I^2=36.6%, P=0.045)		−0.06 (−0.13, 0.02)	100

−1.02　　　0　　　1.02

Figure 3 Pooled standard mean difference for the outcome of "mean reduction in HAMD score from baseline" in the studies comparing St John's wort extract versus SSRI therapy.
Abbreviations: CI, confidence interval; HAMD, Hamilton Rating Scale for Depression; SMD, standard mean difference; SSRIs, selective serotonin reuptake inhibitors.

Study ID		RR (95% CI)	% weight
Gu et al[32]		0.69 (0.45, 1.04)	5.96
Mo et al[33]		0.52 (0.10, 2.62)	0.71
Wang et al[34]		0.75 (0.41, 1.37)	2.15
Zhang et al[35]		0.56 (0.29, 1.07)	2.69
Gao[36]		0.15 (0.02, 1.17)	1.14
Lou et al[37]		0.84 (0.54, 1.31)	3.90
Hu et al[38]		0.57 (0.27, 1.19)	2.51
Hu and Yang[39]		0.64 (0.29, 1.42)	1.97
Li and Wei[40]		0.91 (0.46, 1.81)	1.97
Wang and Chen[45]		0.61 (0.45, 0.83)	10.58
Harrer et al[17]		0.80 (0.41, 1.55)	2.86
Schrader[19]		0.55 (0.32, 0.95)	5.27
Behnke et al[20]		1.10 (0.75, 1.61)	3.59
van Gurp et al[22]		1.16 (0.83, 1.63)	4.48
Bjerkenstedt et al[23]		0.71 (0.57, 0.87)	9.48
Gastpar et al[13]		1.18 (0.94, 1.49)	10.98
Szegedi et al[12]		0.72 (0.60, 0.87)	17.14
Gastpar et al[14]		0.71 (0.51, 1.00)	9.65
Rapaport et al[44]		0.58 (0.32, 1.05)	2.97
Overall (I^2=46.3%, P=0.015)		0.77 (0.70, 0.84)	100

0.0188　　　1　　　53.1

Figure 4 Pooled relative risk of the outcome of "adverse events" in the studies comparing St John's wort extract versus SSRI therapy.
Abbreviations: CI, confidence interval; RR, relative risk; SSRIs, selective serotonin reuptake inhibitors.

St John's wort extract is currently the only pure plant antidepressant and is especially suitable for mild-to-moderate depression. It competitively inhibits absorption of serotonin, noradrenaline, and dopamine; it also downregulates presynaptic membrane-adrenergic receptor density and reduces binding of neurotransmitters to presynaptic membrane-adrenergic receptors, thereby increasing their concentrations in the synaptic cleft, mimicking the effect of antidepressants.[25,26] Studies have shown that St John's wort extract is superior to placebo[8–10] and comparable to SSRIs[27] in efficacy. St John's wort causes mild adverse effects such as occasional dry mouth and constipation, and it causes no memory impairment, an apparent advantage for older patients.[28] Our study demonstrates significantly lower rates of adverse events in depression patients receiving St John's wort extract versus SSRIs, and consistent with the study by Rahimi et al,[16] markedly lower rates of withdrawal due to adverse events.

One limitation of the current meta-analysis is the lack of data on treatment of adolescents with depression. Depression is a significant disease for adolescents. Little literature has been published on adolescent depression. All studies included in our meta-analysis involve only adult patients with depression. A small number of studies have shown that St John's wort extract is superior to placebo in treating teenagers with moderate and severe depression;[29,30] however, a definite conclusion awaits the results of randomized controlled trials involving a larger population of adolescents with depression. Depression is a chronic disease requiring long-term medication therapy, incurring a financial burden on the patients. It is also important to investigate cost-effectiveness of St John's wort extract versus SSRIs, which was not addressed in our meta-analysis. Solomon et al[31] investigated the economic cost of St John's wort extract for mild-to-moderate depression using Markov model and found that St John's wort extract markedly reduced medication costs compared with SSRIs.

Conclusion

Although St John's wort has been used as a herbal remedy for depression for many years, especially in Germany and other European countries, its efficacy is still controversial. Our meta-analysis analyzed 27 studies and 3,126 depression patients and so far represents the most comprehensive analysis of clinical studies on St John's wort for depression. Although this study did not explore neurobiological mechanisms of St John's wort, our results are consistent with the hypothesis that St John's wort is an effective therapy for depression. Furthermore, our analysis demonstrates that in the treatment of depression, especially mild-to-moderate

depression, St John's wort extract has comparable efficacy to SSRIs, while the rate of adverse events and withdrawals is significantly lower than that of traditional SSRIs. Given the low cost of treatment with St John's wort extract versus SSRIs, its significant efficacy, and good safety profile, St John's wort extract may be a preferred therapeutic choice in the management of depression.

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Disclosure

The authors report no conflicts of interest in this work.

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