Int J Clin Exp Med 2015;8(9):14577-14594
www.ijcem.com /ISSN:1940-5901/IJCEM0012924

Review Article

Puerarin injection for treatment of unstable angina pectoris: a meta-analysis and systematic review

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Received July 15, 2015; Accepted July 25, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: Background: Puerarin is an effective ingredient isolated from Radix Puerariae, a leguminous plant. In China, a large number of early studies suggest that puerarin may be used in the treatment of coronary heart disease. In recent years, puerarin injection has been widely used to treat coronary heart disease and angina pectoris. Objective: To systematically evaluate the clinical efficacy and safety of puerarin injection in the treatment of unstable angina pectoris (UAP). Methods: Data were retrieved from digital databases, including PubMed, Excerpt Medica Database (EMBASE), China Biology Medicine (CBM), the Cochrane Library, and Chinese databases. Results: Compared with patients who were treated with conventional Western medicines alone, the patients who were treated with conventional Western medicines in combination with puerarin injection exhibited significant improvements in the incidence of angina pectoris, electrocardiogram findings, nitroglycerin consumption and plasma endothelin levels. Conclusions: Strong evidence suggests that, the use of puerarin in combination with conventional Western medicines is a better treatment option for treating UAP, compared with the use of conventional Western medicines alone.

Keywords: Puerarin injection, unstable angina pectoris, meta-analysis

Introduction

Angina pectoris is a clinical syndrome caused by acute temporary myocardial ischemia and hypoxia due to coronary insufficiency, and episodes of chest pain or discomfort represent the primary manifestations [1]. In the resting state, the appearance or worsening of the above symptoms is diagnosed as unstable angina pectoris (UAP) [2]. UAP is an intermediate state between chronic stable angina pectoris and acute myocardial infarction, with a tendency towards progressive deterioration, and can easily develop into acute myocardial infarction and ischemic sudden death [3]. UAP should be treated immediately once it occurs. Three treatment methods are recommended by the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines: anti-ischemic therapy, anti-platelet therapy and anti-thrombotic therapy. Anti-ischemic therapy includes nitrates, -blockers, angiotensin-converting enzyme (ACE) inhibitors, revascularization and oxygen. Anti-platelet therapy includes aspirin, clopidogrel, and glycoprotein IIb/IIIa receptor antagonists [4, 5]. Anti-thrombotic therapy includes low-molecular-weight heparin. The treatment of UAP aims to alleviate ischemia and to prevent serious adverse reactions and their consequences (namely, death, myocardial infarction or re-infarction). Herbal medicine has been broadly employed in the treatment of angina pectoris in China [6].

In China, herbal medicine is often used together with Western medicines to treat UAP. Puerarin is a flavonoid glycoside that is extracted from the root of the leguminous plants Pueraria lobata and Thomson Kudzuvine Root, and its chemical name is 8-β-D-glucopyranosyl-4',7-dihydroxyisoflavone [7]. A large number of studies suggests that puerarin has the following pharmacological effects on the cardiovascular system: (1) dilating coronary artery to relieve vasospasm, increase coronary blood flow, and thus improve the blood supply to ischemic myocardium [8]; (2) reducing blood pressure, heart rate and myocardial oxygen consumption [9];

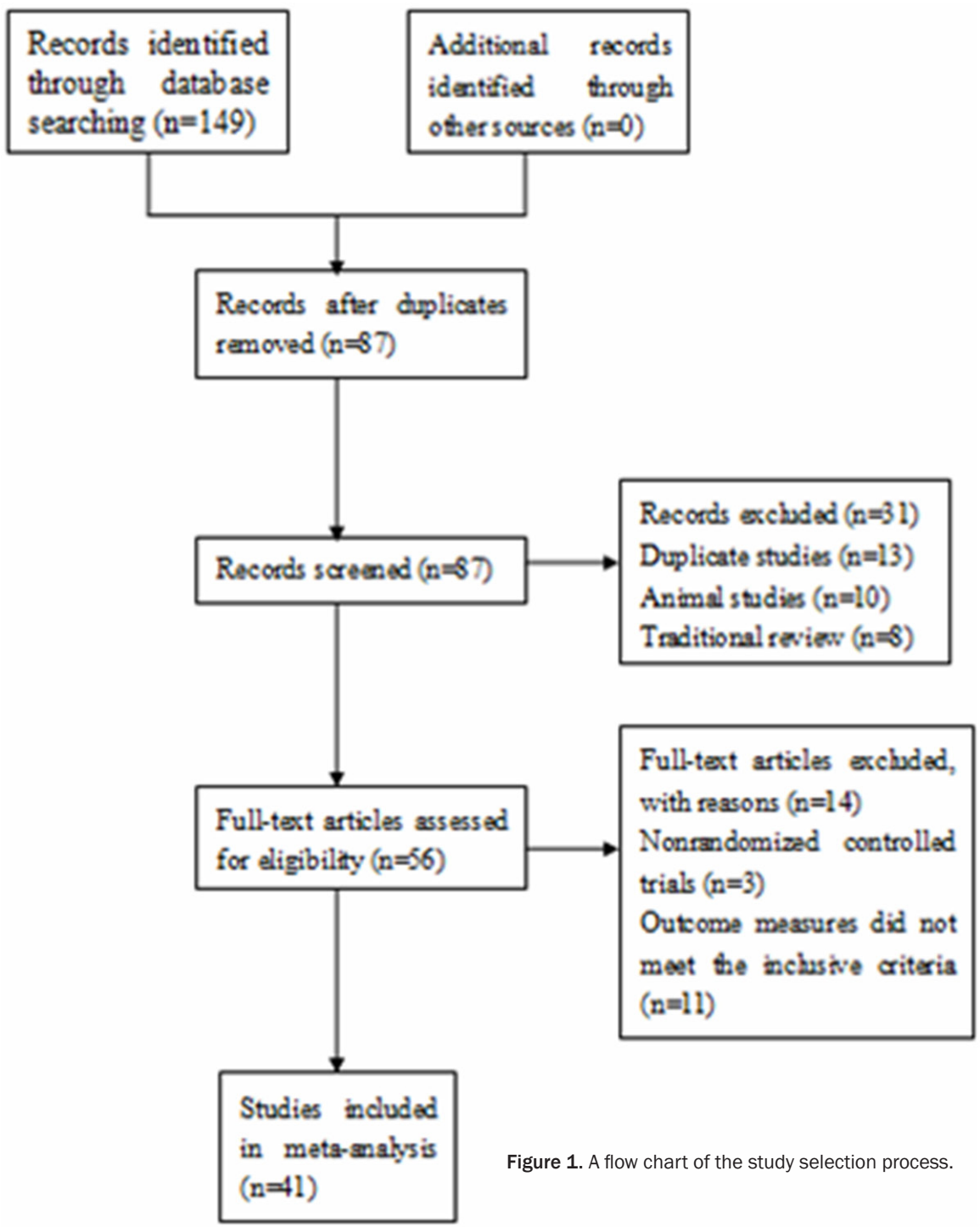

Figure 1. A flow chart of the study selection process.

and (3) inhibiting platelet aggregation, reducing blood viscosity, and improving microcirculation [10].

Currently, puerarin has been widely used in the treatment of UAP, but the clinical studies on its use are limited by small sample sizes and are of varying quality. For this reason, the present study gathered data from randomized controlled studies on puerarin for the treatment of UAP and evaluated the clinical efficacy and safety of puerarin in an objective and scientific manner to provide strong evidence for the use of puerarin in clinical practice.

Table 1. Characteristics of the randomized control trials included in this study

Study	Sample (T/C)	Diagnostic standards	Intervention	Control	Duration (days)	Outcome measure
An 2001 [12]	92 (48/44)	WHO criteria	Puerarin 500 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement 3. Decrease in usage of nitroglycerine 4. ET and NO 5. Systolic pressure, heart rate and oxygen consumption
Bai 2005 [13]	172 (86/86)	WHO criteria	Puerarin 400 mg + Western treatment	Western treatment	15	1. Frequency and length of angina attacks 2. ECG improvement
Bao 2003 [14]	100 (50/50)	WHO criteria	Puerarin 500 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement 3. Decrease in usage of nitroglycerine 4. ET and NO 5. Systolic pressure, heart rate and oxygen consumption 6. Haemorheology plasmic viscosity, platelet aggregation rate, fibrinogen
Cai 2002 [15]	78 (40/38)	WHO criteria	Puerarin 400 mg + Western treatment	Western treatment	20	1. Frequency and length of angina attacks 2. ECG improvement 3. Decrease in usage of nitroglycerine 4. Blood rheology parameters 5. Side effects
Chen 2007 [16]	71 (36/35)	ACC/AHA	Puerarin 300 mg + Western treatment	Western treatment	10	1. Frequency and length of angina attacks 2. ECG improvement 3. Systolic pressure, heart rate 4. Serum CRP
Chu 2005 [17]	51 (26/25)	Criteria from the Chinese Society of Cardiology	Puerarin 400 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement
Deng 2003 [18]	61 (32/29)	WHO criteria	Puerarin 400 mg + Western treatment	Western treatment	15	1. Frequency and length of angina attacks 2. ECG improvement
Dong 1999 [19]	74 (38/36)	WHO criteria	Puerarin 400 mg + Western treatment	Western treatment	20	1. Frequency and length of angina attacks 2. ECG improvement 3. Decrease in usage of nitroglycerine 4. Blood rheology parameters 5. Side effects

Gao 2005 [20]	80 (40/40)	WHO criteria	Puerarin 500 mg + Western treatment	Western treatment	10	1. Frequency and length of angina attacks 2. ECG improvement 3. Side effects
Guo 2000 [21]	55 (28/27)	WHO criteria	Puerarin 500mg+ Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement 3. Blood rheology parameters
Guo 2007 [22]	66 (31/35)	ACC/AHA	Puerarin 500 mg + Western treatment	Western treatment	10	1. Frequency and length of angina attacks 2. ECG improvement 3. Side effects
Hu 2004 [23]	55 (30/25)	ACC/AHA	Puerarin 400 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement 3. Decrease in usage of nitroglycerine 4. Systolic pressure, heart rate and oxygen consumption
Huang 2002 [24]	60 (30/30)	WHO criteria	Puerarin 500 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement 3. Dose and incidence of nitroglycerine 4. Systolic blood pressure, heart rate
Jiang 2001 [25]	48 (24/24)	WHO criteria	Puerarin 400 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement
Li 1999 [26]	74 (38/36)	WHO criteria	Puerarin 300 mg + Western treatment	Western treatment	20	1. Frequency and length of angina attacks 2. ECG improvement 3. Decrease in usage of nitroglycerine 4. Blood rheology parameters 5. Side effects
Li 2003 [27]	102 (58/44)	WHO criteria	Puerarin 400 m + Western treatment	Western treatment	15	1. Frequency and length of angina attacks 2. ECG improvement
Li 2004 [28]	72 (36/36)	WHO criteria	Puerarin 400 mg + Western treatment	Western treatment	15	1. Frequency and length of angina attacks 2. ECG improvement 3. Side effects
Lin 2007 [29]	60 (30/30)	Criteria from the Chinese Society of Cardiology	Puerarin 200 mg + Western treatment	Western treatment	15	1. Frequency and length of angina attacks 2. ECG improvement 3. Side effects

Liu 2012 [30]	124 (62/62)	WHO criteria	Puerarin 500mg+ Western treatment	Western treatment	10	1. Frequency and length of angina attacks 2. ECG improvement 3. Blood rheology parameters 4. Serum CRP
Long 2004 [31]	57 (28/29)	WHO criteria	Puerarin 400 mg + Western treatment	Western treatment	10	1. Frequency and length of angina attacks 2. ECG improvement 3. Systolic pressure, heart rate and oxygen consumption 4. Side effects
Lu 2004 [32]	42 (21/21)	WHO criteria	Puerarin 500 mg + Western treatment	Western treatment	14	1. ET
Luo 2000 [33]	70 (40/30)	WHO criteria	Puerarin 500mg+ Western treatment	Western treatment	20	1. Frequency and length of angina attacks 2. ECG improvement 3. ET and NO
Meng 2004 [34]	60 (30/30)	WHO criteria	Puerarin 400 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement
Ren 2007 [35]	59 (31/28)	ACC/AHA	Puerarin 400 mg + Western treatment	Western treatment	20	1. Frequency and length of angina attacks 2. ECG improvement 3. Decrease in usage of nitroglycerine 4. Systolic pressure, heart rate and oxygen consumption
Shan 2006 [36]	89 (46/43)	Criteria from the Chinese Society of Cardiology	Puerarin 500 mg + Western treatment	Western treatment	10	1. Frequency and length of angina attacks 2. ECG improvement 3. Decrease in usage of nitroglycerine
Tang 2004 [37]	74 (37/37)	Criteria from the Chinese Society of Cardiology	Puerarin 500 mg + Western treatment	Western treatment	10	1. Frequency and length of angina attacks 2. ECG improvement
Tao 2006 [38]	100 (50/50)	Criteria from the Chinese Society of Cardiology	Puerarin 400 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement 3. Decrease in usage of nitroglycerine
Wang 2009 [39]	86 (44/42)	WHO criteria	Puerarin 400 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement
Wang 2011 [40]	60 (30/30)	WHO criteria	Puerarin 500 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement
Xi 2012 [41]	76 (38/38)	Criteria from the Chinese Society of Cardiology	Puerarin 500 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement 3. Side effects

Yang 2001 [42]	46 (26/20)	Criteria from the Chinese Society of Cardiology	Puerarin 500 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement
Yang 2004 [43]	100 (52/48)	Criteria from the Chinese Society of Cardiology	Puerarin 400 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement
Yang 2005 [44]	50 (32/28)	WHO criteria	Puerarin 250 mg + Western treatment	Western treatment	10	1. Frequency and length of angina attacks 2. ECG improvement 3. Systolic pressure, heart rate and oxygen consumption 4. Side effects
Yang 2008 [45]	68 (36/32)	WHO criteria	Puerarin 300 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement 3. Blood rheology parameters 4. Side effects
Yuan 2003 [46]	40 (20/20)	WHO criteria	Puerarin 500 mg + Western treatment	Western treatment	20	1. Frequency and length of angina attacks 2. ECG improvement 3. Heart rate and oxygen consumption
Yuan 2006 [47]	92 (48/44)	Criteria from the Chinese Society of Cardiology	Puerarin 400 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement 3. Side effects
Zhang 2000 [48]	40 (20/20)	WHO criteria	Puerarin 300 mg + Western treatment	Western treatment	10	1. ET 2. Diastolic function
Zhang 2008 [49]	80 (40/40)	Criteria from the Chinese Society of Cardiology	Puerarin 500 mg + Western treatment	Western treatment	28	1. Frequency and length of angina attacks 2. ECG improvement
Zhao 1998 [50]	39 (21/18)	ACC/AHA	Puerarin 400 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement 3. Decrease in usage of nitroglycerine 4. Systolic pressure, heart rate and oxygen consumption
Zheng 2006 [51]	60 (30/30)	Criteria from the Chinese Society of Cardiology	Puerarin 400 mg + Western treatment	Western treatment	14	1. Frequency and length of angina attacks 2. ECG improvement
Zhou 2011 [52]	60 (30/30)	ACC/AHA	Puerarin 500 mg + Western treatment	Western treatment	7	1. Frequency and length of angina attacks 2. ECG improvement

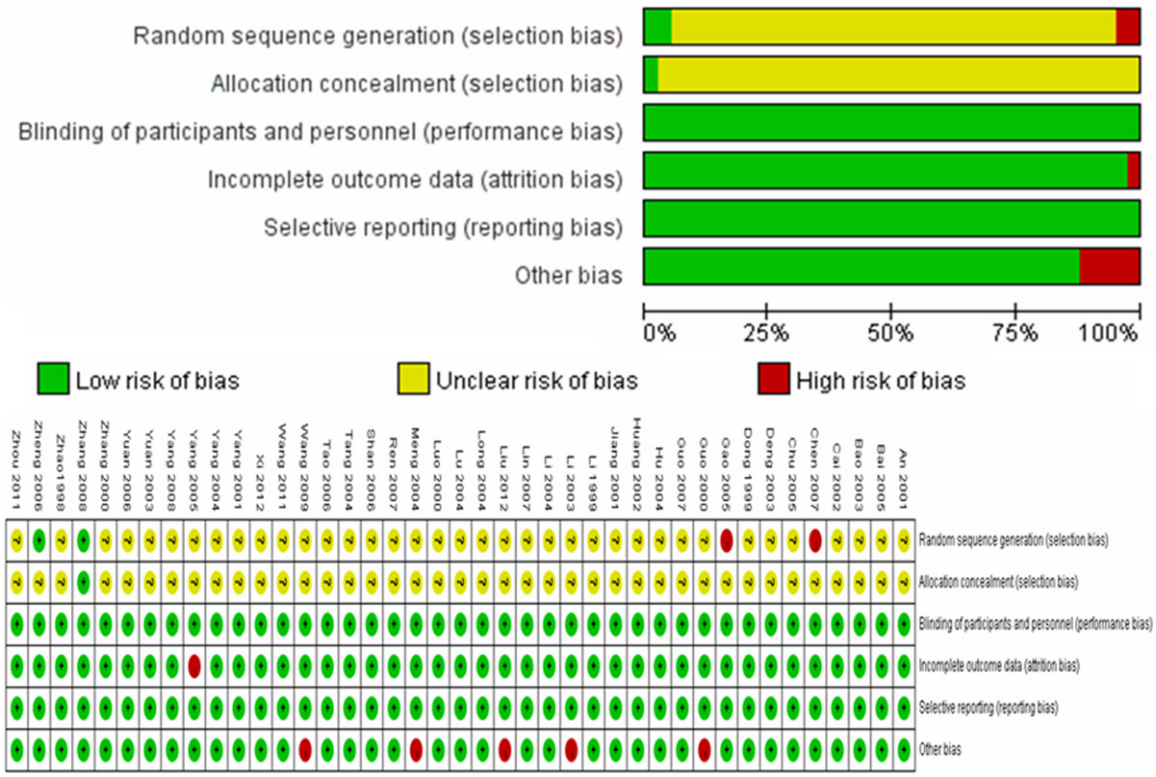

Figure 2. Risk of bias amongst included studies.

Materials and methods

Search strategy

The data were retrieved from digital databases, including PubMed, Excerpt Medica Database (EMBASE), Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Database (VIP), Wanfang Database and the Cochrane Library. The key words used for the database searches were “puerarin injection”, “unstable angina pectoris”, and “randomized controlled trials”. Any disagreements that occurred during the searching process were resolved via discussion or consultation with a third party.

Inclusion criteria

The experimental group was treated with puerarin injection in combination with conventional Western medicines, and the control group was treated with conventional Western medicines alone. The participants were previously diagnosed with UAP.

Exclusion criteria

The clinical studies in which the comparison was not between an experimental group treated with puerarin injection in combination with conventional Western medicines and a control group treated with conventional Western medicines alone were excluded. The studies involving subjects with concurrent acute myocardial infarction, severe heart failure or liver or functional kidney failure were excluded. Studies involving patients with stable angina pectoris were excluded.

Outcome measures

The primary outcome, mortality (sudden death from acute myocardial infraction and malignant ventricular arrhythmia), was not reported in any studies. The secondary outcome measures were as follows: (1) frequency of acute attacks of angina (e.g., reductions of more than 50% in the frequency of acute angina attack), (2) improvements in electrocardiogram (ECG) findings (e.g., normal resting ECG, or elevated ST segment of 0.5 mV or more, or inverted T wave

Table 2. Methodological qualities of the included studies

Study	Risk of bias for randomization	Risk of bias for concealment	Risk of bias for blinding	Risk of bias for incomplete data	Risk of bias for selective outcome reporting	Risk bias for other problem
An 2001 [12]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Bai 2005 [13]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Bao 2003 [14]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Cai 2002 [15]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Chen 2007 [16]	High risk	Unclear	Low risk	Low risk	Low risk	Low risk
Chu 2005 [17]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Deng 2003 [18]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Dong 1999 [19]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Gao 2005 [20]	High risk	Unclear	Low risk	Low risk	Low risk	Low risk
Guo 2000 [21]	Unclear	Unclear	Low risk	Low risk	Low risk	High risk
Guo 2007 [22]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Hu 2004 [23]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Huang 2002 [24]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Jiang 2001 [25]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Li 1999 [26]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Li 2003 [27]	Unclear	Unclear	Low risk	Low risk	Low risk	High risk
Li 2004 [28]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Lin 2007 [29]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Liu 2012 [30]	Unclear	Unclear	Low risk	Low risk	Low risk	High risk
Long 2004 [31]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Lu 2004 [32]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Luo 2000 [33]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Meng 2004 [34]	Unclear	Unclear	Low risk	Low risk	Low risk	High risk
Ren 2007 [35]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Shan 2006 [36]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Tang 2004 [37]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Tao 2006 [38]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Wang 2009 [39]	Unclear	Unclear	Low risk	Low risk	Low risk	High risk
Wang 2011 [40]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Xi 2012 [41]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Yang 2001 [42]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Yang 2004 [43]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Yang 2005 [44]	Unclear	Unclear	Low risk	High risk	Low risk	Low risk
Yang 2008 [45]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Yuan 2003 [46]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Yuan 2006 [47]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Zhang 2000 [48]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Zhang 2008 [49]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zhao 1998 [50]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Zheng 2006 [51]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Zhou 2011 [52]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk

≥ 50% or change of flat T wave to upright T wave), (3) dose and incidence of nitroglycerine taken, and (4) levels of plasma endothelin.

Data extraction and quality assessment

A standard quality assessment form [11] was used by two researchers who independently assessed each document that met the inclusion criteria and extracted the data. The extracted data included the following: (1) general information (e.g., title, study authors, and year of publication), (2) participants (e.g., sample size, baseline characteristics and diagnostics), (3) interventions and controls (e.g., dose, route, and treatment duration), (4) outcome

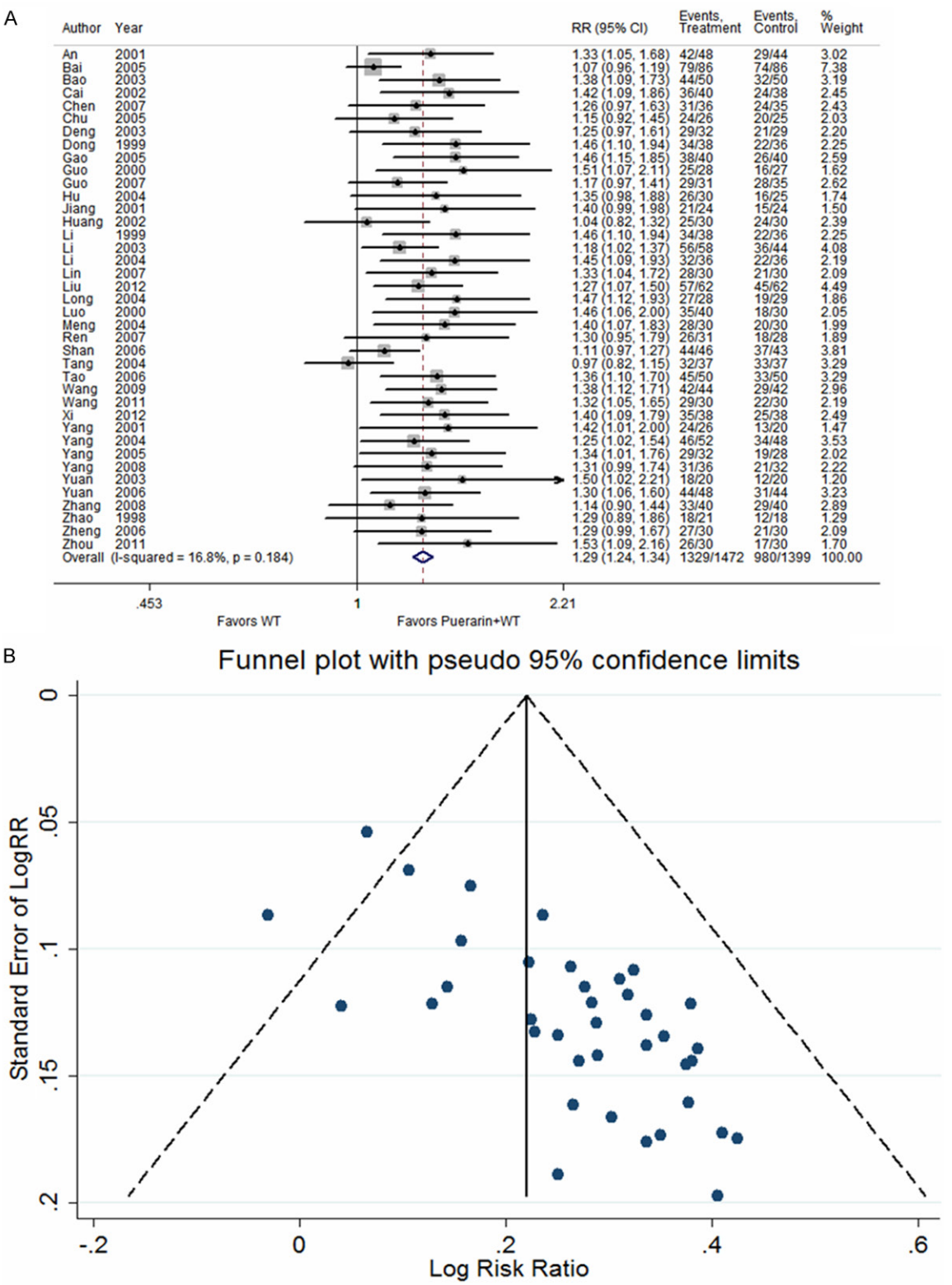

Figure 3. Puerarin injection plus western treatment versus western treatment, Outcome 1 Reduction in attacks of acute angina attack (more than 50%). A. Forest plots; B. Funnel plots.

measures, and (5) adverse side effects. Cross-checking was performed. Discrepancies were resolved through discussion or consultation with a third researcher. The quality of the meth-

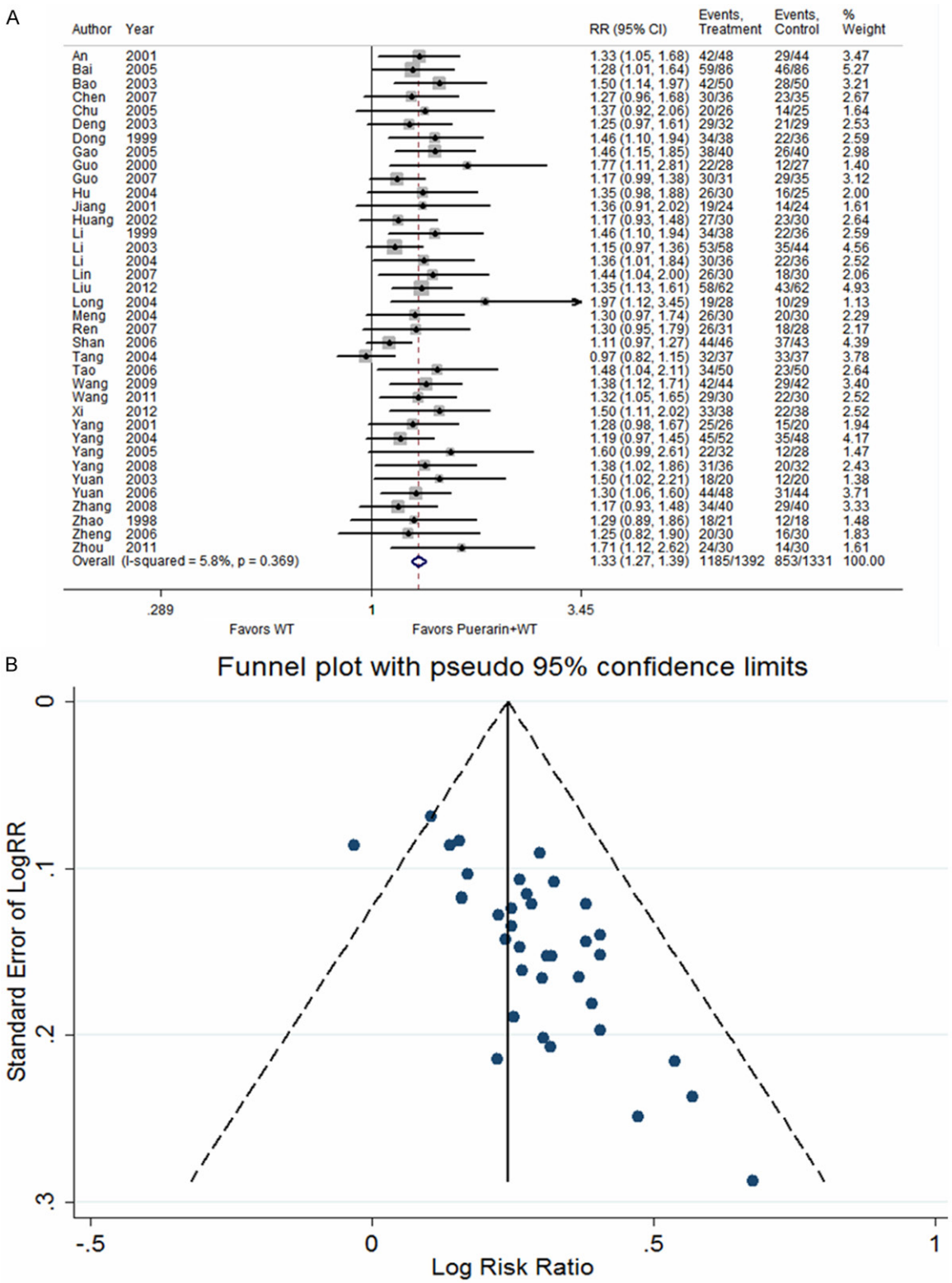

Figure 4. Puerarin injection plus western treatment versus western treatment, Outcome 2 Improvement of ECG. A. Forest plots; B. Funnel plots.

odology adopted in this study was assessed using the risk of bias table provided by the Cochrane Collaboration website, which included six aspects: (1) random sequence genera-

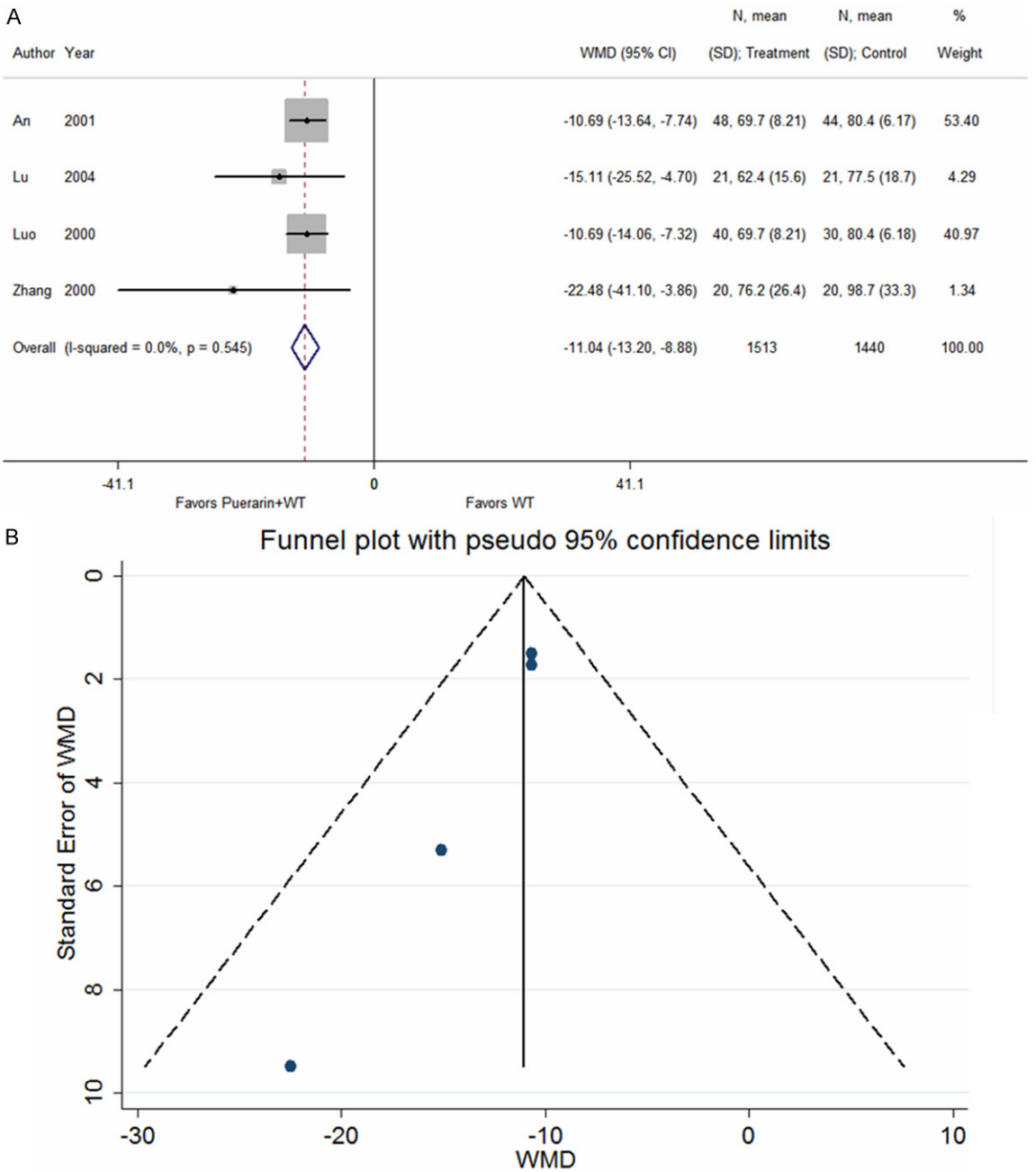

Figure 5. Puerarin injection plus western treatment versus western treatment, Outcome 3 Plasma endothelin concentration (pg/ml). A. Forest plots; B. Funnel plots.

tion, (2) allocation sequence concealment, (3) blinding, (4) incomplete outcome data, (5) selective outcome reporting, and (6) other potential sources of bias.

Statistical analysis

The meta-analysis was performed using Stata version 12.0. The χ^2 test was used for the heterogeneity test. A random effects model was employed when heterogeneity existed ($P < 0.1$, $I^2 > 50\%$), whereas a fixed effects model was adopted in the absence of heterogeneity ($P > 0.1$, $I^2 < 50\%$). Dichotomous data were assessed by relative risk (RR), and continuous variables were analyzed using weighted mean difference (WMD). The meta-analysis results

were compared based on the 95% confidence interval (CI) of these two parameters to examine whether a difference was statistically significant [11]. We aimed to perform sensitivity analyses to explore the influence of each trial on the meta-analysis. A funnel plot was used to assess whether publication bias was present.

Results

Characteristics of the included studies

A total of 149 documents were retrieved. Through review of the abstracts or the full text, 41 studies [12-52] were determined to meet the inclusion criteria, as shown in **Figure 1**. A total of 2953 subjects were included in these 41 studies, with 1440 subjects in the control group and 1513 subjects in the puerarin injection group. The daily dose of puerarin ranged from 200 mg to 500 mg, which administered intravenously. The treatment duration lasted 7-28 days, with most lasting 14 days. Conventional Western medicines were used in most of the control groups. Puerarin injection was used in the puerarin group in addition to the treatment used in the control group. Most of the studies include reduction in attacks of acute angina attack and improvement on ECG as outcome measures, as shown in **Table 1**.

Risk of bias assessment

The quality of the included studies was assessed based on the following aspects: (1) Randomization: the word "randomized" was mentioned in all the studies, but only two of the studies [49, 51] reported the detailed method of randomization; (2) Allocation sequence concealment: no description in any of the documents; and (3) Selective outcome reporting: all of the studies exhibited a low risk. The detailed results are presented in **Figure 2** and **Table 2**.

Primary outcomes

After a follow-up period of three months, a study [41] reported two cases of acute myocardial infarction in the control group, where no incidents of myocardial infarction were reported in the experimental treatment group. In this reported study, there were two cases of death (one case due to heart failure and one case due to ventricular fibrillation) in the control group and one death case in the experimental treatment group (heart failure).

Frequency of acute angina attack

Thirty-nine studies [12-31, 33-47, 49-52] reported the number of angina pectoris attacks in patients with UAP after treatment with puerarin injection. The heterogeneity test indicated that no statistical heterogeneity was present (P = 0.184); thus, a fixed effects model was adopted for analysis. The results indicated that puerarin in combination with conventional Western medicines reduced the number of angina pectoris attacks in UAP patients relative to treatment with conventional Western medicines alone (RR = 1.29, 95% CI: 1.24 to 1.34, Z = 13.07, P < 0.001) (**Figure 3**).

ECG

Thirty-seven studies [12-14, 16-31, 34-47, 49-52] reported improvements in the ECG of patients with UAP after treatment with puerarin injection. The heterogeneity test indicated no statistical heterogeneity (P = 0.369); thus, a fixed effects model was employed for analysis. The results indicated that puerarin in combination with conventional Western medicines improved ECG in UAP patients more than did conventional Western medicines alone (RR = 1.33, 95% CI: 1.27 to 1.39, Z = 12.30, P < 0.001) (**Figure 4**).

The level of plasma endothelin

Four studies [12, 32, 33, 48] reported the plasma endothelin (ET) levels in patients with UAP after treatment with puerarin injection. The heterogeneity test indicated no statistical heterogeneity (P = 0.545); thus, a fixed effects model was used for analysis. The results demonstrated that puerarin in combination with conventional Western medicines markedly reduced the plasma ET levels relative to patients treated with conventional Western medicines alone (WMD = -11.04, 95% CI: -13.20 to -8.88, Z = 10.03, P < 0.001) (**Figure 5**).

Daily dose of nitroglycerine

Seven studies [15, 19, 23, 26, 35, 38, 50] reported the daily dose of nitroglycerine in patients with UAP after treatment with puerarin

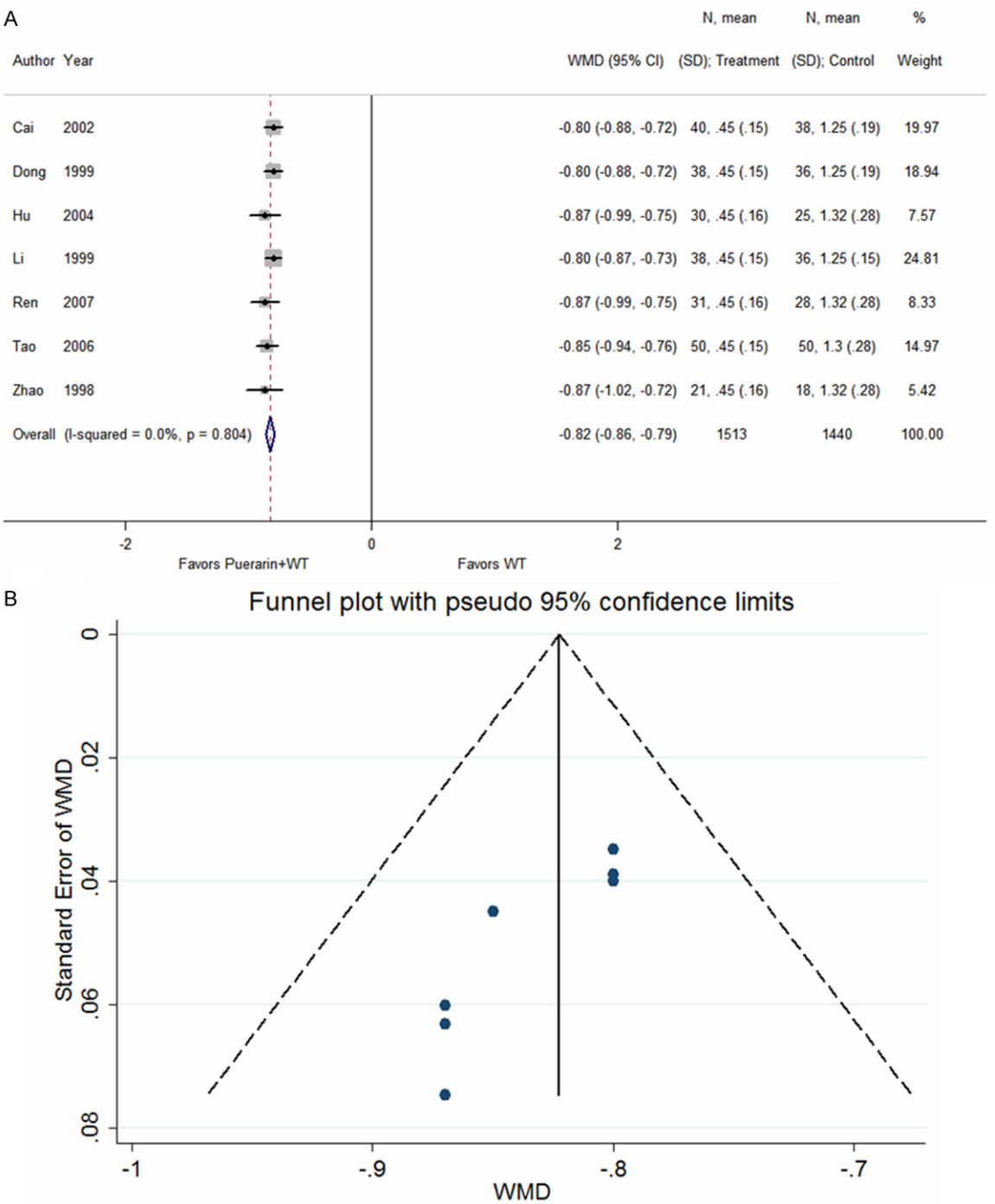

Figure 6. Puerarin injection plus western treatment versus western treatment, Outcome 4 Daily dose of nitroglycerine. A. Forest plots; B. Funnel plots.

injection. The heterogeneity test indicated no statistical heterogeneity (P = 0.804); thus, a fixed effects model was adopted for analysis. The results indicated that the daily dose of nitroglycerin in patients treated with puerarin in combination with conventional Western medicines was significantly reduced relative to patients treated with conventional Western medicines alone (WMD = -0.82, 95% CI: -0.86 to -0.79, Z = 47.32, P < 0.001) (**Figure 6**).

Sensitivity analysis

No significant changes were observed in any efficacy indicator after excluding one study at a time.

Publication bias

The funnel plot of the number of angina pectoris attacks and ECG improvement revealed asymmetry, indicating possible publication bias, which is likely related to unpublished negative results, missing follow-up visits, and small sample sizes (**Figures 3A**, **4A**). Vickers found that in China, a large proportion of published studies reported positive results within the complementary medicine fields [53].

Adverse reactions

Among the 41 included studies, 24 studies [13, 15, 19, 20, 22, 24, 26, 28, 29, 31, 41, 44, 45, 47] described adverse reactions in detail, and no adverse reactions were observed in 10 studies [18, 23, 35-38, 43, 50-52]. The adverse reactions included transient headache and fever [15, 19, 22, 24, 26, 31, 44], dizziness [24], hypotension [13], abdominal distension and nausea [24, 28, 41, 44, 45], allergic skin reactions [20, 22, 29], and sinus bradycardia [47]. All of the adverse reactions were mild, with spontaneous remission and no effect on treatment. No serious adverse reactions were reported. Adverse reactions were not mentioned in the other 17 studies [12, 14, 16, 17, 21, 25, 27, 30, 32-34, 39, 40, 42, 46, 48, 49].

Discussion

Relative to conventional Western medicines alone, the analysis results from this study demonstrated that the addition of puerarin injection increased treatment efficacy in patients with UAP, resulting in improved ECG outcomes and reduction in the number of angina pectoris attacks, nitroglycerine doses and plasma ET levels. A total of 41 randomized studies including 2953 participants were included. All the RCTs claimed that the positive effect of puerarin injection combined with conventional drugs was better than conventional drugs alone. However, because of the various durations of treatment and diverse reporting methods in included trials, we still could not make firm conclusions. Furthermore, the methodological quality of all studies was limited.

The systematic review of this study has its limitations. First, the quality of the included RCTs is poor. Second, publication and other biases may play an important role. The included studies were all conducted in China. Among these studies, many have small sample sizes and positive findings. Third, only two of the studies [49, 51] reported that random sequence was generated by random number table; most studies were not reported. Fourth, blinding of participants and personnel and blinding of outcome assessment were not detailed description. We made attempts to avoid any language or location biases. However, potential publication bias cannot be ruled out.

The systematic review of this study included three diagnosis criterions: “ACC/AHA Guideline for the Diagnosis and Management of Patients with Unstable Ischemic Heart Disease (ACC/AHA)”, “the International society and Federation of Cardiology/World Health Organization (ISFC/WHO)” and “Criteria from the Chinese Society of Cardiology” to diagnose unstable angina patients. ECG improvement, reduction in the number of angina pectoris attacks, nitroglycerine doses and plasma ET levels were used to evaluate the efficacy of puerarin injection for UAP. The main findings of this systematic review were that puerarin injection combined with conventional drugs confirmed that the addition of puerarin injection increased treatment efficacy in patients with UAP, resulting in ECG improvement (RR = 1.33, 95% CI: 1.27 to 1.39, Z = 12.30, P < 0.001) and reduction in the number of angina pectoris attacks (RR = 1.29, 95% CI: 1.24 to 1.34, Z = 13.07, P < 0.001), nitroglycerine doses (WMD = -0.82, 95% CI: -0.86 to -0.79, Z = 47.32, P < 0.001) and plasma ET levels (WMD = -11.04, 95% CI: -13.20 to -8.88, Z = 10.03, P < 0.001).

Several reviews [54, 55] on the pharmacological effects of puerarin were detailed summarized. However, Puerarin has numerous effects on the cardiovascular system: (1) Anti-arrhythmia effect: Puerarin inhibits voltage-gated K+ channels and Na+ channels in rat ventricular myocytes, which may partly contribute to its anti-arrhythmic property [56, 57]. Inhibition of K+ channels has been shown to prolong the duration of the action potential and the refractory period in cardiomyocytes and hence prevent arrhythmia [58, 59]. Blocking Na+ channels can significantly suppress the

velocity of cardiac impulse conduction and prolong the refractory period of cardiac excitability, thereby inhibiting arrhythmia progression [60]. (2) Puerarin has been shown to lower blood pressure and decelerate rhythm of the heart, relieve myocardial ischemic damage through blocking the $P2X_3$ signaling transmission and then depressed the aggravated sympathoexcitatory reflex [61]. (3) Vascular dilation to improve microcirculation: Puerarin can also produce a non-endothelium-dependent vasodilator effect, which is primarily achieved through the cyclic adenosine mono-phosphate (cAMP) pathway [62]. Dong's study showed that puerarin induces an endothelium-independent vasorelaxant effect on rat aortic rings. Its mechanism may involve the reduction in Ca^{2+} influx through the non-voltage-sensitive calcium channels and the activation of the potassium channels [63]. (4) Protective effects on cardiac hypertrophy: Puerarin attenuates Ang II-induced cardiac hypertrophy by inhibiting activation of the redox-sensitive ERK1/2, p38 and the NF-κB pathways [64]. Puerarin may have an ability to retard the progression of cardiac hypertrophy and apoptosis which is probably mediated by the blockade of PI3K/Akt and JNK signaling pathways [65]. (5) Protective effect on the myocardial ischemia and reperfusion injury: Puerarin has been shown that the acylated modification of phenolic hydroxyl at C-7 in the molecular may improve the cardioprotective activity [66]. Gao et al [67] also revealed that puerarin relieve ischemia-reperfusion injury through promoting the opening of calcium-activated potassium channels and the activation of protein kinase C. Tang et al [68] revealed the protective effects of puerarin in cardiomyocytes from ischemia and reperfusion injury via the protein kinase C epsilon signaling pathway. These may be account for the improvement of puerarin injection for the Treatment of Unstable Angina Pectoris.

In summary, when used in combination with conventional angina pectoris treatment, such as nitrates, β-blockers, ACE inhibitors, antiplatelets, and anti-thrombotics, puerarin injection can further improve treatment efficacy in UAP patients, reducing the incidence of angina pectoris attacks and the required dose of nitroglycerin, improve ECG outcomes and decrease plasma ET levels. As an effective treatment, puerarin does not exhibit significant differences in side effects relative to conventional therapies and therefore should be promoted for clinical application. However, only a limited number of studies were included in this systematic review, and these studies have small samples sizes and are of low quality. Therefore, further review of more rigorous, multi-center, randomized, controlled clinical studies with large sample sizes and long-term follow-up is required to demonstrate the efficacy of puerarin injection and to better guide the clinical treatment of angina pectoris.

Disclosure of conflict of interest

None.

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