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Paeoniae Radix-containing herbal medicine for patients with restless legs syndrome: A systematic review and meta-analysis

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ABSTRACT

Background and purpose: Paeoniae Radix has been used for legs discomfort such as restless legs syndrome. The aim of this review is to evaluate efficacy and safety of Paeoniae Radix-containing herbal medicine on restless legs syndrome.

Methods: Literature search was conducted on PubMed, Scopus, CENTRAL, CiNii, KTKP, OASIS, and CNKI for randomized controlled trials that evaluated the effects of Paeoniae Radix-containing herbal medicines on restless legs syndrome.

Results: Twelve studies (n = 639) were included. The overall methodological quality was low. In the herbal group, meta-analysis indicated statistically significant improvements in the total effective rate, the restless legs syndrome rating scale and the Pittsburgh Sleep Quality Index as compared with those in the non-herbal group. Herbal treatments were found to be relatively safe.

Conclusion: Paeoniae Radix-containing herbal medicines might promote improvements in restless legs syndrome. However, we are unable to draw concrete conclusions owing to limitations of the included studies.

1. Introduction

Restless legs syndrome is a disease characterized by discomfort in the legs that intensifies in the night; symptoms can be alleviated by mild exercise [1]. In particular, the disease often manifests in the calf region, and then in the thighs, the arms, and the face. Restless legs syndrome reduces quality of sleep, and causes insomnia [1]. As a result, this accumulation of mental stress causes depression and anxiety, which adversely affects the quality of life. According to a previous study, 50.5% of patients with restless legs syndrome stated that the condition has negative effects on their mood [2].

Both non-pharmacological and pharmacological treatments exist for restless legs syndrome. Non-pharmacological treatments include avoiding ingestion of substances that can aggravate symptoms (eg, caffeine, alcohol, tobacco, etc.), massages, repetitive magnetic stimulations, exercise, infrared therapy, standard acupuncture, and intake of iron-containing foods [3]. Iron, dopamine agonists in combination with levodopa, antiepileptics, and opioid drugs are used as pharmacological treatments [4]. Among them, the most commonly used drugs are dopamine agonists. Dopamine agonists such as pramipexole and ropinirole revealed good therapeutic responses in most restless legs syndrome patients [5]. However, long-term usage of dopamine agonists may lead to increased compulsive gambling [6] or augmentation [7].

In East Asian countries, herbal medicines have been used for treatment of restless legs syndrome. Among the various herbs, the most commonly used herb is Paeoniae Radix. Accoridng to our literature search, a number of randomized controlled trials evaluating the effect of herbal medicines on restless legs syndrome have been published until October 2017 (16 studies) [8–23], many of which (12/16 studies) [12–23] contain Paeoniae Radix. Paeoniae Radix has traditionally been used for discomfort in lower extremities such as calf cramps and lower extrimities pain. Therefore, it is natural that Paeoniae Radix is widely used for restless legs syndrome, which is clinically expressed mainly as a legs' discomfort [24].

Despite continued clinical studies and publication on the effects of herbal medicine on restless legs syndrome, there has been no systematic literature review and meta-analysis that summarizes the results of these randomized clinical trials (RCTs). Therefore, in the present study, we will systematically review the clinical effect of herbal medicines contained Paeoniae Radix, which seems to be the most used, on restless legs

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syndrome based on results of published clinical studies.

2. Methods

2.1. Database search

Electronic databases including PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), CiNii, Korean Traditional Knowledge Portal (KTKP), Oriental Medicine Advanced Searching Integrated System (OASIS), and Chinese National Knowledge Infrastructure (CNKI) were searched until October 2017. The search strategies were modified based on characteristics of individual databases. The main keywords used were “Restless legs syndrome”, “Randomized Controlled Trial”, and “Herbal medicine”, which were appropriately combined for each database search. There was no language restriction in the study selection process. Following the electronic search, two independent researchers (KSW and JWS) screened and selected the studies. After removing duplicated studies, the remaining studies were assessed based on the title and abstract of individual studies.

2.2. Eligibility criteria

The initially screened studies were subsequently reviewed and selected according to the following eligibility criteria. For trial design, only RCTs were included; non-randomized clinical trials (NCTs) were excluded. Observational studies including case reports and series were also excluded from the meta-analysis. Eligible participants were defined as patients with idiopathic restless legs syndrome and restless legs syndrome induced by diabetes and renal failure. For diagnosis of restless legs syndrome, clinical criteria or polysomnography were used. For the intervention, studies that used various oral forms of Paeoniae Radix-containing herbal medicines including decoction, extracted powder, and extracted capsules were included. For the control group, studies with placebo and conventional therapies were included. In contrast, studies using herbal medicines that differed from the intervention group were excluded, while studies that evaluated the combined effect of herbal and western medicine, as well as other alternative therapies like acupuncture, moxibustion, and exercise programs were also excluded.

2.3. Outcome assessment

The primary outcome index was the total effective rate (TER) based on changes in overall symptoms of restless legs syndrome. In this study, TER was calculated as the sum of the numbers of ‘cure’ or ‘improved’ or ‘slightly improved’. In other words, it is calculated from items other than ‘unchanged’ or ‘worse’ categories. The secondary outcomes included (1) the restless legs syndrome rating scale (RLSRS) based on changes in symptoms, and (2) Pittsburgh Sleep Quality Index (PSQI) for symptoms of sleep disturbance. The frequencies and types of adverse events were also investigated.

2.4. Data extraction and quality assessment in individual studies

Two independent reviewers (KSW and JWS) gathered the data from all qualified studies, and assessed the risk of bias. Disagreement between the two reviewers were solved by an arbiter (CKH), who made the final decision. All extracted data were recorded in a pre-defined extraction form. Details of the extracted data were as follows: (1) total number of participants (herbal medicine group and control group), (2) types of herbal medicines, including the name of herbal prescriptions and details of the compounds, (3) concomitant treatment including conventional therapies, (4) control group intervention, (5) main outcomes during final outcome assessment, (6) final outcome assessment time (days), and (7) reports of all adverse events.

Quality assessment was performed based on the Cochrane risk of bias assessment tool [25], which was performed by two independent reviewers (KSW and JWS); similarly, the arbiter (CKH) made the final decision when disagreements arose between the researchers. A total of seven domains including sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome, selective outcome reporting, and other risks of bias were assessed. Each domain was evaluated as high risk of bias (H), low risk of bias (L), or unclear risk of bias (U).

2.5. Synthesis of data and meta-analysis

Dichotomous data, such as the TER, were presented with the risk ratio (RR) and 95% confidence interval (CI). Continuous data such as the RLSRS and the PSQI were presented with the mean difference (MD). If no statistical heterogeneity was found, the fixed effect model was used for meta-analysis. The heterogeneity of the risk factors among the trials was analysed by I^2, where $I^2 < 50\%$ indicated no statistical heterogeneity. In addition, heterogeneity in the methodology of studies was also evaluated. If the heterogeneity of the study is greater than the others, the relevant study was excluded from the analysis. The RevMan 5.3 software recommended by the Cochrane Collaboration (Oxford, UK) was used for all data analyses (http://tech.cochrane.org/revman/). When calculating the TER-related RR with RevMan 5.3, numbers of events are entered as a number that is the sum of ‘worse’ or ‘unchanged'.

3. Results

3.1. Study selection and characteristics

A total of 763 studies were retrieved by electronic search, and were included in the first screening stage. Of those, 35 studies were further assessed for eligibility to be included in the meta-analysis by reading the full article. Twenty three studies were excluded due to the following reasons (Fig. 1): duplicates (n = 4), ineligible designs of trials (n = 13), ineligible interventions (n = 4), and ineligible control interventions (n = 2). After reviewing the full text from each study, 12 studies (639 patients with restless legs syndrome) were included for the meta-analysis. The types of restless legs syndrome were found to be idiopathic (n = 408), diabetes-associated (n = 66), or renal failure-associated (n = 165).

There were two types of comparison in the included studies: (1) herbal medicine + conventional therapies *vs.* conventional therapies alone [12–19], and (2) herbal medicine *vs.* conventional therapies [20–23].

Among the included studies, the overall restless legs syndrome symptom severity was evaluated by the TER in 10 studies [12,13,15–20,22,23], the RLSRS in 6 studies [12,14,16,18,21,23], and the PSQI in 2 studies [14,16].

Herbal medicines included in the studies were Yangxie Rougan Fang (YRF, n = 1) [12], An Tui Tang (ATT, n = 1) [13], Jiawei Shaoyao Tang (JST, n = 1) [14], Huangqi Guizhi Wuwu Tang and Huangqi Guizhi Wuwu Tang Jiawei (HGWT and HGWTJ, n = 2) [15,22], Huangqi Jianzhong Tang (HJT, n = 1) [20], Guizhi jia Shaoyao Tang (GST, n = 1) [21], Danggui Liuhuang Tang Jiawei (DLTJ, n = 1) [23], Danggui Shaoyao San + Ganjiang Fuzi Tang (DSS + GFT, n = 1) [16], Yiqi Hexeu Tongluo Fa (YHTF, n = 1) [17], Wenyangtongjing Roujinhuanji Tang (WRT, n = 1) [18], and Buyang Huanwu Tang (BHT, n = 1 [19]) (Tables 1 and 2). The conventional therapies included in the studies consisted of dopamine replacement therapy represented by levodopa and pramipexole, common diabetes therapy in diabetic restless legs syndrome patients, hemodialysis, anaemia correction, blood pressure control, and calcium and phosphate metabolism correction in renal failure patients.

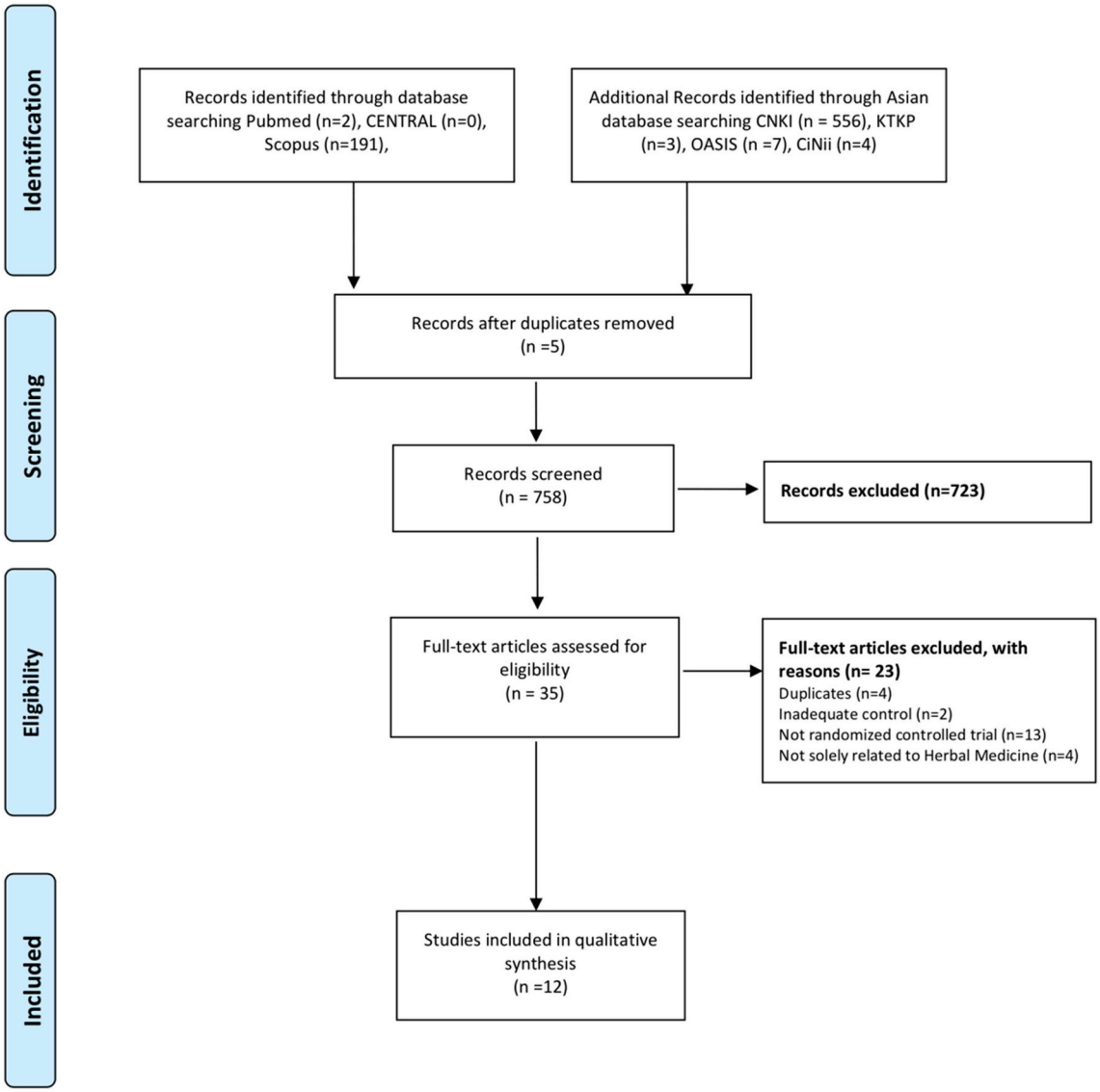

Fig. 1. PRISMA flow diagram of study selection.

3.2. Risk of bias within the studies

In most studies, the risk of bias was not low. Among the seven risk of bias domains, random sequence generation, allocation concealment, blinding of participants, and outcome assessors revealed methodological concerns. Two studies were associated with low risk of bias in the random sequence generation, and showed incomplete outcome data [20,21]. All remaining studies [12–19,22,23] demonstrated low risk of bias in incomplete outcome data. A summary of risk of bias is shown in Fig. 2.

3.3. Total effective rate (TER) of herbal medicines treatment for restless legs syndrome

Ten studies that compared add-on herbal medicine (conventional therapies plus herbal medicines) with control treatment (conventional therapies only) assessed the TER for restless legs syndrome. Among those, seven types of herbal complexes were studied [12,13,15–19]. There was significantly low RR (for no effect or aggravation) in the herbal medicines group when compared with that of the control group (RR 0.34, 95% CI [0.21, 0.55]). In subgroup analysis according to types of herbal medicines, inconsistent results were found (YRF [12]: RR 0.20, 95% CI [0.03, 1.56]; ATT [13]: RR 0.29, 95% CI [0.08, 1.00]; HGWTJ [15]: RR 0.05, 95% CI [0.00, 0.89]; DSS + GFT [16]: RR 0.33, 95% CI [0.11, 1.04]; YHTF [17]: RR 0.23, 95% CI [0.05, 0.99]; WRT [18]: RR 0.50, 95% CI [0.22, 1.14]; and BHT [19]: RR 0.43, 95% CI [0.13, 1.40]) (Fig. 3(a)). In subgroup analysis according to the restless legs syndrome type, consistent results were found in each type (Idiopathic [12,13,15]: RR 0.22, 95% CI [0.08, 0.58], and Renal failure [16–19]: RR 0.40, 95% CI [0.23, 0.68]) (Fig. 3(b)).

Three RCTs [20,22,23] compared the TER of herbal medicine to that of conventional therapy. The herbal medicines group showed significantly lower RR as compared with that of the control group (0.22, 95% CI [0.09, 0.54]) (Fig. 3(c)). One study [20] compared the TER of HJT to flunarizine + alprazolam (0.14, 95% CI [0.02, 1.05]. Another two studies compared the TER of HGWT [22] to that of levodopa/benserazide, and the TER of DLTJ [23] to that of levodopa/benserazide (0.24, 95% CI [0.09, 0.68]) (Fig. 3(d)). In subgroup analysis according to the restless legs syndrome type, consistent results were found in each type (Idiopathic [20,22]: RR 0.25, 95% CI [0.08, 0.81], and Renal failure [23]: RR 0.40, 95% CI [0.04, 0.76]) (Fig. 3(e)).

Table 1
Characteristics of included studies.

Study (First author, year)	Subjects (Herbal/ Control)	RLS type	Interventions		Main outcomes (Herbal/control)	Outcome assessment time (weeks)	Adverse events (Herbal/control)
			Herbal medicines	Control group			
Cheng, 2016 [12]	40 (20/20)	Idiopathic	YRF + Flupentixol/Melitracen	Flupentixol/Melitracen	TER (%)-95.0/75.0 RLSRS-8.14 ± 2.40/12.5 ± 3.31	4	Unreported
Wang, 2010 [13]	114 (58/56)	Idiopathic	ATT + Clonazepam + Levodopa/Benserazide	Clonazepam + Levodopa/Benserazide	TER (%)-94.8/82.2	2–4	Unreported
Xue, 2014 [14]	46 (26/20)	Idiopathic	JST + Levodopa/Benserazide	Levodopa/Benserazide	RLSRS-10.12 ± 7.84/11.15 ± 8.13 PSQI-6.15 ± 2.99/ 10.10 ± 4.00	4	Dizziness 1/4 Constipation 1/8 Abdominal discomfort 2/3
Li, 2010 [15]	56 (21/35)-36/20	Idiopathic	HGWTJ + Flunarizine + Vitamin E	Flunarizine + Vitamin E	TER (%)-100/75.0	2	Unreported
Feng, 2015 [20]	36 (18/18)	Idiopathic	HJT	Flunarizine + Alprazolam (Insomnia)	TER (%)-94.4%/ 61.1%	6	Unreported
Nie, 2013 [21]	40 (20/20)	Idiopathic	GST	Levodopa/Benserazide	RLSRS-7.12 ± 2.43/9.56 ± 3.25 RLSQoL-86.68 ± 14.46/71.35 ± 12.12	4	Nausea 0/1
Liu, 2012 [22]	40 (20/20)	Idiopathic	HGWT	Levodopa/Benserazide	TER (%)-90.0/70.0	4	Unreported
Yu, 2013 [23]	66 (33/33)	Diabetic	DLTJ	Levodopa/Benserazide	TER (%)-93.9/66.7 RLSRS-10.92 ± 1.94/15.72 ± 2.73	4	Symptoms of digestive system 0/2
Xiao, 2017 [16]	38 (16/22)-19/19	Renal failure	DSS + GFT + Hemodialysis + Anaemia correction + Calcium and phosphate metabolism correction	Hemodialysis + Anaemia correction + Calcium and phosphate metabolism correction	RLSRS-11.55 ± 8.45/15.45 ± 9.67 PSQI-7.85 ± 3.57/ 9.95 ± 4.08 TER (%)-84.2/52.6	4	Unreported
Zhang, 2016 [17]	54 (28/26)	Renal failure	YHTF + Hemodialysis + Anaemia correction + Blood pressure control + Calcium and phosphate metabolism correction	Hemodialysis + Anaemia correction + Blood pressure control + Calcium and phosphate metabolism correction	TER (%)-92.9/69.2	4	Unreported
Wang, 2013 [18]	73 (41/32)	Renal failure	WRT + Hemodialysis + Anaemia correction + Blood pressure control + Blood glucose control	Hemodialysis + Anaemia correction + Blood pressure control + Blood glucose control	TER (%)-82.93%/ 65.63% RLSRS-3.88 ± 1.03/5.91 ± 1.30	8	Unreported
Sun, 2017 [19]	36 (18/18)	Renal failure	BHT + Hemodialysis + Anaemia correction + Blood pressure control + Blood glucose control	Hemodialysis + Anaemia correction + Blood pressure control + Blood glucose control	TER (%)-83.3%/ 61.1%	4	Unreported

ATT: An Tui Tang; BHT: Buyang Huanwu Tang; DLTJ: Danggui Liuhuang Tang Jiawei; DSS + GFT: Danggui Shaoyao San + Ganjiang Fuzi Tang; GST: Guizhi jia Shaoyao Tang; HGWT: Huangqi Guizhi Wuwu Tang; HGWTJ: Huangqi Guizhi Wuwu Tang Jiawei; HJT: Huangqi Jianzhong Tang; JST: Jiawei Shaoyao Tang; PSQI: Pittsburgh Sleep Quality Index; RLS: Restless Legs Syndrome; RLSRS: Restless Legs Syndrome Rating Scale; TER: Total Effective Rate; WRT: Wenyangtongjing Roujinhuanji Tang; YHTF: Yiqi Hexeu Tongluo Fa; YRF: Yangxie Rougan Fang.

Table 2
Herbal medicines and treatment details.

Study (first author, year)	Name of treatment	Components of Herbal medicines
Cheng, 2016	Yangxie Rougan Fang	Paeoniae Radix Alba 30 g, Rehmanniae Radix Preparat 20 g, Lycii Fructus 15 g, Ligustri Lucidi Fructus 10 g, Ecliptae Herba 10 g, Angelicae Gigantis Radix 10 g, Rhizoma Ligustici Chuanxiong 15 g, Corydalis Tuber 30 g, Glycyrrhizae Radix Praeparata 6 g
Wang, 2010	An Tui Tang	Paeoniae Radix Alba 30 g, Glycyrrhizae Radix 6 g, Achyranthis Radix 15 g, Chaenomelis Fructus 10 g, Puerariae Radix 15 g, Saposhnikovia Radix 10 g, Taxilli Ramulus 15 g, Fossilia Ossis Mastodi 30 g, Ostreae Concha 30 g
Xue, 2014	Jiawei Shaoyao Tang	Paeoniae Radix 30 g, Glycyrrhizae Radix 9 g, Polygoni Multiflori Ramulus 9 g, Albizziae Cortex 12 g, Margaritifera Usta Concha 30 g, Zizyphi Spinosae Semen 12 g, Poria (Hoelen) 9 g, Rehmanniae Radix Preparat 9 g, Chaenomelis Fructus 9 g, Angelicae Gigantis Radix 9 g, Fossilia Ossis Mastodi 30 g, Ostreae Concha 30 g
Liu, 2012	Huangqi Guizhi Wuwu Tang	Astragali Radix 30 g, Cinnamomi Ramulus 12 g, Paeoniae Radix Alba 30 g, Zingiberis Rhizoma Recens 30 g, Zizyphi Fructus 12 pieces
Li, 2010	Huangqi Guizhi Wuwu Tang Jiawei	Astragali Radix ~30–60 g, Cinnamomi Ramulus 15 g, Puerariae Radix 15 g, Achyranthis Radix 15 g, Paeoniae Radix Alba 20 g, Chaenomelis Fructus 30 g, Lycopodii Herba 30 g, Albizziae Cortex 30 g, Zingiberis Rhizoma Recens 3 pieces, Zizyphi Fructus 3 pieces
Feng, 2015	Huangqi Jianzhong Tang	Codonopsis Pilosulae Radix 30 g, Astragali Radix 30 g, Zingiberis Rhizoma Siccus 15 g, Cinnamomi Ramulus 20 g, Paeoniae Radix Alba 20 g, Zizyphi Fructus 13 g, Glycyrrhizae Radix Praeparata 15 g
Nie, 2013	Guizhi jia Shaoyao Tang	Paeoniae Radix Alba 20 g, Glycyrrhizae Radix Praeparata 6 g, Cinnamomi Ramulus 10 g, Zizyphi Fructus 10 g
Yu, 2013	Danggui Liuhuang Tang Jiawei	Astragali Radix 30 g, Paeoniae Radix Alba 30 g, Angelicae Gigantis Radix 15 g, Rehmanniae Radix 20 g, Rehmanniae Radix Preparat 20 g, Scutellariae Radix 6 g, Phellodendri Cortex 6 g, Coptidis Rhizoma 10 g, Glycyrrhizae Radix Praeparata 10 g
Xiao, 2017	Danggui Shaoyao San + Ganjiang Fuzi Tang	Angelicae Gigantis Radix 15 g, Paeoniae Radix Alba 15 g, Rhizoma Ligustici Chuanxiong 15 g, Poria (Hoelen) 15 g, Alismatis Rhizoma 10 g, Atractylodis Rhizoma Alba 15 g, Pulvis Aconiti Tuberis Purificatum 10 g, Zingiberis Rhizoma Siccus 10 g
Zhang, 2016	Yiqi Hexeu Tongluo Fa	Astragali Radix 30 g, Cinnamomi Ramulus 12 g, Paeoniae Radix Alba 12 g, Angelicae Gigantis Radix 18 g, Scolopendra Corpus 2 pieces, Scorpio 4 g, Spatholobi Caulis 30 g, Zingiberis Rhizoma Recens 18 g, Zizyphi Fructus 4 pieces
Wang, 2013	Wenyangtongjing Roujinhuanji Tang	Pulvis Aconiti Tuberis Purificatum 10 g, Zingiberis Rhizoma Siccus 12 g, Cinnamomi Ramulus 12 g, Asari Herba Cum Radix 5 g, Coicis Semen 30 g, Chaenomelis Fructus 12 g, Puerariae Radix 12 g, Paeoniae Radix Alba 30 g, Glycyrrhizae Radix 10 g, Mume Fructus 12 g, Achyranthis Radix 30 g, Cibotii Rhizoma 15 g, Lamii Radix 15 g, Fossilia Ossis Mastodi 30 g, Ostreae Concha 30 g, Spatholobi Caulis 30 g
Sun, 2017	Buyang Huanwu Tang	Astragali Radix 60 g, Persicae Semen 10 g, Carthami Flos 10 g, Angelicae Gigantis Radix 10 g, Rhizoma Ligustici Chuanxiong 12 g, Paeoniae Radix Rubra 10 g, Pheretimae Corpus 12 g, Cinnamomi Ramulus 10 g, Chaenomelis Fructus 20 g, Puerariae Radix 30 g, Achyranthis Radix 10 g

3.4. Restless legs syndrome rating scale (RLSRS)

Four studies [12,14,16,18] that compared add-on herbal medicine (conventional therapies plus herbal medicines) with control treatment (conventional therapies only) assessed the total RLSRS score. In the herbal medicines group, the RLSRS score was 2.82 less as compared with that of the control group; this difference was statistically significant (MD –2.82, 95% CI [–4.45 to −1.48]). Based on the I^2 value (I^2 = 54%), we found significant statistical heterogeneity between the studies (Fig. 4). Therefore, a subgroup analysis according to the types of herbal medicines was performed, which provided inconsistent results. YRF (MD –4.36, 95% CI [–6.15, −2.57]) [12], and WRT (MD –2.03, 95% CI [–2.58, −1.48]) [18] yielded significantly lower RLSRS scores as compared with that of the control group. On the other hand, JST (MD –1.03, 95% CI [–5.70, 3.64]) [14] and DSS + GFT (MD –3.90, 95% CI [–9.67, 1.87]) [16] exhibited lower RLSRS scores as compared with that of the control group, albeit insignificant. We also conducted subgroup analysis according to restless legs syndrome type which revealed consistent results (Idiopathic [12,14]: MD -3.42, 95% CI [-6.36, −0.48], and Renal failure [16,18]: MD -2.05, 95% CI [-2.59, −1.50]) (Fig. 4(b)).

Two studies [21,23] that compared herbal medicine and control treatment (levodopa/benserazide only) assessed the total RLSRS score. In these studies, the herbal medicine group exhibited significantly lower RLSRS score as compared with that of the levodopa/benserazide conventional therapy (MD –3.72, 95% CI [–6.03, −1.42]) (Fig. 4(c)). Based on the I^2 value (I^2 = 79%), we found significant statistical heterogeneity between the studies. However, the number of studies was insufficient to carry out additional subgroup analysis.

3.5. Pittsburgh Sleep Quality Index (PSQI) for symptoms of sleep disturbance

Two studies [14,16] that compared add-on herbal medicine (conventional therapies plus herbal medicines) with control treatment (conventional therapies only) assessed the total PSQI score. In the herbal medicines group, the PSQI score was 3.13 less than that of the control group; this difference was statistically significant (MD –3.13, 95% CI [–4.93 to −1.33]) [14,16] (Fig. 5). In a subgroup analysis, only JST revealed significantly lower RLSRS score as compared with that of conventional therapy (MD –3.95, 95% CI [–6.05 to −1.85]) [14].

3.6. Safety

Of the 12 studies, only three studies [14,21,23] examined adverse event occurrence, while the remaining nine studies did not. All three studies recorded only the number of adverse events. For the herbal medicine group, one study [14] reported dizziness (n = 1), constipation (n = 1), and abdominal discomfort (n = 2). For the control group, three studies [14,21,23] reported dizziness (n = 4), constipation (n = 8), abdominal discomfort (n = 3), nausea or vomiting (n = 1), and unspecified symptoms of the digestive system (n = 2). However, no serious or frequently occurring adverse events were reported in any of the included studies (Table 1).

4. Discussion

Present findings indicated that adjunctive or single herbal medicine treatments containing Paeoniae Radix induce significant improvements

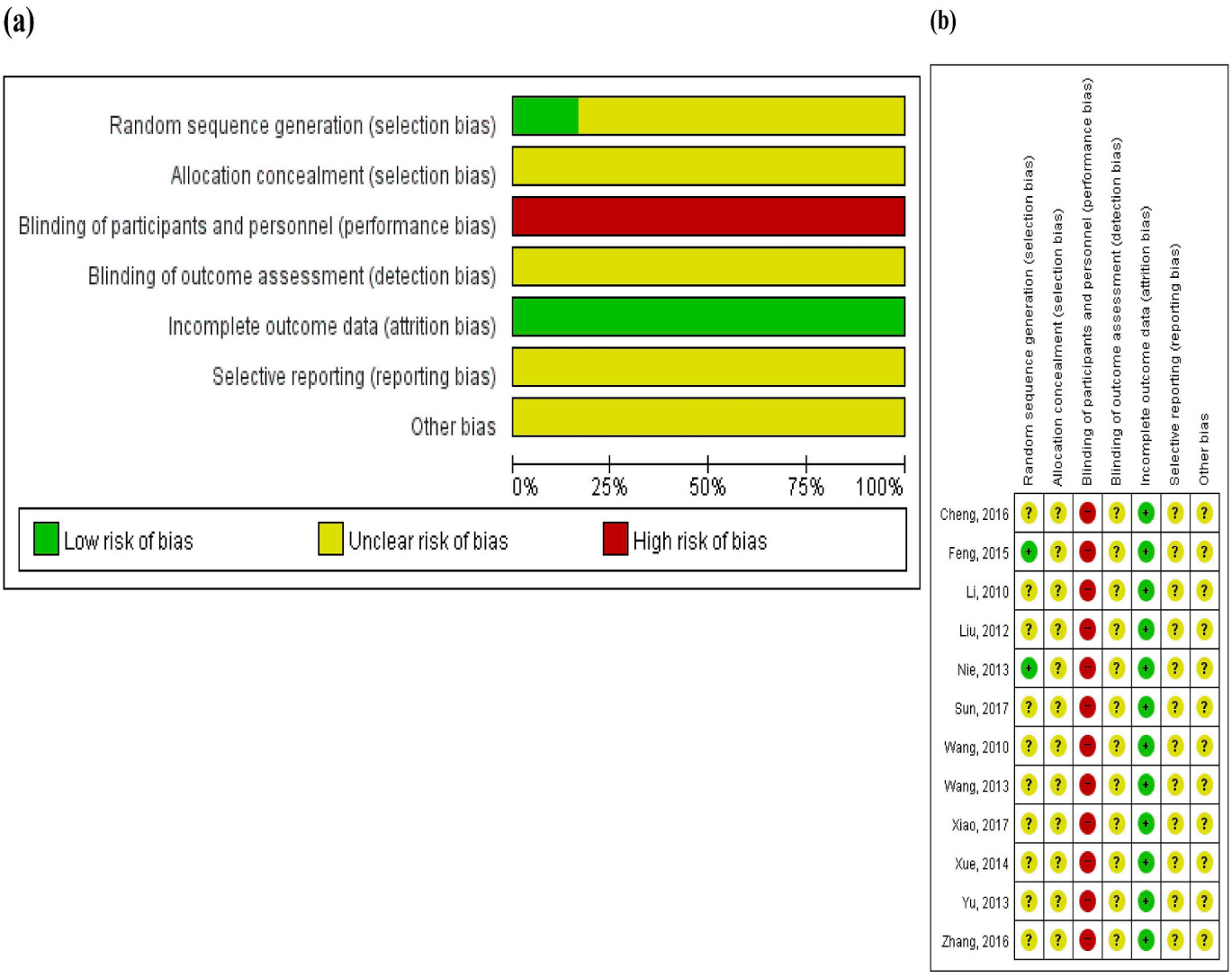

Fig. 2. (a) Risk of bias graph; review of authors' judgements regarding each risk of bias item is presented as percentages across all included studies (b) Risk of bias summary; review of authors' judgements regarding each risk of bias item for each included study. "+": low risk, "?": unclear risk, and "−": high risk.

in patients with restless legs syndrome. Especially, this improvement is considered to be clinically significant. The minimal clinically important difference (MCID) of RLSRS and PSQI is 3 [26,27]. The results of the meta-analysis for each scale were either higher (RLSRS: herbal medicine vs conventional therapies only −3.72; PSQI: herbal medicine + conventional therapies vs conventional therapies only −3.13) or slightly lower (RLSRS: herbal medicine + conventional therapies vs conventional therapies only −2.82). Furthermore, we could also suggest that treatments consisting of adjunctive or single Paeoniae Radix-containing herbal medicine were relatively safe for restless legs syndrome in available studies.

The assumptive therapeutic mechanism of Paeoniae Radix-containing herbal medicine for the restless legs syndrome is via activation of adenosine A1 receptors (A1Rs). Paeoniflorin, which is a major active component of Paeoniae Radix, is known to activate A1R in various experimental studies and clinical applications [28,29]. A1R is a member of the adenosine receptor group of G protein-coupled receptors with adenosine as the endogenous ligand [30]; it shows inhibitory function in most of the tissues it is present in Refs. [31,32]. In particular, it acts in the synapse to reduce synaptic vesicle release, and slows metabolic activity in the brain [33,34]. In experimental studies, Paeoniae Radix has been shown to activate A1Rs to prevent paclitaxel-induced mechanical allodynia [35], promote non-rapid eye movement sleep [36], and improve neuroinflammation and dopaminergic neurodegeneration in the MPTP Parkinson's disease model [37].

Furthermore, it has been recently noted that A1R may be a marker of brain iron deficiency [38], which is one of the major pathological mechanisms of restless legs syndrome. One experimental study reported downregulation of A1R and dopamine D2 receptors in the brain cortex and striatum of rodents on iron-deficient diets [38]. This result suggested that A1R downregulation plays a key role in the hyperarousal state of restless legs syndrome [39]. Therefore, A1R activation by Paeoniae Radix is thought to play a role in improving the hyperaesthetic state of restless legs syndrome via actions on dopaminergic neurons.

This study also showed that Paeoniae Radix-containing herbal medicines for patients with restless legs syndrome might be a safer therapeutic choice than conventional medications. The most widely used dopamine receptor agonists in restless legs syndrome such as pramipexole and ropinirole have been reported to cause rebound, compulsive disorders, and increased drug tolerance due to long-term use [40]. In addition, pergolide or cabergoline, an ergot-derived dopamine agonist, may cause serious complications such as pulmonary and cardiac fibrosis [41]. Therefore, while treatment effect on restless legs syndrome is important, it is also essential to confirm the occurrence of serious complications. We investigated the incidence of adverse

(a)

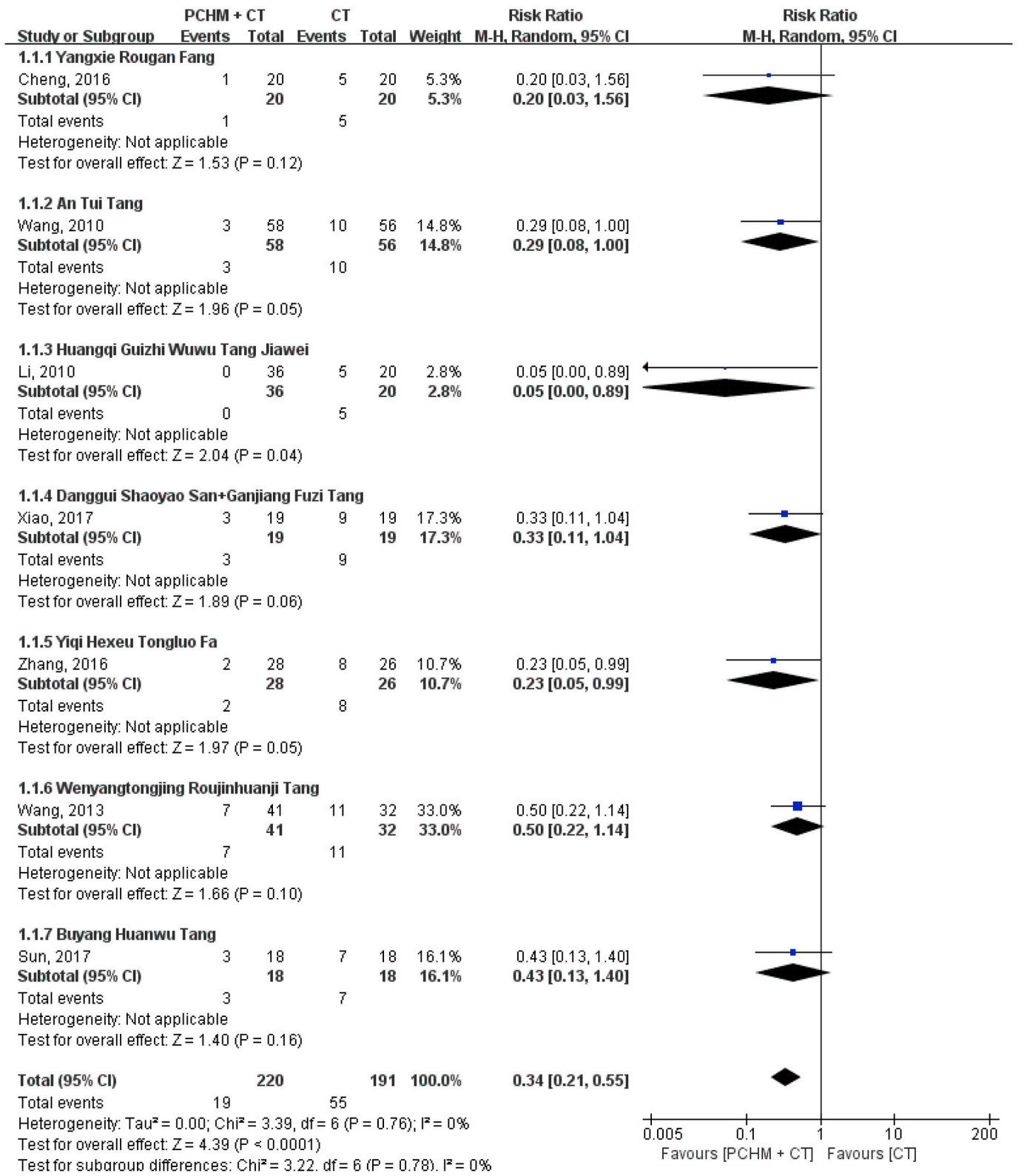

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Fig. 3. (a) TER: Paeonia Radix-containing herbal medicine + conventional therapies vs conventional therapies only.
(b) TER: Paeonia Radix-containing herbal medicine + conventional therapies vs conventional therapies only-subgroup analysis according to the restless legs syndrome type.
(c) TER: Paeonia Radix-containing herbal medicine vs conventional therapies only.
(d) TER: Paeonia Radix-containing herbal medicine vs conventional therapies only according to the conventional therapies type.
(e) TER: Paeonia Radix-containing herbal medicine vs conventional therapies only according to the restless legs syndrome type.
TER; Total Effective Rate. PCHM; Paeoniae Radix containing Herbal Medicine. CT; Conventional Therapy. The number of events in this figure is the sum of the numbers of 'unchanged' or 'worse'.

events in the included studies. Only dizziness and mild gastrointestinal symptoms were noted in a few studies; no significant life-threatening adverse events were identified. Therefore, Paeoniae Radix-containing herbal medicine might be relatively safe for restless legs syndrome. However, it is difficult to make a definitive conclusion for safety because the studies investigating the adverse effect were very few.

In addition, Paeoniae Radix Alba and Paeniae Radix Rubra were included in this study. Two herbs are distinguished based on the plant species or drug processing method according to the literature [42]. However, there has been no clear distinction, and the distinction is different depending on the region such as Korean, China and Japan. Thus, we decided focus on Paeoniflorin, which has been widely used as a key ingredient of Paeoniae Radix Alba and Rubra. Paeoniflorin acts on A1Rs to alleviate the symptoms of restless legs syndrome ad mentioned previously. Therefore, we concluded that the distinction between Paeoniae Radix Alba and Paeoniae Radix Rubra was not significant when biochemical approach was used. For this reason, Paeoniae Radix Alba and Paeoniae Radix Rubra are not distinguished from each other in this study.

This study is the first systematic review and meta-analysis that examines the effects of herbal medicine treatments on restless legs syndrome. We conducted an extensive literature search without language restrictions; through this search strategy, we were able to find and review the maximum number of available documents. The evaluation of various aspects of restless legs syndrome was made possible through numerous evaluation tools. The total effective rate was used to evaluate completely subjective improvements, and the degree of subjective improvement was quantified using the RLSRS. In addition, the PSQI was used to evaluate the effect of restless legs syndrome on sleep itself. Overall, this study summarized detailed intervention strategies used in each study. These findings are expected to be helpful to clinical practitioners who utilize herbal medicine in clinical practice.

Although our results denoted the effects and safety of Paeoniae Radix-containing herbal medicines for restless legs syndrome, we were unable to achieve a definitive conclusion due to limitations associated with risk of bias in study analysis. First, most of the studies included in this analysis exhibited methodological problems such as selection and performance biases. In addition, nine out of 12 studies did not report adverse events. Furthermore, most RCTs did not provide detailed protocol information, such as protocol registration numbers. Therefore, while results of meta-analysis suggested that Paeoniae Radix-containing herbal medicine is effective for restless legs syndrome, concrete conclusions could not be drawn from current literature. Second, the specific details of the interventions were all different, although Paeonia Radix is commonly found in herbal medicines used in clinical studies. Similarly, the duration of medication administration and the etiology of restless legs syndrome (eg, idiopathic, diabetic or renal failure) were differed between studies. In our meta-analysis, the etiology of seven studies [12–15,20–22] was idiopathic, while that of four studies [16–19] was renal failure; another study [23] focused on restless legs syndrome in diabetes patients. Third, three out of the twelve studies used inadequate treatment methods in the control group. The standard therapy for

(b)

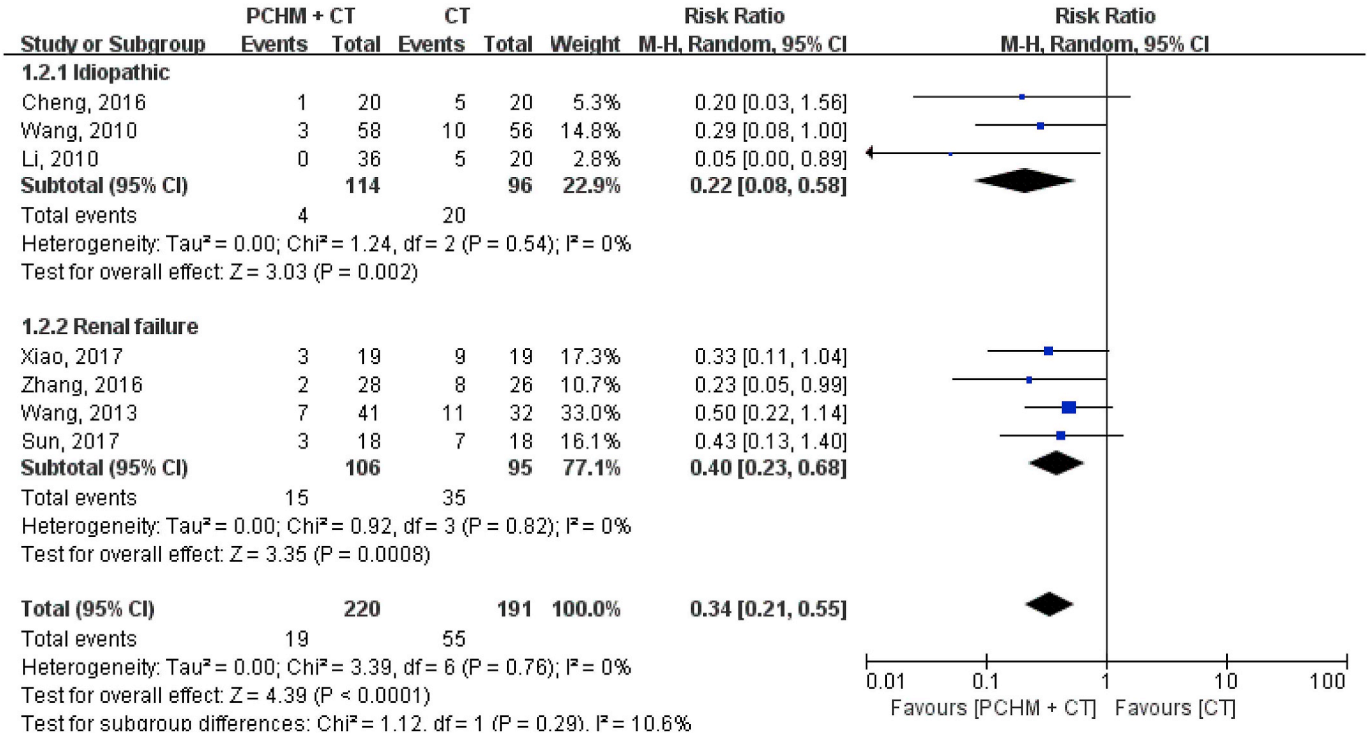

Fig. 3. (*continued*)

(c)

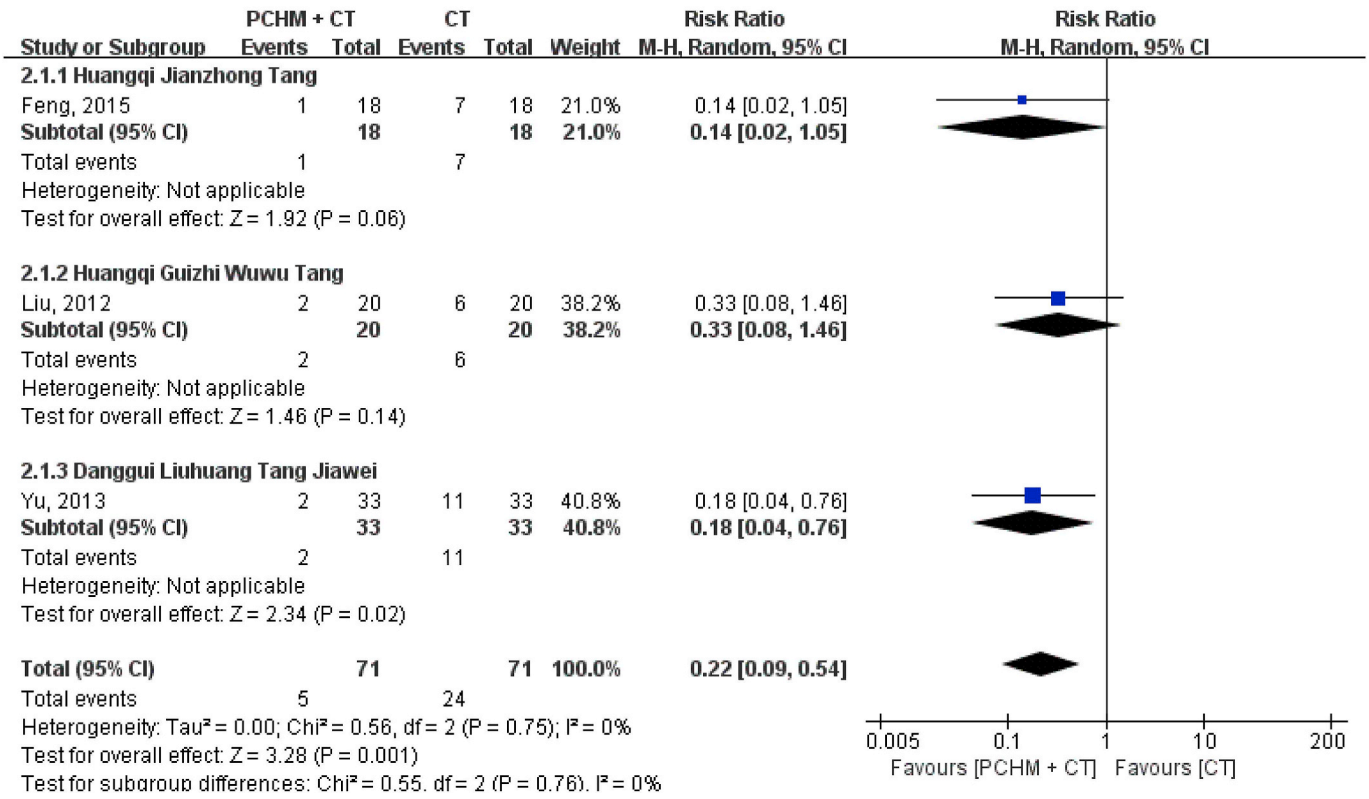

Fig. 3. (*continued*)

restless legs syndrome is dopamine replacement therapy. Therefore, dopamine agonists or levodopa are the first therapeutic agents used to treat this condition. However, psychoactive agents, flupentixol/melitracen [12] and flunarizine [15], which are generally used to treat migraine or dizziness, were used as control therapies. Another limitation of this meta-analysis is that all studies included in the analysis were conducted in China. A previous study has indicated that clinical studies conducted in China show high rates of success [43]. In this respect, there is a possibility that publication bias is present in the studies included in this review. Furthermore, since all subjects included in this review are Chinese, it is questionable whether results of this meta-analysis could be extended to patients of other ethnic backgrounds.

(d)

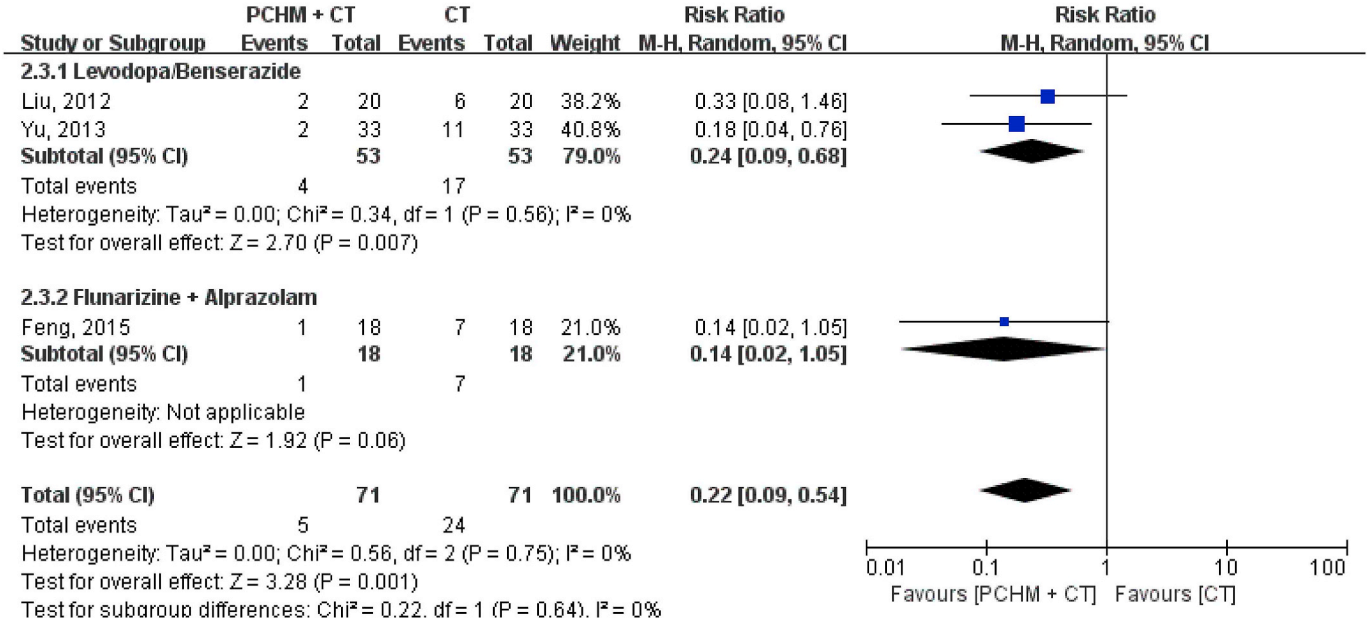

Fig. 3. (*continued*)

(e)

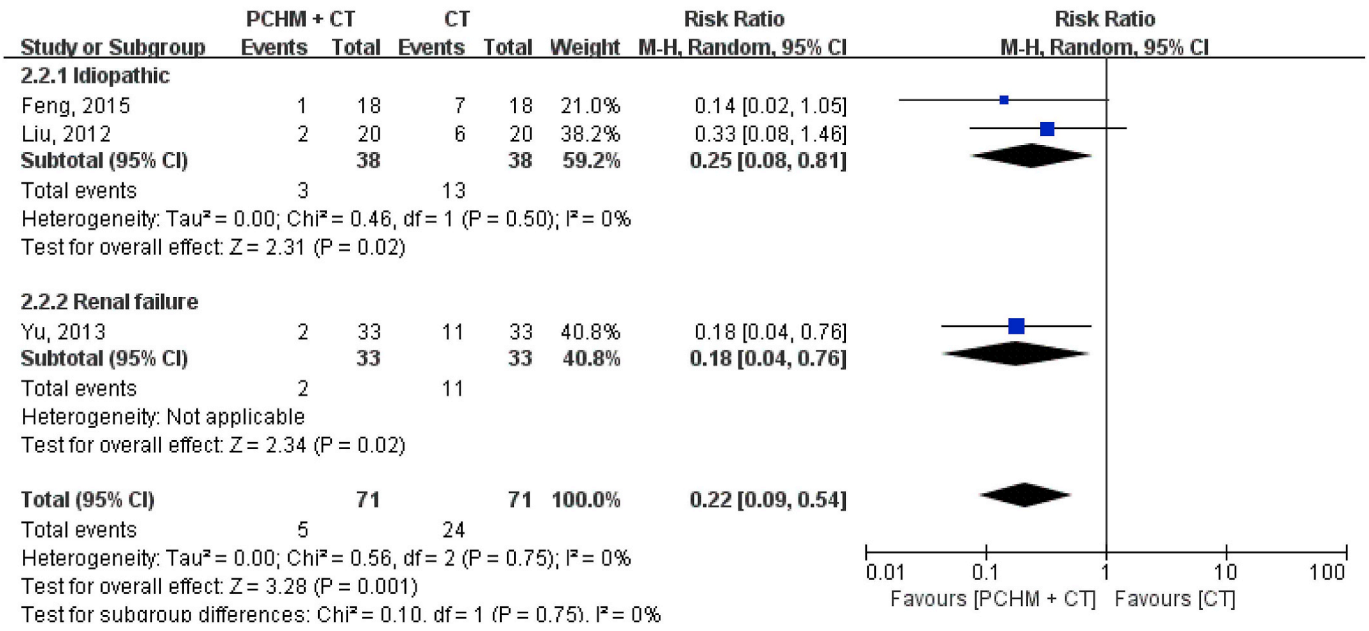

Fig. 3. (*continued*)

(a)

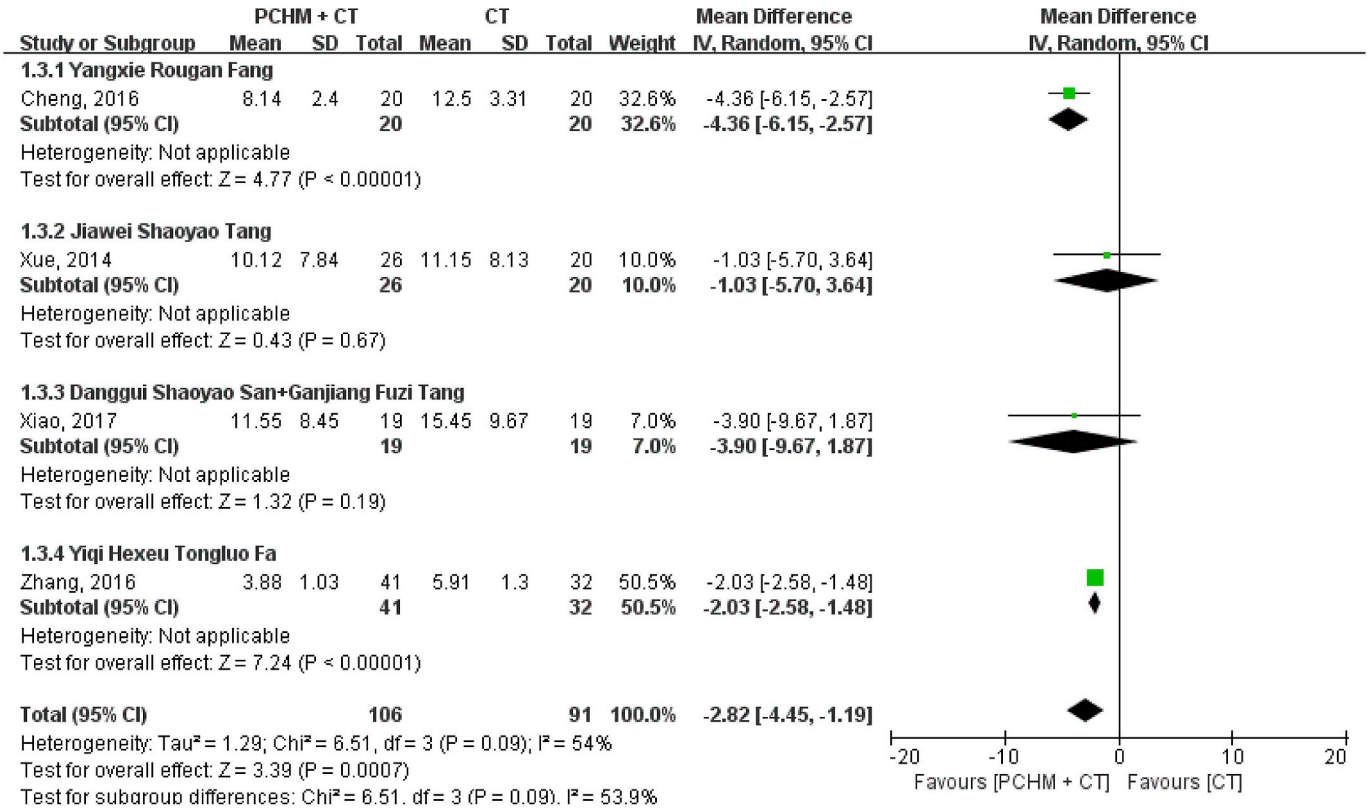

Fig. 4. (a) RLSRS: Paeonia Radix-containing herbal medicine + conventional therapies vs conventional therapies only.
(b) RLSRS: Paeonia Radix-containing herbal medicine + conventional therapies vs conventional therapies only according to the restless legs syndrome type.
(c) RLSRS: Paeonia Radix-containing herbal medicine vs Levodopa/Benserazide.
RLSRS; Restless Legs Syndrome Rating Scale. PCHM; Paeoniae Radix containing Herbal Medicine. CT; Conventional Therapy. LB; Levodopa/Benserazide.

(b)

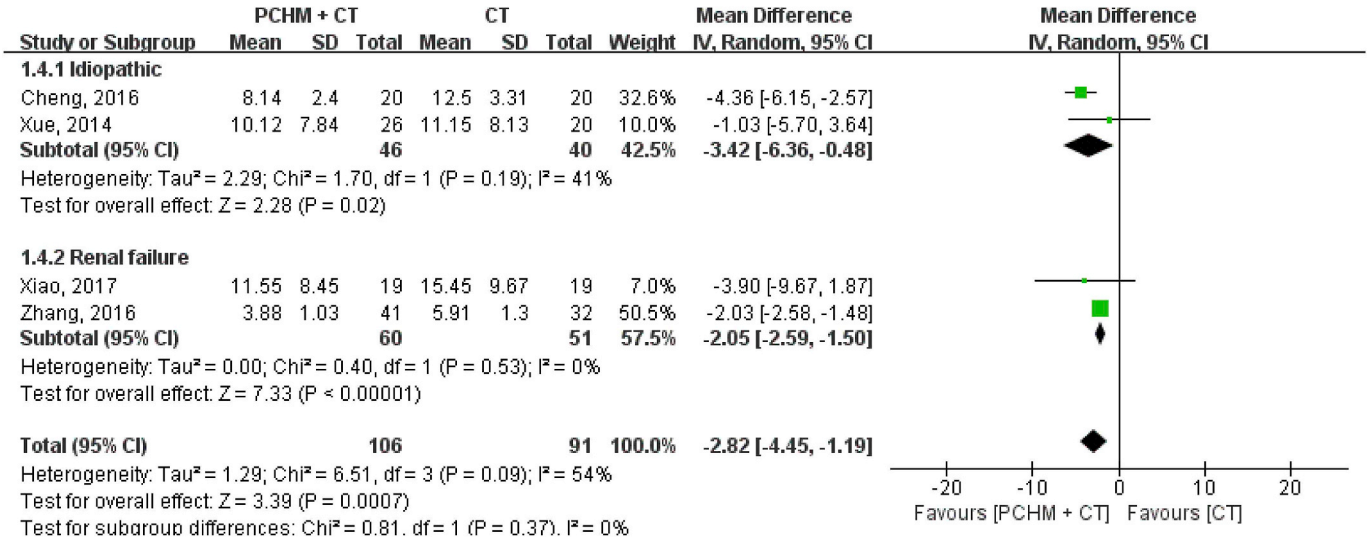

Fig. 4. (*continued*)

While this study contains a number of limitations, it is the first systematic review and meta-analysis that investigated the effects of herbal medicine on restless legs syndrome. Since China is the largest country that use and research herbal medicines in the world, and there is a lack of complementary and alternative medicine research on restless legs syndrome, the present meta-analysis is a valuable source of information.

5. Conclusion

In conclusion, combination or single therapy of Paeoniae Radix-containing herbal medicine in patients with restless legs syndrome can exert significant treatment effect. However, the quality of the studies that were analysed was low, and there was insufficient data to draw concrete conclusions for the effects and safety of herbal medicine on restless legs syndrome. Further studies are needed in the future.

For future studies, blinding of participants, investigators, and statisticians will be essential; all studies included in this meta-analysis used active medications as control and did not use placebo. The lack of allocation concealment, lack of blinding of participants, investigators, and statisticians caused bias. Therefore, positive results may be induced by patients and evaluators with preference for herbal medicine treatment. This methodological flaw makes it difficult to derive a concrete conclusion from the results of this study. However, it is difficult to set a placebo for the herbal medicine and/or the conventional medicine to ensure blinding, because of the unique flavour and taste of herbal medicines. In order to solve this problem, the development of related pharmaceutical technology must be accompanied. In addition, protocol-associated information, including protocol registration number and specific information on randomization, is essential. Most studies included in this review did not provide specific information on randomization or protocol registration numbers.

(c)

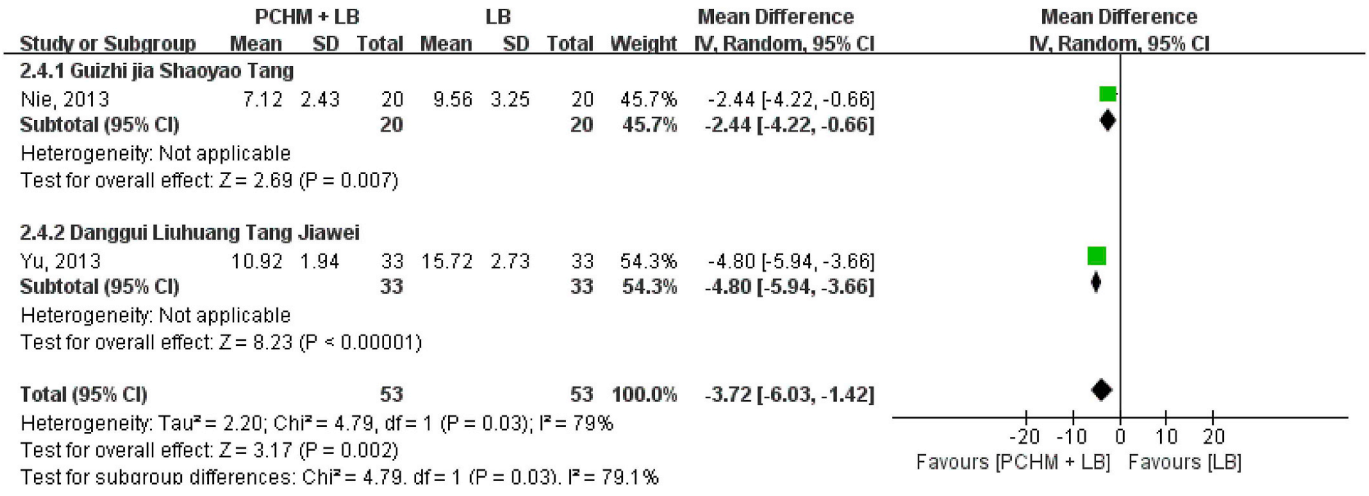

Fig. 4. (*continued*)

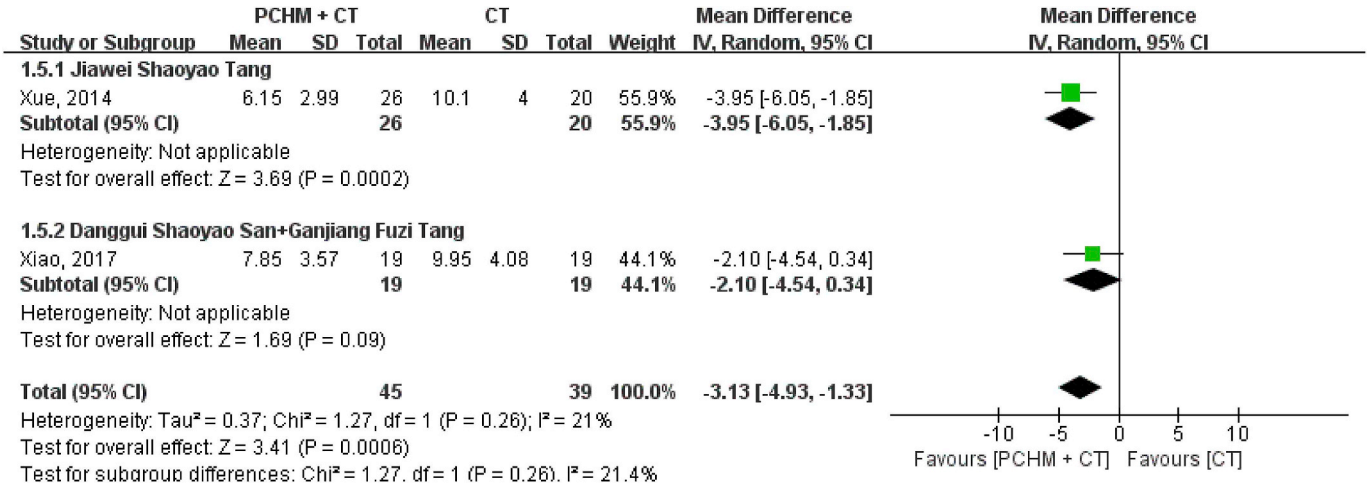

Fig. 5. PSQI: Paeonia Radix-containing herbal medicine + conventional therapies vs conventional therapies only.
PSQI; Pittsburgh Sleep Quality Index. PCHM; Paeoniae Radix containing Herbal Medicine. CT; Conventional Therapy.

Conflicts of interest

The authors declare no conflicts of interest regarding the publication of this study.

Data statement

No data were used to support this study.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.03.015.

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