Efficacy and safety of Shaoyao Gancao Tang for restless leg syndrome: A systematic review and meta-analysis

Zhining Tian[1†], Rong Li[1†], Jingwen Wei[2], Wenying Huai[1], Jun Xia[1], Hua Jiang[1], Ying Xiong[2*], Yunhui Chen[1*]

[1]College of Basic Medicine/College of Acupuncture and Moxibustion/College of International Education/Hospital, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China; [2]West China Hospital, West China School of Medicine, Sichuan University, Chengdu, Sichuan, China

[†]Zhining Tian and Rong Li contributed equally to this work.

***Corresponding authors:** Ying Xiong, West China Hospital, West China School of Medicine, Sichuan University, Chengdu, Sichuan, China. Email: xiongying@wchscu.cn; Yunhui Chen, College of Basic Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China. Email: chenyunhui@cdutcm.edu.cn

Received: 28 November 2022; Accepted: 4 January 2023; Published: 12 February 2023

RESEARCH ARTICLE

Abstract

Restless leg syndrome (RLS) is a common and chronic neurological disease characterized by an irresistible and overwhelming urge to move the legs. In recent years, a growing body of clinical trials has demonstrated that traditional Chinese herbal medicine Shaoyao Gancao Tang (SG-Tang) may improve RLS. However, a critical examination of the available evidence is warranted. This study aimed to evaluate the efficacy and safety of SG-Tang in the treatment of RLS. The protocol of this study was registered and published at International Prospective Register of Systematic Reviews (PROSPERO; CRD42020173520). Randomized clinical trials (RCTs) on the efficacy and safety of SG-Tang in the treatment of RLS were identified by searching the Cochrane Library, PubMed, EMBASE, Web of Science, the Chinese Biological Medicine Database, China National Knowledge Infrastructure, Wanfang Database, and VIP Information Database from inception to February 14, 2022. The primary outcome measurements were the total effective rate, and the secondary outcome measurements included the International Restless Legs Syndrome Study Group Rating Scale for Severity of Restless Legs Syndrome (IRLS), the Pittsburgh Sleep Quality Index (PSQI), and the incidence of adverse events. The Review Manager 5.3 software was utilized to conduct quantitative synthesis according to the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Six eligible RCTs were included in this meta-analysis. Compared to conventional medications, SG-Tang intervention showed significant improvements in the total effective rate (risk ratio [RR] = 1.22, 95% confidence interval [CI] (1.09,1.36), $P = 0.004$), the IRLS (mean difference [MD] = −4.74, 95% CI (−8.65, −0.83), $P = 0.02$), and the PSQI (MD = −2.54, 95% CI (−4.34, −0.74), $P = 0.006$) with less incidence of adverse events (RR = 0.21, 95% CI (0.09, 0.31), $P = 0.0005$). SG-Tang may be effective and safe as a complementary and alternative treatment to relieve RLS. However, the results need to be interpreted with caution because of limited data and the undesirable methodological quality of the included studies. More well-designed, large-scale, high-quality, and multi-center RCTs are required to be performed for further verification.

Keywords: restless leg syndrome; natural products; Shaoyao Gancao Tang; effectiveness; safety

Introduction

Restless legs syndrome (RLS, also known as Willis–Ekbom disease [WED]) was first described by Sir Thomas Willis in 1672 as "…so great a Restlessness and Tossing of their Members ensue, that the diseased are no more able to sleep, than if they were in a Place of the greatest torture" (Ekbom, 1960). It is a chronic and neurological disorder characterized by an irresistible urge and restlessness to move the legs. Its clinical symptoms commonly occur and exacerbate in evening and night or at rest, and are temporarily alleviated upon movement (Gossard *et al.*, 2021). Epidemiological studies have demonstrated the commonality of RLS affecting approximately 5–14.3% of the general population, and the prevalence increases with age (Ohayon *et al.*, 2012; Rubí, 2018; Wijemanne and Ondo, 2017). Compelling evidence has demonstrated that RLS impairs sleep quality and quantity, triggers anxiety and depression, and is associated with hypertension, cardiovascular disorders, and cerebrovascular diseases (Trenkwalder *et al.*, 2018). It significantly impairs patients' health-related quality of life with the loss of work productivity; therefore, just as Dr. Ekbom wrote in 1960 "…the syndrome is so common and causes such suffering that it should be known to every physician."

The explicit pathogenesis of RLS is still ambiguous but has been well-recognized as a complex condition attributed to predisposing genetic factors, iron deficiency, dysfunctional dopaminergic and nociceptive systems, altered adenosine and glutamatergic pathways, environmental factors, and such comorbidities as renal disease and diabetes mellitus (Vellieux and d'Ortho, 2020). Currently, its therapeutic options include iron preparations, opioids, and dopamine agonists, such as pramipexole, ropinirole, and rotigotine (Wijemanne and Ondo, 2017). However, potential side effects, including sleepiness, fatigue, dizziness, and augmentation risks with dopaminergic medications, reduce their compliance (Anguelova *et al.*, 2020), yielding a therapeutic field sorely in need of innovation. Consequently, in recent years, increasing attention has been paid to natural products.

Shaoyao Gancao Tang (SG-Tang; to date also known as Jakyakgamcho-tang in South Korea and Shakuyaku-kanzo-to in Japan) has a time-honored history of treating RLS that can be dated back to over 1,800 years when Dr. Zhongjing Zhang (150–219 AD) recorded his clinical thoughts and experiences of halting restlessness, spasms, and cramps in legs in his works *Treatise on Cold Damage* (*Shanghan Lun*, also known as the "Bible" of traditional Chinese medicine [TCM]). SG-Tang consists of Paeoniae Radix Alba and Glycyrrhizae Radix et Rhizoma in a ratio of 1:1, and is reported to exert desirable effects on RLS because of its multiple well-documented pharmacological actions, including spasmolysis, analgesic effect, anti-inflammatory, sedation, and neuroprotection (Chen *et al.*, 2018; Lee *et al.*, 2013). Moreover, its component Glycyrrhizae Radix et Rhizoma (also named glycyrrhiza or "Gan-Cao" in China and licorice or liquorice in Europe) is of a food and medicine continuum, and in 2002, Paeoniae Radix Alba was listed by the Ministry of Health of China as a Chinese material medica that can be used to prepare food for health preservation (Heinrich *et al.*, 2021; National Health Commission of the People's Republic of China, 2002).

In recent years, a growing body of randomized controlled trials (RCTs) has been performed to investigate the effectiveness and safety of SG-Tang in the treatment of RLS.

However, systematic reviews and meta-analyses that summarized and assessed the relevant evidence remain unreported. Consequently, this study aimed to evaluate systematically the effectiveness and safety of SG-Tang in RCTs for treating RLS, hopefully providing useful information for the patients and physicians with an evidence-based approach.

Methods

The protocol of this review was registered and published on International Prospective Register of Systematic Revi ews (PROSPERO; CRD42020173520; Chen *et al.*, 2020). This meta-analysis was performed with RevMan (version 5.3) (The Cochrane Collaboration, NCC, *Copenhagen*, Denmark) by following the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (Moher *et al.*, 2009).

Search strategy

Two reviewers (Ying Xiong and Rong Li) independently searched Cochrane library, PubMed, EMBASE, Web of Science, the Chinese Biological Medicine Database, China National Knowledge Infrastructure, Wanfang Database, and VIP information database from inception to February 14, 2022. The search was conducted to identify eligible studies without any restriction of language using the following terms in a combination: restlessness leg syndrome, RLS, Willis–Ekbom disease, periodic leg movement, quiescegenic focal akathisia, Shaoyao Gancao Tang, SG-Tang, Shakuyakukanzoto, SKT, Paeonia lactiflora and Glycyrrhiza uralensis decoction, and Chinese peony and licorice combination, as randomized control, randomization, randomized clinical trials, RCT, and trials. Additionally, the references of retrieved studies were manually searched. Any inconsistency was solved by a

third reviewer (Zhining Tian). The specific search strategy for PubMed is shown in the supplementary material. This has been modified correspondingly to accommodate the requirements of different databases.

Eligibility criteria

The retrieved studies were deemed eligible if they fulfilled the following pre-specified inclusion criteria: (1) type of study: RCT; (2) population: patients with RLS, regardless of age, gender, source of cases, duration of disease, ethnicity, or nationality; (3) intervention: SG-Tang treatment (no restriction on the mode and dosage of administration and course of treatment) clearly stated in the trial group either solely or in combination with other treatments versus conventional treatment, placebo, or no treatment; and (4) outcome variables: the total effective rate, the International Restless Legs Syndrome Study Group Rating Scale for Severity of Restless Legs Syndrome (IRLS), the Pittsburgh Sleep Quality Index (PSQI), and the incidence of adverse events. Non-RCTs, reviews, animal-based research, conference proceedings, literature review, studies with unclear diagnostic criteria and absence of outcome measurements, reports unable to obtain original data or complete information of the trial, and duplicated publications were excluded.

Outcome measurements

Primary outcomes were the total effective rate, and the secondary outcomes included IRLS, PSQI, and the incidence of adverse events. The "total effective rate" was predefined as the sum of cured, markedly effective, and effective rates of certain therapeutic interventions in which, "cure" was the disappearance of RLS symptoms; "markedly effective" was the significant remission of RLS symptoms; "effective" was relieving of RLS symptoms; and "ineffective rate" meant no remission of symptoms.

$$\text{Total effective rate} = (\text{Cured} + \text{Markedly Effective} + \text{Effective}) \div \text{Total Number of Cases} \times 100\%.$$

Study selection

Two reviewers (Zhining Tian and Ying Xiong) independently screened the titles and abstracts of eligible studies and then reviewed the full text following the pre-specified eligibility criteria. Disagreements were solved by the third reviewer (Yunhui Chen).

Data extraction

Two reviewers (Ying Xiong and Zhining Tian) independently extracted the following information: reference ID, name of the first author, year of publication, name of the journal, design of the trial, characteristics of the patient, details of the trial intervention, details of control intervention, outcome measurements, and adverse events. Disagreements were solved by the third reviewer (Yunhui Chen). All data were cross checked and imported into the RevMan software (version 5.3).

Risk of bias assessment

Two reviewers (Ying Xiong and Jingwen Wei) independently applied the *Cochrane Handbook for Systematic Reviews of Interventions* to assess the methodological quality of the included studies in terms of the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. Each domain was evaluated and ranked as "low-risk," "unclear," and "high-risk" (Higgins *et al.*, 2019). Any discrepancy was referred to the third reviewer (Jun Xia).

Statistical analysis

The RevMan (version 5.3) software was utilized for meta-analysis. A risk ratio (RR) with 95% confidence interval (95% CI) was used for dichotomous variables, while a mean difference (MD) with 95% CI was applied for continuous data. Statistical heterogeneity was investigated using the Chi-square and heterogeneity (I^2) statistics. The random-effects model was applied when heterogeneity ($I^2 \geq 50\%$) existed in the pooled studies; otherwise, the fixed-effects model was employed. The difference was deemed as statistically significant at $P < 0.05$. Sensitivity analysis was performed to evaluate the robustness of the pooled effects of studies. Publication bias was evaluated with a funnel plot.

Results

Eligible studies

Following the search strategy, 61 relevant studies were retrieved from the mentioned electronic databases. After excluding 12 duplicate publications, the abstract and title of 49 studies were reviewed to exclude 21 articles. Then, 22 studies were excluded upon full-text screening for the following reasons: 18 studies of expert opinion, case report, or without comparison; three reviews; and one trial without accessibility to the full text. Eventually, six eligible studies were included in this meta-analysis (Huang and Rao, 2018; Li *et al.*, 2020; Liu and Wang, 2015; Xue *et al.*, 2014; Zhang, 2017; Zhao *et al.*, 2019).

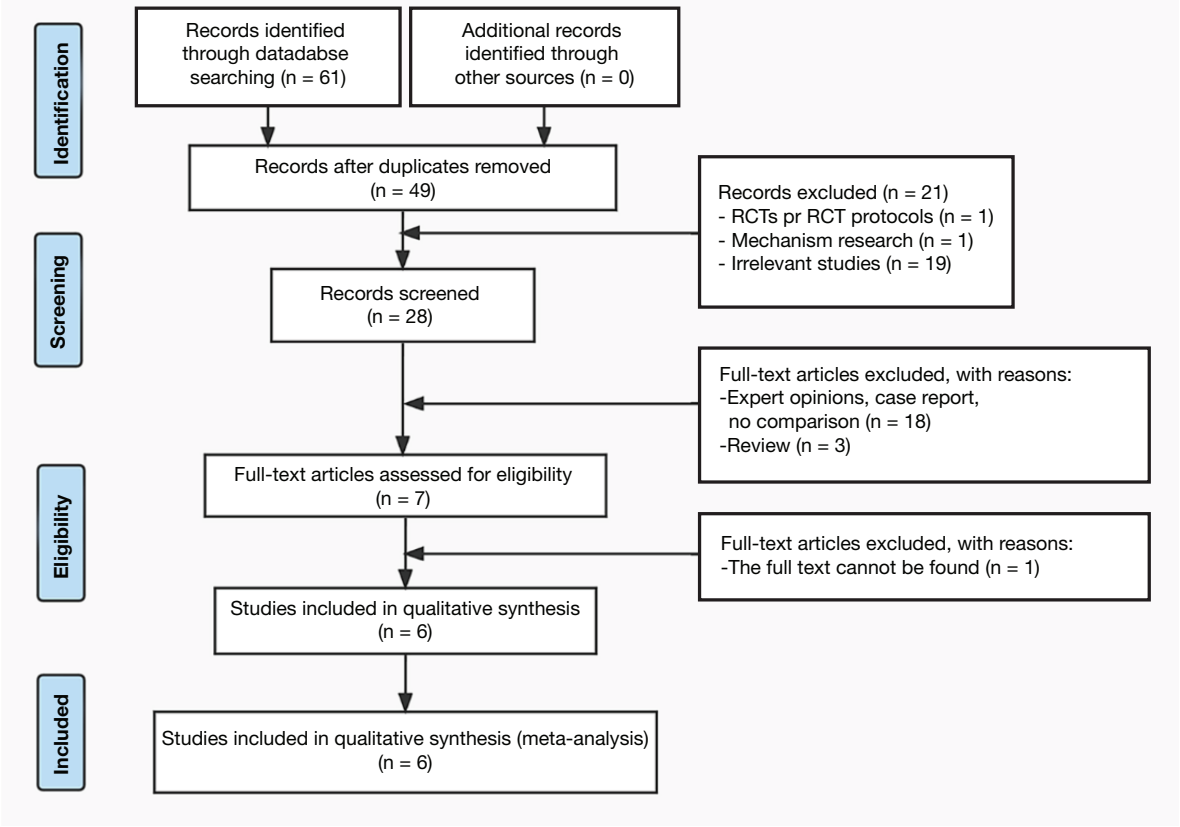

Figure 1. The PRISMA flow diagram of study selection and identification.

The PRISMA flowchart of the study selection and identification process is presented in Figure 1.

Characteristics of included studies

Six RCTs enrolling 331 participants (170 in trial groups and 161 in control groups) were included in this meta-analysis (Huang and Rao, 2018; Li *et al.*, 2020; Liu and Wang, 2015; Xue *et al.*, 2014; Zhang, 2017; Zhao *et al.*, 2019). All these studies were conducted in China and published in Chinese. The diagnosis of RLS was clearly identified in all studies. In the included RCTs, patients in the intervention group received STG decoction exclusively in two studies (Huang and Rao, 2018; Zhang, 2017) and together with conventional drugs in three studies (Liu and Wang, 2015; Xue *et al.*, 2014; Zhao *et al.*, 2019) and acupuncture in one study (Li *et al.*, 2020). All patients in the control group were treated with conventional drugs, including Madopar in two trials (Xue *et al.*, 2014; Zhang, 2017), pramipexole in three trials (Huang and Rao, 2018; Liu and Wang, 2015; Zhao *et al.*, 2019), and carbamazepine in one trial (Li *et al.*, 2020). The duration of the treatment varied from 4 to 12 weeks. For outcome variables, five trials presented the total effective rate (Huang and Rao, 2018; Li *et al.*, 2020; Liu and Wang, 2015; Zhang, 2017; Zhao *et al.*, 2019), four trials reported the IRLS (Huang and Rao, 2018; Li *et al.*, 2020; Wijemanne and Ondo W, 2017; Xue *et al.*, 2014; Zhao *et al.*, 2019), four trials evaluated the PSQI (Huang and Rao, 2018; Li *et al.*, 2020; Xue *et al.*, 2014; Zhao *et al.*, 2019), and two trials stated adverse events (Huang and Rao, 2018; Xue *et al.*, 2014). The characteristics of the included studies are summarized in Table 1.

Assessment of methodological quality

Generally, the quality of the included RCTs in this review was methodologically poor. Four of the six studies were rated as unclear risk because they just mentioned "random" and did not explicitly describe the generation methods (Huang and Rao, 2018; Liu and Wang, 2015; Zhao *et al.*, 2019; Zhang, 2017). Five studies were classified as unclear risk because of lack of report on the process of allocation concealment and blinding (Huang and Rao, 2018; Li *et al.*, 2020; Liu and Wang, 2015; Zhao *et al.*, 2019; Zhang, 2017). One study was unblinded by design and ranked as a high risk study (Huang and Rao, 2018). All the included studies presented complete data, and the attrition bias was evaluated as of low risk. Reporting bias and other biases were assessed as unclear because of insufficient data to classify the risk. The results of risk of bias evaluation are presented in Figure 2.

Table 1. Characteristics of included studies.

Author	Publication year	Sample size (T/C)	Average age (years) (T/C)	Course of disease (T/C)	Diagnostic criteria	Intervention		Treatment duration	Outcome variables
						TC			
Xue *et al.*	2014	26/20	75.15/ 74.50	–	CMA criteria 2009	SG-Tang and Madopar	Madopar	30 days	②+③+④
Liu and Wang	2015	25/25	–	41.2 ± 8.1 months/ 50.0 ± 10.2 months	IRLSSG criteria 2003	SG-Tang, Banxia Xiexin decoction, and pramipexole	Pramipexole	8 weeks	①
Zhang	2017	28/25	57.4/59.5	9 to 16 months/8 to 77 months	IRLSSG criteria 2003	SG-Tang	Madopar	4 weeks	①
Huang and Rao	2018	32/32	47.3/44.5	44.5 ± 6.4 months/ 46.2 ± 8.3 months	IRLSSG criteria 2003	SG-Tang	Pramipexole	12 weeks	①+②+③+④
Zhao *et al.*	2019	21/21	68/–	–	IRLSSG criteria 2014	SG-Tang and pramipexole	Pramipexole	4 weeks	①+②+③
Li *et al.*	2020	38/38	59.94/ 58.62	3.1 ± 2.6 years/ 4.1 ± 2.2 years	IRLSSG criteria 2014	SG-Tang and acupuncture	Carbamazepine	4 weeks	①+②+③

T: treatment group; C: control group; –: not reported; CMA: Chinese Medical Association; IRLSSG: International Restless Legs Syndrome Study Group; SG-Tang: Shaoyao Gancao decoction; ①Total effective rate; ②IRLS: International Restless Legs Syndrome Study Group Rating Scale for Severity of Restless Legs Syndrome; ③PSQI: Pittsburgh Sleep Quality Index; ④Adverse events.

Assessment of efficacy and safety

Total effective rate

Five of the six trials reported the total effective rate (Huang and Rao, 2018; Li *et al.*, 2020; Liu and Wang, 2015; Zhang, 2017; Zhao *et al.*, 2019). A fixed effects model was applied due to no significant heterogeneity (I^2 = 3%, P = 0.39). The pooled effect of meta-analysis demonstrated that the total effective rate in the patients treated with SG-Tang was significantly higher than conventional therapy (RR = 1.22, 95% CI (1.09, 1.36), P = 0.004) (Figure 3A).

IRLS

Four trials reported changes in the IRLS (Huang and Rao, 2018; Li *et al.*, 2020; Xue *et al.*, 2014; Zhao *et al.*, 2019). A random-effects model was utilized due to significant heterogeneity (I^2 = 96%, P = 0.001). The pooled effect of meta-analysis demonstrated that IRLS in the SG-Tang treatment group decreased more than the control group, and the difference was statistically significant (MD = –4.74, 95% CI (–8.65, –0.83), P = 0.02) (Figure 3B).

PSQI

Four trials reported the PSQI (Huang and Rao, 2018; Li *et al.*, 2020; Xue *et al.*, 2014; Zhao *et al.*, 2019). A random-effects model was utilized due to significant heterogeneity (I^2 = 78%, P = 0.004). The pooled effect of meta-analysis demonstrated that compared to the control group, the SG-Tang trial group exhibited statistically significant decrease in the PSQI (MD = –2.54, 95% CI (–4.34, –0.74), P = 0.006) (Figure 3C).

Adverse events

Two trials reported adverse events (Huang and Rao, 2018; Xue *et al.*, 2014), including dizziness, weary, nausea, and vomiting. A fixed-effects model applied as the heterogeneity was not significant (I^2 = 0%, P = 0.87). The pooled effect of the meta-analysis showed that the incidence of adverse events in the SG-Tang treatment group was significantly less than that of the conventional group (RR = 0.21, 95% CI (0.09, 0.31), P = 0.0005) (Figure 3D).

Sensitivity analysis

Sensitivity analysis demonstrated that eliminating any individual trial for the total effective rate did not alter the pooled effect, suggesting that the results of the meta-analysis were relatively robust (Figure 4).

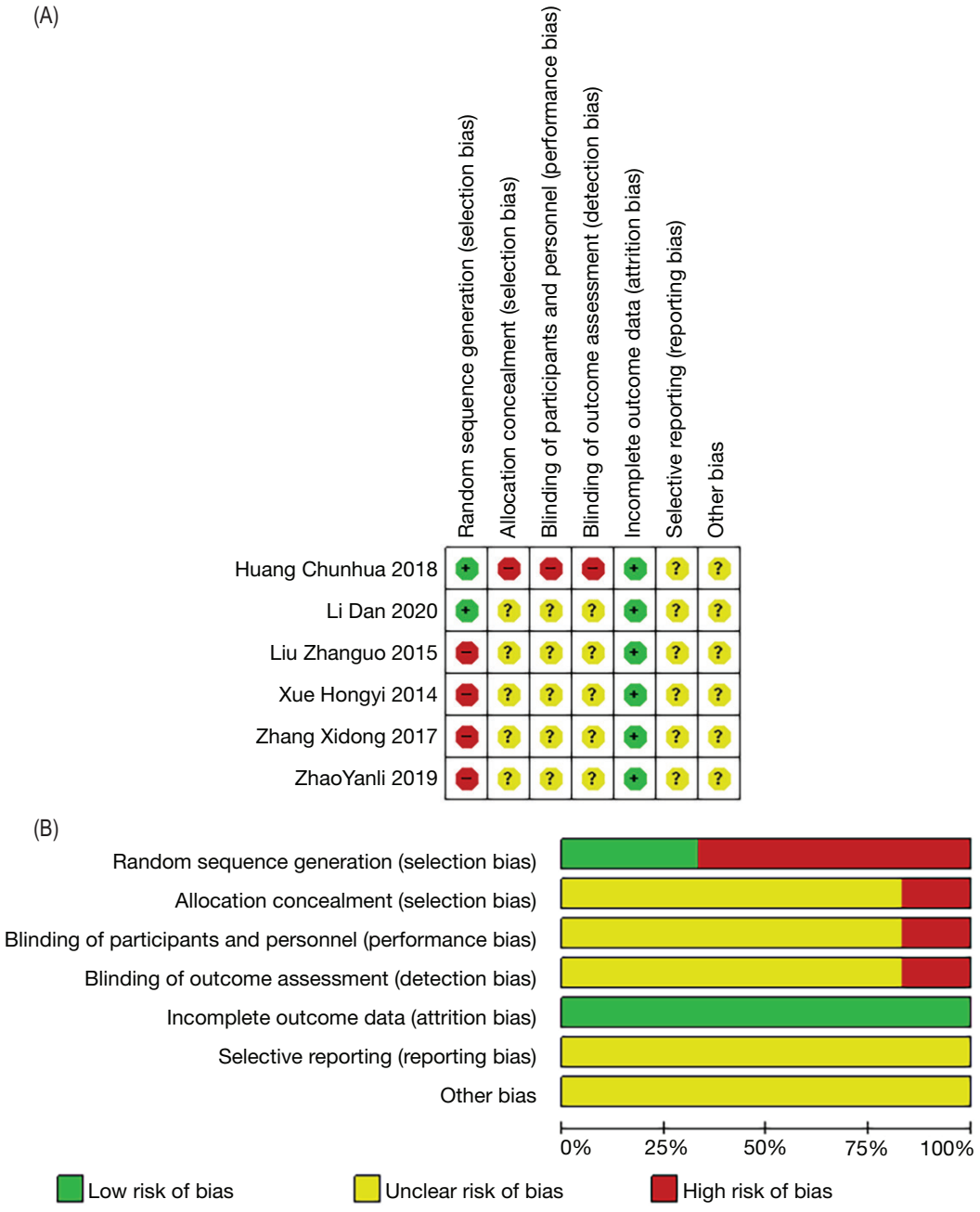

Figure 2. Assessment of methodological quality. (A) Risk of bias graph; (B) risk of bias summary.

Publication bias

Publication bias was evaluated using the inverted funnel plot analysis in terms of the effective rate. The funnel plot displayed a slight asymmetry, suggesting minor possibility of publication bias (Figure 5).

Discussion

Research in RLS has increased dramatically over the past decades. Although a cure for RLS is not available yet, appropriate treatment can keep the disease under control, minimize its symptoms, and improve patients' quality of life. IRLS has been extensively applied as the gold-standard outcome measure in almost all clinical trial settings of RLS. It was specifically developed for RLS severity scaling with desirable clinimetric properties to investigate responsiveness to changes (Walters *et al.*, 2003). The results of this meta-analysis have displayed overall (pooled) improvements in the total effective rate and IRLS, indicating that SG-Tang might yield an effective complementary and alternative approach in the treatment of RLS. Moreover, as impaired sleep

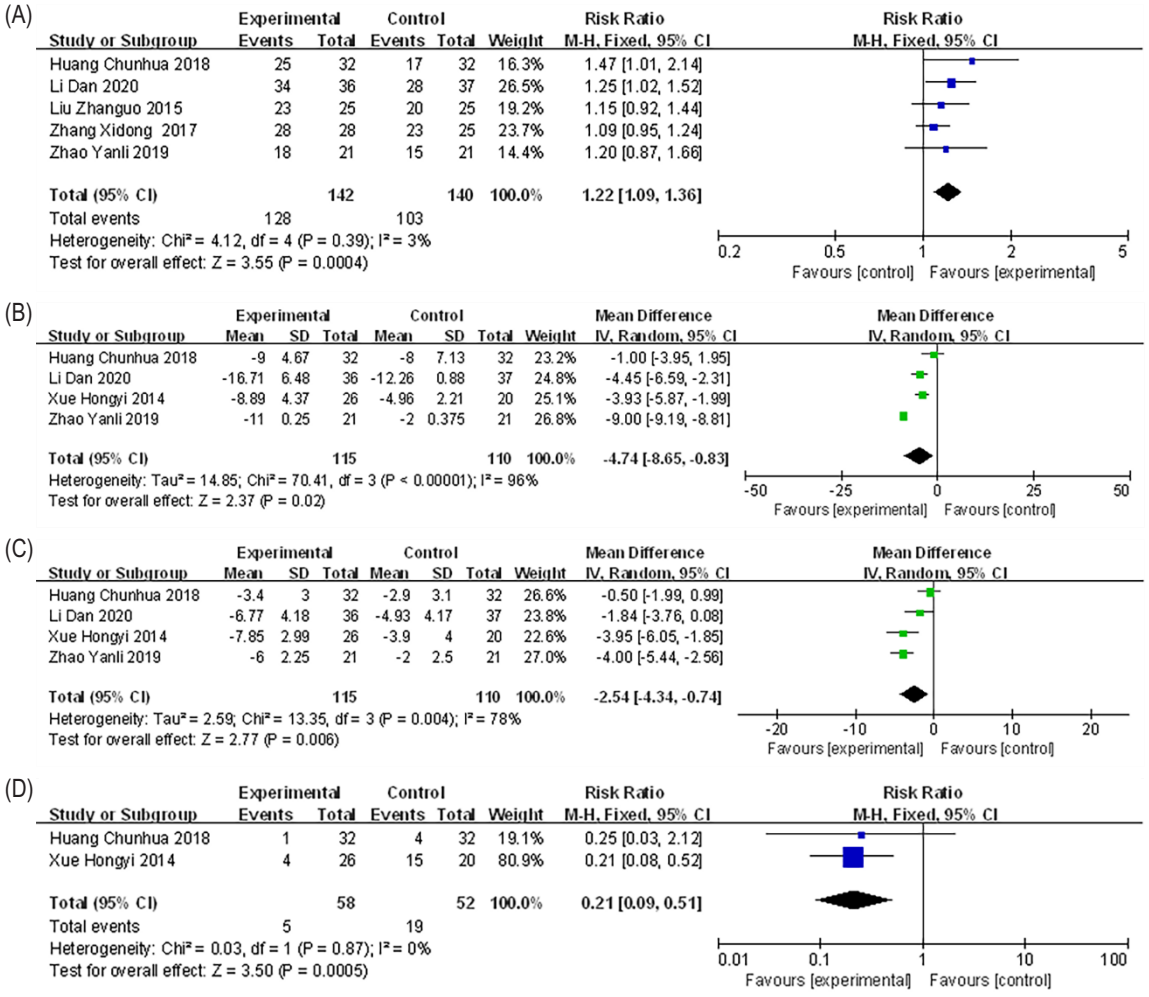

Figure 3. Forest plot for the effectiveness and safety of SG-Tang trial group versus conventional group for outcome variables of (A) total effective rate; (B) IRLS; (C) PSQI; and (D) adverse events.

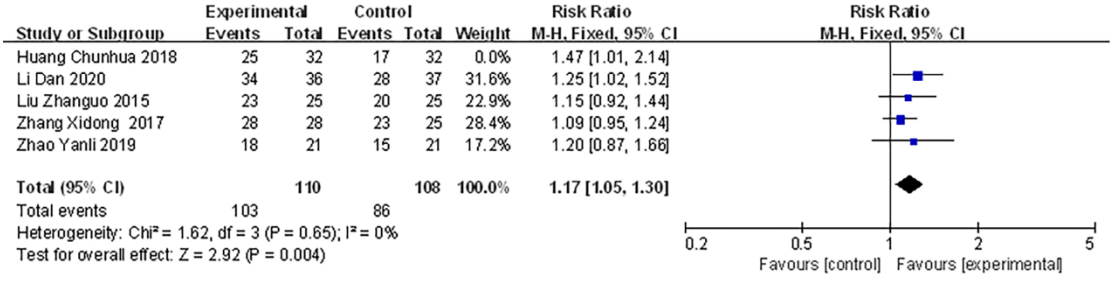

Figure 4. Sensitivity analysis plots of total effective rate.

quantity and quality are the most frequent complaints in RLS, besides efficacy parameters, the PSQI has been utilized as well in the clinical trial settings of RLS as the most common measure of sleep quality with high validity and reliability (Didato *et al.*, 2020; Pilz *et al.*, 2018). The PSQI-rated results in this study showed that the quality of sleep was improved significantly for patients receiving SG-Tang, suggesting an associated relationship between alleviated RLS symptoms and improved sleep. In sum, these findings indicate that SG-Tang, either solely or in combination with other interventions, can significantly improve the total effective rate, IRLS, and PSQI with fewer adverse effects for RLS patients.

Pathologically, RLS is considered a complex disease attributable to the overall dysfunction of the body. Therefore, physicians should be concerned about the local pathology and, most importantly, must identify

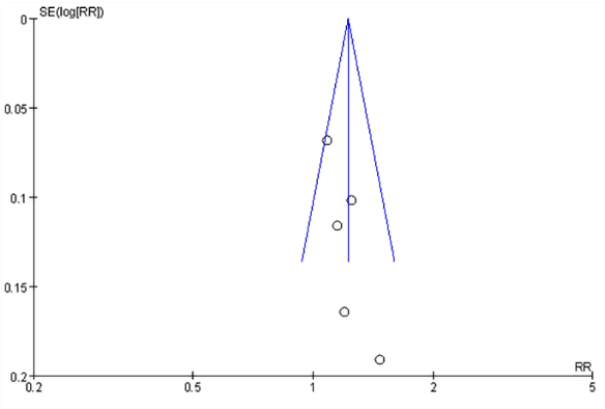

Figure 5. Funnel plot of publication bias for total effective rate.

and analyze the underlying multifactorial dysfunction to provide appropriate treatment. In recent years, various effective compounds, such as flavonoids, triterpene glycosides, monoterpene glycosides, phenolic acids, tannins, alkaloids, and saccharides, have been identified from this formula (Wu *et al.*, 2021). Furthermore, a compelling body of research has demonstrated that its pharmacological effects of spasmolysis, analgesic, sedative, hypnotic, and neuroprotection could be associated with its ingredients of paeoniflorin, benzoyl paeoniflorin, albiflorin, paeoniflorin oxide, glycyrrhizic acid, liquiritin, isoliquiritigenin, and ammonium glycyrrhetate, which may act synergically to treat RLS with improved symptoms and better sleep quantity and quality (Gu *et al.*, 2016; Huang *et al.*, 2019; Ji, 2003; Yin *et al.*, 2016; Zhu *et al.*, 2015).

Although the effectiveness and safety of SG-Tang for RLS treatment were meta-analyzed, this study has several limitations: (1) considerably high heterogeneity was notified in the outcome measurements of IRLS and PSQI, and the possible reasons could be the small sample size and different baseline conditions of each included trial. However, subgroup analysis cannot be conducted due to the limited number of studies, which could affect the accuracy and practicality of the results; (2) a limited number of studies were included, and the sample size of the studies was small, which carried a considerable risk of overrating the effectiveness and could result in downgraded confidence levels in results; (3) most RCTs were poor in methodological quality and could also result in overestimation of the therapeutic effect; (4) there was no consistent criteria for the effectiveness and therapeutic duration across studies; (5) only published RCTs were retrieved. The search strategy did not cover gray literature or preprint, which could have resulted in an overestimated pooled outcome; and (6) although the literature was searched without language restrictions, all the publications were from China and might have caused publication bias.

In addition, large-size, well-designed, and high-quality studies are required to tackle several key problems unresolved by the available studies, including: (1) allowing confidence in the evaluation of therapeutic benefits of SG-Tang, currently based on small studies with few participants and without follow-up or followed for a relatively shorter period; (2) understanding the effect of SG-Tang intervention on such variables in patients with RLS as the quality of life and sleep quantity and quality; and (3) optimal timing of SG-Tang intervention and monitoring of patients' treatment responses based on the severity of RLS.

Conclusion

In summary, this study demonstrates that *Shaoyao Gancao Tang* may be effective and safe for RLS as a complementary and alternative approach to conventional therapy. However, the results are required to be interpreted with caution because of the limited data and the low methodological quality of the included studies, and further verified with more well-designed and high-quality multi-center RCTs in a larger sample size.

Author contributions

Yunhui Chen, Zhining Tian, and Dan Liu conceptualized the study. Rong Li, Ying Xiong, and Zhining Tian did data curation for this study. Formal analysis of the data was exercised by Ying Xiong, Jingwen Wei, Wenying Huai, and Yunhui Chen. Yunhui Chen acquired funding for this research. Ying Xiong, Jingwen Wei, and Yunhui Chen carried investigations. Methodology was undertaken by Ying Xiong and Yunhui Chen. Yunhui Chen did project administration and supervision. Validation of the study was done by Jingwen, Hua Jiang, and Jun Xia. Original draft of the study was written by Zhining Tian, Yunhui Chen, Ying Xiong, and Jingwen Wei. Finally, Yunhui Chen and Ying Xiong wrote, reviewed, and editing the paper.

Funding statement

This study was supported by the International Cooperation and Exchange Project of Science & Technology Department of Sichuan Province (grant Nos. 23GJHZ0048 and 2017HH0004), the Sichuan Provincial Administration of Traditional Chinese Medicine (grant No. 2021MS464), the National Natural Science Foundation of China (grant No. 81603537), and the Young Scholar Program of Chengdu University of Traditional Chinese Medicine (grant No. QJRC2022004). The funders had no role in study design, data collection

and analysis, decision to publish, or preparation of the manuscript.

Competing interests

The authors declared that no competing interests existed.

Availablity of data, code, and other material

All relevant data are within the manuscript and its supporting information files.

References

Anguelova GV, Vlak MHM, Kurvers AGY, *et al.*, 2020. Pharmacologic and nonpharmacologic treatment of restless legs syndrome. Sleep Medicine Clinics 15(2): 277–288. https://doi.org/10.1016/j.jsmc.2020.02.013. PMID: 32386701.

Chen Y, Huang W, Liu L, *et al.*, 2020. Effectiveness and safety of traditional Chinese medicine Shaoyao Gancao Tang for the treatment of restless leg syndrome: a protocol for systematic review and meta-analysis. Medicine 99: 40(e22401). https://doi.org/10.1097/MD.0000000000022401. PMID: 33019415.

Chen IC, Lin TH, Hsieh YH, *et al.*, 2018. Formulated Chinese medicine Shaoyao Gancao Tang reduces tau aggregation and exerts neuroprotection through anti-oxidation and anti-inflammation. Oxidative Medicine and Cellular Longevity 2018: 9595741. https://doi.org/10.1155/2018/9595741. PMID: 30510632.

Didato G, Di Giacomo R, Rosa GJ, *et al.*, 2020. Restless legs syndrome across the lifespan: symptoms, pathophysiology, management and daily life impact of the different patterns of disease presentation. International Journal of Environmental Research and Public Health 17(10): 3658. https://doi.org/10.3390/ijerph17103658. PMID: 32456058.

Ekbom KA, 1960. Restless legs syndrome. Neurology 10(9): 868–873. https://doi.org/10.1212/wnl.10.9.868. PMID: 13726241.

Gossard TR, Trotti LM, Videnovic A, *et al.*, 2021.Restless legs syndrome: contemporary diagnosis and treatment. Neurotherapeutics 18(1): 140–155. https://doi.org/10.1007/s13311-021-01019-4. PMID: 33880737.

Gu XS, Wang F, Zhang CY, *et al.*, 2016. Neuroprotective effects of paeoniflorin on 6-OHDA-lesioned rat model of Parkinson's disease. Neurochemical Research 41(11): 2923–2936. https://doi.org/10.1007/s11064-016-2011-0. PMID: 27447883.

Heinrich M, Yao R and Xiao P, 2021. Food and medicine continuum—why we should promote cross-cultural communication between the global East and West. Chinese Herbal Medicine (CHM) 14(1): 3–4. https://doi.org/10.1016/j.chmed.2021.12.002. PMID: 36120124; PMCID: PMC9476788.

Higgins JPT, Thomas J, Chandler J, *et al.*, 2019. Cochrane handbook for systematic reviews of interventions. 2nd edition. John Wiley, Chichester, UK.

Huang CH and Rao WF, 2018. Randomized study on method of Zhongjing "Yin converted by sour and sweet combination" in the treatment of primary restless legs syndrome. Journal of Jiangxi University of Traditional Chinese Medicine 30: 31–35.

Huang RC, Zhao BB, Kong J, *et al.*, 2019. Effect of Shaoyao Gancao decoction on neurotransmitter and myotonia in rat brain with Parkinson's disease. Journal of Chinese Medicine 34(4): 760–765. https://doi.org/10.16368/j.issn.1674-8999.2019.04.181

Ji YB, 2003. Traditional Chinese medicine compound chemistry and pharmacology. People's Medical Publishing, Beijing, China, 150 p.

Lee KK, Omiya Y, Yuzurihara M, *et al.*, 2013. Antispasmodic effect of shakuyakukanzoto extract on experimental muscle cramps in vivo: role of the active constituents of glycyrrhizae radix. Journal of Ethnopharmacology 145: 286–293. https://doi.org/10.1016/j.jep.2012.11.005. PMID: 23164761.

Li D, Li XL, Li GN, *et al.*, 2020. Effect of Shaoyao Gancao decoction combined with acupuncture on restless legs syndrome and its influence on sleep quality. China Practical Medicine 15: 26–28. https://doi.org/10.14163/j.cnki.11-5547/r.2020.19.009

Liu ZG and Wang HP, 2005. Clinical trials of using pramipexole, Banxia Xiexin Tang, and Shaoyao Gancao Tang to treat 25 cases of restless legs syndrome. Jiangxi Journal of Traditional Chinese Medicine 46: 37–38.

Moher D, Liberati A, Tetzlaff J, *et al.*, 2009. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine 6: e1000097. https://doi.org/10.1016/j.jclinepi.2009.06.005. PMID: 19631508.

National Health Commission of the People's Republic of China, 2002. Notice of the Ministry of Health on further standardization of health-preservation food raw materials. Available at: http://www.nhc.gov.cn/sps/s3593/200810/bc239ea3d226449b86379f645dfd881d.shtml [Accessed: Jan. 10, 2022]

Ohayon MM, O'Hara R and Vitiello MV, 2012. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Medicine Reviews 16(4): 283–295. https://doi.org/10.1016/j.smrv.2011.05.002. PMID: 21795081.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.*, 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. British Medical Journal 372: n71. https://doi.org/10.1136/bmj.n71.

Pilz LK, Keller LK, Lenssen D, *et al.*, 2018. Time to rethink sleep quality: PSQI scores reflect sleep quality on workdays. Sleep 41(5): zsy029. https://doi.org/10.1093/sleep/zsy029. PMID: 29420828.

Rubí GP, 2018. Síndrome de piernas inquietas/Willis Ekbom desde la mirada del psiquiatra (Restless legs syndrome from the perspective of psychiatry). Revista Medica de Chile 146: 1041–1049. https://doi.org/10.4067/s0034-98872018000901041. PMID: 30725026.

Trenkwalder C, Allen R, Högl B, *et al.*, 2018. Comorbidities, treatment, and pathophysiology in restless legs syndrome. Lancet Neurology 17(11): 994–1005. https://doi.org/10.1016/S1474-4422(18)30311-9. PMID: 30244828.

Vellieux G and d'Ortho MP, 2020. Le syndrome des jambes sans repos (Restless legs syndrome). Revue de Médecine Interne 41(4): 258–264. https://doi.org/10.1016/j.revmed.2020.01.001. PMID: 32007297.

Walters AS, LeBrocq C, Dhar A, *et al.*, 2003. Validation of the International Restless Legs Syndrome Study Group rating

scale for restless legs syndrome. Sleep Medicine 4(2): 121–132. https://doi.org/10.1016/s1389-9457(02)00258-7. PMID: 14592342.

Wijemanne S and Ondo W, 2017. Restless legs syndrome: clinical features, diagnosis and a practical approach to management. Practical Neurology 17: 444–452. https://doi.org/10.1136/practneurol-2017-001762. PMID: 29097554.

Wu LF, Li YT, Tang YZ, *et al.*, 2021. Research progress on chemical constituents and pharmacological activities of Shaoyao Gancao Decoction. Drug Evaluation Research 44(06): 1354–1360.

Xue HY, Wu XW and Tian T, 2014. Clinical trials of using integrated traditional Chinese and western medicine to treat restless legs syndrome. Heilongjiang Medical Journal 27: 904–906. https://doi.org/10.14035/j.cnki.hljyy.2014.04.224

Yin D, Liu YY, Wang TX, *et al.*, 2016. Paeoniflorin exerts analgesic and hypnotic effects via adenosine A1 receptors in a mouse neuropathic pain model. Psychopharmacology (Berlin) 233(2): 281–293. https://doi.org/10.1007/s00213-015-4108-6. PMID: 26514553.

Zhang XD, 2017. Clinical trials of using heavy dosage of Shaoyao Gancao decoction to treat 28 cases of restless legs syndrome. Yunnan Journal of Traditional Chinese Medicine and Materia Medica 38: 62. https://doi.org/10.3969/j.issn.1007-2349.2017.01.027

Zhao YL, Wang SZ and Liang L, 2019. Clinical trials of using modified Shaoyao Gancao Tang to treat restless legs syndrome of hemodialysis patients. Yunnan Journal of Traditional Chinese Medicine and Materia Medica 40: 43–45. https://doi.org/10.16254/j.cnki.53-1120/r.2019.02.016

Zhu GW, Zhang GJ, Wang JJ, *et al.*, 2015. Effect of single factor compatibility dose on pharmacodynamic components of Shaoyao Gancao decoction. Practical Pharmacy and Clinical Remedies 18(2): 168–173. https://doi.org/10.14053/j.cnki.ppcr.201502013

Supplementary

Table S1. Search strategy for the PubMed.

No.	Search terms
1	Restless Legs Syndrome [Mesh]
2	Restless Legs
3	Willis–Ekbom Disease
4	Disease, Willis–Ekbom
5	Wittmaack–Ekbom Syndrome
6	Syndrome, Wittmaack–Ekbom
7	Willis–Ekbom Disease
8	Disease, Willis–Ekbom
9	Willis–Ekbom Syndrome
10	Syndrome, Willis–Ekbom
11	Wittmaack–Ekbom Syndrome
12	Syndrome, Wittmaack–Ekbom
13	Restless Leg Syndrome
14	Syndrome, Restless Leg
15	Willis–Ekbom Syndrome
16	Syndrome, Willis–Ekbom
17	RLS
18	periodic leg movement
19	quiescegenic focal akathisia
20	OR 1–19
21	Shaoyao Gancao Tang
22	SG Tang
23	Shakuyakukanzoto
24	SKT
25	Paeonia lactiflflora and Glycyrrhiza uralensis decoction
26	Chinese Peony and Licorice Combination
27	OR 21–26
28	randomized controlled trial [pt]
29	controlled clinical trial [pt]
30	randomized [tiab]
31	placebo [tiab]
32	randomly [tiab]
33	trial [tiab]
34	OR 28–33
35	20 AND 27 AND 34

Table S2. PRISMA 2020 Checklist

Section and topic	Item #	Checklist item	Location where item is reported
Title			
Title	1.	Identify the report as a systematic review.	Ekbom, 1960
Abstract			
Abstract	2.	See the PRISMA 2020 for Abstracts checklist.	Gossard, *et al.*, 2021; Ohayon *et al.*, 2012
Introduction			
Rationale	3.	Describe the rationale for the review in the context of existing knowledge.	Rubí, 2018; Trenkwalder *et al.*, 2018; Wijemanne and Ondo, 2017
Objectives	4.	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Trenkwalder *et al.*, 2018
Methods			
Eligibility criteria	5.	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Trenkwalder *et al.*, 2018; Vellieux and d'Ortho, 2020
Information sources	6.	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Trenkwalder *et al.*, 2018; Vellieux and d'Ortho, 2020
Search strategy	7.	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Trenkwalder *et al.*, 2018
Selection process	8.	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Vellieux and d'Ortho, 2020; Wijemanne and Ondo, 2017
Data collection process	9.	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Wijemanne and Ondo, 2017
Data items	10a.	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, and analyses), and if not, the methods used to decide which results to collect.	Wijemanne and Ondo, 2017
	10b.	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources, etc.). Describe any assumptions made about any missing or unclear information.	Wijemanne and Ondo, 2017
Study risk of bias assessment	11.	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study, and whether they worked independently, and if applicable, details of automation tools used in the process.	Anguelova *et al.*, 2020; Wijemanne and Ondo, 2017
Effect measures	12.	Specify for each outcome the effect measure(s) (e.g., risk ratio and mean difference) used in the synthesis or presentation of results.	Anguelova *et al.*, 2020
Synthesis methods	13a.	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Anguelova *et al.*, 2020
	13b.	Describe any methods required to prepare data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Anguelova *et al.*, 2020
	13c.	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Anguelova *et al.*, 2020
	13d.	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s) and method(s) to identify the presence and extent of statistical heterogeneity, and the software package(s) used.	Anguelova *et al.*, 2020
	13e.	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis and meta-regression).	Anguelova *et al.*, 2020
	13f.	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Anguelova *et al.*, 2020

Section and topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14.	Describe any methods used to assess risk of bias because of missing results in a synthesis (arising from reporting biases).	Anguelova *et al.*, 2020
Certainty assessment	15.	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Anguelova *et al.*, 2020
Results			
Study selection	16a.	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Anguelova *et al.*, 2020
	16b.	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Anguelova *et al.*, 2020; Lee *et al.*, 2013
Study characteristics	17.	Cite each included study and present its characteristics.	Heinrich *et al.*, 2021; Lee *et al.*, 2013
Risk of bias in studies	18.	Present assessments of risk of bias for each included study.	Chen *et al.*, 2018
Results of individual studies	19.	For all outcomes, present, for each study the following: (a) summary statistics for each group (where appropriate), and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Chen *et al.*, 2020; National Health Commission of the People's Republic of China, 2002
Results of syntheses	20a.	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	Chen *et al.*, 2020; National Health Commission of the People's Republic of China, 2002
	20b.	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Chen *et al.*, 2020; National Health Commission of the People's Republic of China, 2002
	20c.	Present results of all investigations of possible causes of heterogeneity among study results.	Chen *et al.*, 2020; National Health Commission of the People's Republic of China, 2002
	20d.	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Chen *et al.*, 2020; National Health Commission of the People's Republic of China, 2002
Reporting biases	21.	Present assessments of risk of bias because of missing results (arising from reporting biases) for each synthesis assessed.	Chen *et al.*, 2020
Certainty of evidence	22.	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Chen *et al.*, 2020
Discussion			
Discussion	23a.	Provide a general interpretation of the results in the context of other evidence.	Chen *et al.*, 2020; Moher *et al.*, 2009
	23b.	Discuss any limitation of the evidence included in the review.	Higgins *et al.*, 2019
	23c.	Discuss any limitation of the review processes used.	Higgins *et al.*, 2019
	23d.	Discuss implications of the results for practice, policy, and the future research.	Higgins *et al.*, 2019; Moher *et al.*, 2009
Other information			
Registration and protocol	24a.	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Trenkwalder *et al.*, 2018
	24b.	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Trenkwalder *et al.*, 2018
	24c.	Describe and explain any amendments to information provided at registration or in the protocol.	Trenkwalder *et al.*, 2018
Support	25.	Describe sources of financial or nonfinancial support for the review, and the role of the funders or sponsors in the review.	Liu and Wang, 2015
Competing interests	26.	Declare any competing interests of review authors.	Zhang, 2017
Availability of data, code, and other material	27.	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; and any other material used in the review.	Zhang, 2017

From: Page *et al.* (2020). For more information, visit: http://www.prisma-statement.org/