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Efficacy and safety of oral Panax Notoginseng saponins for unstable angina patients: a meta-analysis and systematic review

Lian DUAN\textsuperscript{a,b,1}, Xingjiang XIONG\textsuperscript{b,1}, Junyuan HU\textsuperscript{a,b}, Yongmei Liu\textsuperscript{b}, Jie WANG\textsuperscript{b,*}

\textsuperscript{a}Graduate School, Beijing University of Traditional Chinese Medicine No.11 North Third Ring Road, Chaoyang District, Beijing
\textsuperscript{b}Department of Cardiology, Guang’an Men Hospital, China Academy of Chinese Medical Science
No.5 Bei xiang, Xicheng District, Beijing, China

*Corresponding author
WANG Jie
Address: Department of Cardiology, Guang’an Men Hospital, No.5 Beixiange, Xicheng District, Beijing, 100029, China
Tele: 010-88001817
E-mail address: wangjiedoctor2015@163.com

\textsuperscript{1} authors who contributed equally to the work
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ABSTRACT

Background: Panax notoginseng saponins (PNS) is one of the most important active ingredients in Panax notoginseng, which plays an important role against cardiovascular diseases in Traditional Chinese Medicine (TCM).

Methods: This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. We searched the following databases from their inception to Feb 2017: CENTRAL, MEDLINE, EMBASE Database, WHO ICTRP, CNKI, WANFANG, VIP and SinoMed. All the randomised controlled trials (RCTs) based on PNS in patients with unstable angina(UA) which meet the standard were included.

Result: Seventeen studies were included in this systemic review. The included studies indicated that PNS has promising therapeutic effects on reduction of the primary end point [RR 0.05 (95% CI -0.07, −0.02); P < 0.001], electrocardiography (ECG) [RR 0.32 (95% CI 0.23, 0.46); P < 0.001], the frequency and duration of angina attacks [MD -1.88 (95% CI -2.03, −1.72); P < 0.001], and dosage of nitroglycerin [MD -1.13 (95% CI -1.70, −0.56); P < 0.001] of UA patients. Adverse events were described 9 included RCTs.

Conclusion: Oral PNS could reduce the end point, and improve the ECG, the frequency and duration of angina pectoris, dosage of nitroglycerin and lipids in UA patients. And the results indicated oral PNS is safe up to now. However, we need more multi-centre, large-sample, high-quality RCTs to provide high-quality evidence.

Keywords: Panax notoginseng saponins, Unstable angina, Efficacy, safety, Systematic review

Abbreviations

CIs, confidence intervals; CAD, Coronary artery disease; ECG, electrocardiography; MI, myocardial infarction; NHIS, National Health Interview Survey; PNS, Panax notoginseng saponins; PPCM, PNS plus conventional medicine; RCTs, randomised controlled trials; RR, relative risk; TCM, Traditional Chinese Medicine; UA, unstable angina.
1. Introduction

Coronary artery disease (CAD) is among the leading cause of morbidity and mortality worldwide. The number of deaths due to CAD totalled 56 million globally (WHO, 2014). In 2010, CAD accounted for 13.3% of all deaths worldwide (Lozano et al, 2012). In 2013, the mortality from CAD was 222.9 million in the United States (Centers for Disease Control and Prevention, 2014). The total number of hospitalized cardiovascular operations increased by 28% from 5,939,000 in 2000 to 7,588,000 in 2010 (Mozaffarian et al, 2016).

Although UA may be the initial manifestation of CAD, most patients have preceding stable angina or myocardial infarction (MI). Even though conventional medicine benefits the patients of UA, the increasing burden and its complications urgently call for approaches of the management. Many problems of strategies for treating UA still exist, including nitrate failure, aspirin resistance, clopidogrel resistance, complex coronary lesions that cannot be revascularized, complex risk factors and so on. At the end of the nineteenth century, drug resistance of organic nitrates was soon observed (Dilidar et al, 2009; Münzel et al, 2011). Aspirin resistance had been observed in 1994 (Helgason et al, 1994). In addition, long-term administration of aspirin is often accompanied by adverse reactions such as gastrointestinal reactions and upper gastrointestinal bleeding with an increasing risk of bleeding. Clopidogrel has been widely used in various thrombotic diseases, especially in UA patients (O’Gara et al, 2013). Approximately 25% of patients treated with standard loading or maintenance doses of clopidogrel display poor responsiveness (Serebruany et al, 2005). The frequency of side effects to statins particularly muscle-related symptoms, is not commonly identified but appears 10% higher of all statin users (Joy et al, 2009). Due to the complexity of CAD, most patients need lifelong medication; varying degrees of drug resistance and adverse reactions raise the difficulty of the treatment.

In recent years, an increasing number of studies have confirmed the efficacy of TCM for treating CAD, including case reports, case series, and RCTs. According to the 2012 National Health Interview Survey (NHIS), which included a comprehensive survey on the use of complementary health approaches by Americans, 17.7 percent of American adults had used a dietary supplement other than vitamins and minerals in the past year (https://nccih.nih.gov/health/integrative-health). Panax notoginseng is the typical Chinese herb...
for blood circulation in cardiovascular diseases, which has been one of the most acclaimed herbs in China for 400 years. Panax notoginseng is traditionally applied as an anodyne and a haemorheologic-altering drug. The main medical component is the radix of Panax notoginseng, also known as Sanqi, Tianqi, or Shanqi in East Asian countries. “Compendium of Materia Medica” (Bencao Gangmu) recorded the official detailed medical applications of Panax notoginseng in 1758, in which Panax notoginseng is called “more precious than gold” (jinbuhuan). Panax notoginseng has continued to be a dietary supplement in many countries. In 2012, the production of Panax notoginseng touched 8000 tons and 20%-30% was exported (https://www.cir.cn).

PNS is one of the most important active ingredients of Panax notoginseng. Multiple animal experiments have shown that PNS can improve the energy metabolism of myocardial cells (Yin Yingji et al, 2010), reduce myocardial damage (Chen et al, 2001; Yue et al, 2012) in rats with acute MI (Han Shuyan et al, 2012). Oral PNS drugs include PNS tablets, Xuesaitong soft capsules, Xuesaitong dripping pills, Xueshuantong capsules, and other formulations. Based on conventional medicine, TCM intervention showed broad prospects. Several studies have shown that oral PNS can help relieve symptoms and improve the quality of life of patients (Yu et al, 2010; Liu et al, 2008). PNS may be used as complementary treatment by patients who refuse aspirin and statins because of adverse reactions, nitrate failure, aspirin resistance, clopidogrel resistance and statin intolerance.

In fact, the earliest study in vivo to demonstrate the effects of Panax notoginseng on CAD was a study published in 1972, in which the oral administration of Panax notoginseng reduced the dosage requirement of nitroglycerin and improved ECG in clinic. And Panax notoginseng significantly increased coronary blood flow in dogs (Department et al, 1972). PNS was shown to obviously alleviate the degree of myocardial ischaemia and narrow the ischaemic area subjected to myocardial ischaemia and infarction (Fu et al, 2006). PNS could enhance left ventricular systolic and diastolic functions, decrease peripheral resistance, and improve the cardiac function of rats with post-myocardial infarction left ventricular remodelling (Guo et al, 2009). The endothelium was denudated completely after balloon endothelial denudation (BED). PNS could sustain anti-restenotic effects after BED injury. PNS promoted endothelial regeneration and reduced ECM thickening (Chen et al, 2004).
Increasing evidence showed that it had anti-inflammatory, anti-apoptotic, anti-hypoxic, lowering lipids, anti-coagulation and pro-angiogenesis properties. PNS inhibited NF-κB DNA binding activity (Gerits et al, 2007) and secreting pro-inflammatory factors, interleukin (IL)-6 and MCP-1 in macrophages (Fan et al, 2012). The size of atherosclerotic lesions and the number of macrophages in apolipoprotein E (apoE) (-/-) mice were reduced by PNS. In addition, PNS reduced the expression of proinflammatory cytokines VCAM-1, ICAM-1 and MCP-1 with inhibition of NF-κB, JNK, p38 (MAPK) and ERK1/2 activation and RAGE (Dou et al, 2012). PNS could markedly reduce TC, TG, and LDL-C (Zhang et al, 2008) and increase HDL-C significantly (Liu et al, 2010) probably by increasing the expression of FABP4 and CPT-1A (Wang et al, 2016). Meanwhile, PNS decreased some inflammatory cytokines including integrins, IL-18, IL-1 beta and matrix metalloproteinases 2 (MMP2) and 9 in atherosclerosis rats (Zhang et al, 2008). In addition, PNS could decrease platelet activation, inhibit adhesion and aggregation of platelet, prevent thrombosis and improve microcirculation (Wang et al, 2004). PNS protected ECs from injury by suppressing platelet adhesion, in which PNS was superior to aspirin. The underlying mechanism is related to the COX pathway in both ECs and platelets (Wang et al, 2016). Meanwhile, PNS could protect myocardial cells from apoptosis induced by ischaemia both in vitro and in vivo by activating the PI3K/Akt signalling pathway (Tello-Montoliu et al, 2006). PNS significantly up-regulated p-Akt in H9c2 cells and ischaemic myocardial tissues. PNS attenuated cell apoptosis via chromatin concentration and condensation by up-regulating the antioxidative abilities of SOD and MDA (Li et al, 2014). PNS also suppressed proliferation and induced apoptosis in VSMCs (Wang et al, 2009) by up-regulating p53, Bax, and caspase-3 and down-regulating Bcl-2 (Xu et al, 2011). Besides, PNS could enhance angiogenesis and the proangiogenic effects including the VEGF-KDR/Flk-1 and PI3K-Akt-eNOS signalling pathways in vivo and in vitro (Hong et al, 2009).

At present, there is no systematic review regarding oral PNS for treating UA. Published systematic reviews of the oral administration of Panax notoginseng for UA have certain relevance to this study (Shang et al, 2013; Yang et al, 2013; Song et al, 2017). Recently, a systematic review about Panax notoginseng preparations for unstable angina pectoris identified 18 RCTs including 1828 patients. Sixteen studies were prescribed Panax notoginseng injections, and two studies were oral Panax notoginseng preparations. However, the results of only oral Panax notoginseng preparations reached up to 17 by 2017 Feb. And because of the insufficient RCTs in this
systematic review, cardiac mortality and duration of angina pectoris were not statistically significant in this review. In addition, this systematic review didn’t refer to the safety of Panax notoginseng preparations. Another review included 17 articles about Panax notoginseng preparations for CAD. It indicates that oral Panax notoginseng preparations can relieve angina-pectoris-related symptoms. However, CAD is a large conception that chronic stable angina, unstable angina, NSTEMI and STEMI means different in clinic. So, they were unsuitable to discuss together. While the results regarding the primary end point are inadequate and inaccurate. The other study included 6 articles exploring, Xuesaitong soft capsule, one of drugs which the main constituent is PNS, for treating unstable angina pectoris of CAD. Due to the research time, there are insufficient publications and incomplete methodological analyses in the systematic reviews. With the development of Chinese medicine research, new related clinical trials must be considered. However, a comprehensive and systematic review of the efficacy and safety of the oral administration of PNS for treating CAD is still lacking. In this systematic review, we will evaluate efficacy and safety of oral PNS for UA patients.

2. Methods

This systematic review protocol has been registered on PROSPERO (No. CRD42015015702). Our team has investigated the protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) statement guidelines (Larissa et al, 2015).

2.1 Search strategies

The search expression used in MEDLINE was ((‘coronary artery disease’ [MeSH Terms] OR ‘coronary artery disease’ [All Fields]) OR (‘coronary artery disease’ [MeSH Terms] OR ‘coronary artery disease’ [All Fields]) OR ‘unstable angina’ [MeSH Terms] OR ‘unstable angina’ [All Fields]) (‘Panax notoginseng’ [MeSH Terms] OR Panax notoginseng [Text Word] OR sanqi [Text Word] OR sanchi [Text Word]) OR Xuesaitong [Text Word] OR Xueshuantong [Text Word]) AND ‘Randomized Controlled Trial’ [Publication Type:NoExp]. Similar expressions were used in the other databases.

2.2 Inclusion criteria

All RCTs for evaluating the efficacy and safety of PNS were included in the literature regardless of language and the type of publication. The participants met the diagnostic criteria for UA. The treatment duration was at least 4 weeks. The conventional medicine group comprised the blank control group or the conventional drug (angiotensin converting enzyme inhibitors, beta blockers, calcium antagonists, nitrate esters, statin and so on) group. Traditional Chinese medicine or Chinese patent medicine as a control group was excluded. Oral PNS invention were included instead of PNS injection. Trials were excluded if there were other Chinese herbal medicines in the intervention group. The outcome measures met the primary or secondary outcomes. The primary outcome was the primary end point, which was defined as the composite of all-cause mortality, myocardial infarction (MI), revascularization, and rehospitalization for unstable angina. Secondary outcomes included ECG, attacks of angina pectoris (including the frequency and duration of angina pectoris) and the dosage of nitroglycerin and lipids. We defined the efficacy of angina pectoris as an improvement of greater than 50%; the efficacy of ECG as an elevation of the ST segment was more than 0.05 mv. Myocardial (re-)infarction was in all trials defined as elevated cardiac biomarkers together with ischaemic symptoms or ECG changes (ST-elevation or -depression, new left bundle branch block, or new
Q-waves).

2.3 Data collection and analysis

Two authors (DL, HJY) performed the literature review independently of each other by the Cochrane handbook for systematic reviews of interventions in the Cochrane Collaboration (Higgins et al, 2011). They scanned the titles and abstracts of every record retrieved for eligibility assessment. All studies selected by the two authors were cross checked. Any disagreement was resolved by discussion with a third author (CG).

Two authors (DL, HJY) independently extracted data. A standard form was predesigned for this review. The data extracted were as follows: study ID, researcher ID, study characteristics (authors, location, title, etc.), methodological information (randomization, allocation concealment, blinding, loss to follow-up, selective outcome reporting), patient characteristics (number of patients, age, gender, race, baseline disease severity, etc.), intervention, control, and outcomes. The authors of the original studies were consulted for unclear or missing information when necessary. Any disagreements were resolved by discussion.

2.4 Assessment of the risk of bias

We evaluated the risk of bias for each study with reference to the Cochrane Handbook (Higgins et al, 2011) according to the following seven considerations: a. random sequence generation method, b. allocation concealment, c. blinding (subjects, test personnel), d. blinding (outcome evaluator), e. incomplete outcome report, f. selective report study results, g. other offset source. Each criterion was divided into "low risk", "high risk", or "unclear" according to the actual situations in the studies.

2.5 Data analysis

A meta-analysis was performed using RevMan5.3 software. The mean difference (MD) and 95% confidence intervals (CIs) were calculated between groups at the end of treatment for continuous data. Relative risk (RR) was calculated for dichotomous data. A fixed effects model was used if there was no significant heterogeneity of the data $I^2 \leq 50$; a random effects model
was used if significant heterogeneity existed ($I^2 > 50\%$). A sensitivity analysis was used if there was any heterogeneity (including differences in clinical characteristics among trials and the statistical heterogeneity). In the subgroup analysis, PNS plus conventional medicine (PPCM) interventions with the same drug were grouped. For example, oral PNS in the studies were Xuesaitong capsules, Sanqi Tongshu capsules, and PNS tablets. Xuesaitong capsules with more combination studies can be prescribed with a subgroup analysis.

3. Results

3.1 Description of the Studies

We identified 106 potentially eligible reports by reviewing the study titles and abstracts. Ultimately, 2315 patients included in 17 trials (published between 2005 and 2016) were randomly assigned to an oral PNS treatment strategy (Table 1) or blank based on conventional treatment. The sample size of individual trial ranged between 55 and 1200 participants (mean of 193). The literature search chart is shown in Fig. 1. The specific characteristics of the literature are shown in Table 1.
3.2 Risk of bias in included studies

The quality of the 17 RCTs was evaluated from 7 aspects using the ROB scale in the Cochrane handbook of the Cochrane Collaboration (Higgins et al., 2011) (Fig. 2). Three RCTs (Meng et al., 2013; Teng et al., 2014; Han et al., 2008) indicated that random numbers were used, and the other studies did not describe the random method in detail. Two RCTs (Teng et al., 2014; Han et al., 2008) referred to random concealment and blindness, and the other studies did not mention them. Only one RCT (Teng et al., 2014) reported case shedding.

![Fig. 1 flow diagram of study selection](image)

![Fig. 2 Risk of bias graph](image)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Sample(T/C)</th>
<th>Age, Mean ±SD, y</th>
<th>M/F</th>
<th>Diagnosis standard</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Course(week)</th>
<th>Outcome measures</th>
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<tr>
<td>Author</td>
<td>Year</td>
<td>Cases</td>
<td>T</td>
<td>C</td>
<td>Diagnoses</td>
<td>Treatments</td>
<td>Follow-up</td>
<td>Follow-up Details</td>
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<td>------------------</td>
</tr>
<tr>
<td>Du</td>
<td>2009</td>
<td>56/56</td>
<td>T: 58.8±9.2</td>
<td>C: 58.8±9.2</td>
<td>NR</td>
<td>Unstable angina pectoris diagnostic criteria (NR)</td>
<td>CM (aspirin, β-blocker, ACEI, CCB, nitrates, etc., no details)</td>
<td>4w</td>
</tr>
<tr>
<td>Feng</td>
<td>2016</td>
<td>36/35</td>
<td>T: 69.3±4.8</td>
<td>C: 69.4±5.2</td>
<td>Coronary angiography, AHA/ACC</td>
<td>PNS</td>
<td>atorvastatin</td>
<td>12w</td>
</tr>
<tr>
<td>Han</td>
<td>2008</td>
<td>30/30</td>
<td>T: 64.1±10.8</td>
<td>C: 63.7±11.7</td>
<td>1979 WHO</td>
<td>PNS + CM</td>
<td>CM (aspirin, β-blocker, ACEI, CCB, nitrates, etc., no details)</td>
<td>12w</td>
</tr>
<tr>
<td>Hou</td>
<td>2016</td>
<td>42/42</td>
<td>T: 62.3±2.31</td>
<td>C: 62.4±2.32</td>
<td>Unstable angina pectoris diagnostic criteria (NR)</td>
<td>PNS + CM</td>
<td>CM (aspirin, β-blocker, ACEI, CCB, nitrates, etc., no details)</td>
<td>4w</td>
</tr>
<tr>
<td>Kong</td>
<td>2006</td>
<td>52/52</td>
<td>T: 61.21±5.73</td>
<td>C: 60.77±5.61</td>
<td>Unstable angina pectoris diagnostic criteria (NR)</td>
<td>PNS + CM</td>
<td>CM (aspirin, β-blocker, ACEI, CCB, nitrates, etc., no details)</td>
<td>4w</td>
</tr>
<tr>
<td>Kuang</td>
<td>2011</td>
<td>90/90</td>
<td>T: 56.3±6.9</td>
<td>C: 57.1±7.2</td>
<td>Unstable angina pectoris diagnostic criteria</td>
<td>PNS + CM</td>
<td>CM (no details)</td>
<td>4w</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Patients</td>
<td>T:</td>
<td>C:</td>
<td>Diagnostics</td>
<td>Treatment</td>
<td>Duration</td>
<td>Additional Notes</td>
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<tr>
<td>Liu</td>
<td>2008</td>
<td>30/30</td>
<td>64.6±5.4</td>
<td>63.6±4.5</td>
<td>NR</td>
<td>PNS + CM</td>
<td>4w</td>
<td>ECG, lipid</td>
</tr>
<tr>
<td>Meng</td>
<td>2013</td>
<td>600/600</td>
<td>68±11</td>
<td>69±9</td>
<td>ACS or stable angina pectoris diagnostic criteria</td>
<td>PNS tablet + CM</td>
<td>52w</td>
<td>PEP</td>
</tr>
<tr>
<td>Song</td>
<td>2005</td>
<td>50/50</td>
<td>61.2±5.7</td>
<td>60.7±5.6</td>
<td>1979 WHO</td>
<td>PNS + CM</td>
<td>4w</td>
<td>FAA, DN, ECG</td>
</tr>
<tr>
<td>Teng</td>
<td>2014</td>
<td>40/40</td>
<td>70.6±6.8</td>
<td>71.6±4.3</td>
<td>ACC/AHA 2011</td>
<td>PNS + CM</td>
<td>4w</td>
<td>FAA, lipid</td>
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<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Mean Age</td>
<td>Diagnosis Criteria</td>
<td>Treatment</td>
<td>Follow-Up</td>
<td>Outcome</td>
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<tr>
<td>Wan 2011</td>
<td>26/26</td>
<td>65.7</td>
<td>Unstable angina pectoris diagnostic criteria (NR)</td>
<td>PNS + CM</td>
<td>4w</td>
<td>ECG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Wei 2010     | 90/90       | T: 60.4 ±3.5  
C: 60.4 ±3.5 | 1979 WHO | PNS + CM | 4w        | FAA, DAA |
| Yan 2015     | 28/27       | T: 76.32±9.0  
C: 76.32±9.0 | CAD diagnostic criteria (NR) | Sanqi Tongshu capsule + aspirin | 24w       | PEP     |
| Yu 2010      | 50/50       | T: 64.18±12.13  
C: 62.8±10.8  
T: 29/2  
C: 28/2 | ACC/AHA | PNS + CM | 4w        | PEP, ECG |
| Zhang 2014   | 30/30       | T: 60±3.4  
C: 61±4.0 | 1979 WHO | PNS + CM | 4w        | FAA, DAA |
| Zheng 2014   | 56/56       | T: unclear  
C: unclear | 1993 "diagnostic criteria for coronary heart disease" | PNS + CM | 4w        | ECG     |
15

angina in China

metoprolol 50mg/d)

Zhou 2009 43/43 T: 65±6
C: 65±6 T: 32/1
1
C: 34/9

1979 WHO PNS + CM CM
(Nitrates, metoprolol, aspirin, nitroglycerin)

4w ECG

T/C: treatment group/control group; M/F: Male/female; NR: not report; CM: conventional medicine; FAA: frequency of angina attack; DAA: duration of angina attack; DN: dosage of nitroglycerin; PEP: the primary end point

3.3 Effect of the interventions

3.3.1 Main outcome measures

PPCM versus conventional medicine

Four included RCTs reported the primary end point. There was low between-trial heterogeneity ($\chi^2 = 1.56, P = 0.082; I^2 = 0\%$). A meta-analysis was performed using a fixed effect model. The mortality of PPCM group was lower than that of the conventional medicine group, and the difference was statistically significant. Oral PNS significantly reduced the primary end point (Fig. 3), as 21 of 680 patients (3.0%) from oral PPCM compared with 53 of 680 patients (7.8%) treated with conventional medicine alone [RR 0.05 (95% CI 0.22, 0.63); P < 0.001, Fig. 3].

Fig. 3 Meta-analysis of the primary end point in PPCM and conventional medicine groups

Square data markers represent risk ratios and horizontal lines the 95% confidence intervals with a
marker size reflecting the statistical weight of the study using inverse variance fixed effects meta-analysis. CM: conventional medicine.

**PPCM versus statin or aspirin therapy**

One trial (Feng et al, 2016) evaluated the effect of PNS on the end point compared with atorvastatin. Compared to the statin group, the administration of PNS for 12 weeks decreased the rate of the end point (0/36 versus 3/35, \( p < 0.05 \)). Another trial (Yan et al, 2015) evaluated the effect of PNS on the end point compared with aspirin (1/26 versus 1/27). The treatment of PNS for 24 weeks depressed the end point than aspirin alone. The study illustrated long-term treatment of PNS can reduce the end point which is the most important method of therapeutic evaluation in CAD. The effect of PNS probably is equals to aspirin and stronger than atorvastatin.

### 3.3.2 Secondary outcome measures

**Frequency of angina attack**

Eight included RCTs reported the frequency of angina attacks. These eight RCTs used the same intervention, which was Xuesaitong soft capsules (each containing Panax notoginseng (60 mg), Kunming Torch Pharmaceutical Co., Ltd., production). Eight RCTs showed that PPCM group was more effective than the conventional medicine group, with significant differences (Fig. 4).

In view of high heterogeneity, our team conducted a consistency source analysis. After the elimination of methodological and statistical heterogeneity, clinical heterogeneity was found in the study of different diagnostic criteria, which may be one of the important reasons. Of eight RCTs, four did not provide a definite diagnostic criterion (Du et al, 2009; Hou et al, 2016; Kong et al, 2006; Kuang et al, 2011). One RCT used the "Classification and Diagnostic Criteria for Ischemic Heart Disease" (Song et al, 2005); one RCT, The American Heart Association (ACC) / American Heart Association (AHA) 2002 standard diagnoses CAD unstable angina (Teng et al, 2014); and two RCTs WHO diagnostic criteria for CAD (Wei et al, 2010; Zhang et al, 2014). Different criteria may affect the baseline level of patients in different groups.
Fig. 4 Meta-analysis of frequency of angina attack in PPCM and conventional medicine groups

Duration of angina attack

Four included RCTs reported the duration of angina attacks (minutes for each attack). Four RCTs used the same intervention, which was Xuesaitong soft capsules. There was low between-trial heterogeneity ($\chi^2 = 1.73$, $P < 0.001$; $I^2 = 0\%$). A meta-analysis was performed using a fixed effect model. The effective rate of PPCM group was higher than that of the conventional medicine group, and the difference was statistically significant [MD $-1.88$ (95% CI $-2.03$, $-1.72$); $P < 0.001$, Fig. 5].

Fig. 5 Meta-analysis of the angina attack duration in PPCM and conventional medicine groups

Dosage of nitroglycerin

Two included RCTs reported the dosage of nitroglycerin (mg each week). There was low between-trial heterogeneity ($\chi^2 = 0.47$, $P = 0.49$; $I^2 = 0\%$). A meta-analysis was performed using a fixed effect model. The effective rate of PPCM group was higher than that of the conventional medicine group, and the difference was statistically significant [MD $-1.13$ (95% CI $-1.70$, $-0.56$); $P < 0.001$, Fig. 6].

Fig. 6 Meta-analysis of the nitroglycerin dosage in PPCM and conventional medicine groups
ECG

Improvement of ECG was defined as an elevation of the ST segment more than 0.05 mv. Eight RCTs reported improvement of ECG. Xuesetong soft capsules were chosen as the intervention drug. There was low between-trial heterogeneity ($\chi^2 = 0.47, P = 0.49; I^2 = 32\%$). A meta-analysis was performed using the fixed effect model. The effective rate of PPCM group was higher than that of the conventional medicine group, with a significant difference [RR 0.32 (95% CI 0.23, 0.46); $P < 0.001$, Fig. 7].

![Fig. 7 Meta-analysis of ECG in PPCM and conventional medicine groups](image)

Lipid

**PPCM versus conventional medicine**

Four included RCTs reported TC, TG, LDL and HDL (mmol/l). TC in PPCM group was lower than that in the conventional medicine group, and the difference was statistically significant (Fig. 8). In addition, compared with conventional medicine, a meta-analysis of four trials demonstrates PNS could lower TG, LDL and increase HDL between PPCM group and the conventional medicine group (Fig. 9, 10, 11). However, analysis of the source of heterogeneity revealed that it is likely to be related to different lipid baselines.

![Fig. 8 Meta-analysis of TC in PPCM and conventional medicine groups](image)
In the other groups, PNS plus conventional medicine was compared with conventional medicine, while (Feng et al, 2016) compared PNS with atorvastatin. After treatment, the levels of TC, TG and LDL of the patients in the two groups decreased, but atorvastatin appeared to be more effective (TC: 2.91 ± 0.92 mmol/l versus 2.79 ± 0.87 mmol/l, p < 0.05; TG: 4.91 ± 0.52 mmol/l versus 4.79 ± 1.27 mmol/l, p < 0.05; LDL: 2.91 ± 0.62 mmol/l versus 2.79 ± 0.67 mmol/l, p > 0.05). However, PNS could be more effective to increase HDL than atorvastatin (HDL: 1.15 ± 0.32 mmol/l versus 1.09 ± 0.47 mmol/l, p > 0.05). The trial demonstrated that PNS has weaker effect on TC, TG, LDL, and stronger effect on HDL than atorvastatin.

3.4 Adverse events

Nine included RCTs described adverse events, which indicated that oral PNS for treating CAD is not related to adverse reactions. The team (Feng et al, 2016) reported 2 cases with elevated transaminase, 1 case with muscle pain, and 1 case with gastrointestinal discomfort in the conventional medicine group. No obvious adverse reactions appeared in the treatment group.
Another team (Meng et al, 2013) mentioned bleeding events in both groups. Most of mild bleeding events (bleeding gums and gastrointestinal bleeding) were related to a history of stomach disease. Discontinuation of aspirin alleviated the bleeding. The team (Teng et al, 2014) found 2 patients with headache and dizziness after treatment, for whom withdrawal relieved the symptoms. After treatment, the liver and kidney functions exhibited no significant changes. One case with subcutaneous haemorrhage and 1 case with faecal occult blood positivity occurred in PPCM group (Yan et al, 2015); 1 case with nausea and 1 case with faecal occult blood positivity occurred in the conventional medicine group. There was no significant difference in the incidence of adverse reactions between the two groups. In the team (Yu et al, 2010), 1 patient in PPCM group showed a small rash after 3 days of treatment without an influence of the treatment. The rash disappeared after 2 days of oral chlorpheniramine administration. No significant adverse reactions were observed in the conventional medicine group. Another 5 RCTs mentioned no obvious abnormalities of liver and kidney function.

Table 2 The incidence of adverse reactions with PNS for CAD

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>The incidence of adverse reactions (experimental)</th>
<th>The incidence of adverse reactions (control)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>elevated transaminase</td>
<td>0/36</td>
<td>2/35</td>
<td>Feng 2016</td>
</tr>
<tr>
<td>gastrointestinal discomfort</td>
<td>0/36</td>
<td>1/35</td>
<td>Feng 2016</td>
</tr>
<tr>
<td>muscle pain</td>
<td>0/36</td>
<td>1/35</td>
<td>Feng 2016</td>
</tr>
<tr>
<td>subcutaneous haemorrhage</td>
<td>1/28</td>
<td>0/27</td>
<td>Yan 2015</td>
</tr>
<tr>
<td>faecal occult blood positive</td>
<td>1/28</td>
<td>1/27</td>
<td>Yan 2015</td>
</tr>
<tr>
<td>nausea</td>
<td>0/28</td>
<td>1/27</td>
<td>Yan 2015</td>
</tr>
<tr>
<td>rash</td>
<td>1/50</td>
<td>0/50</td>
<td>Yu 2010</td>
</tr>
<tr>
<td>Total</td>
<td>3/214</td>
<td>6/208</td>
<td></td>
</tr>
</tbody>
</table>
3.5 Sensitivity analysis

A sensitivity analysis was performed based on the quality of the original study. Based on the original studies with a low risk of bias (Han et al, 2008, Meng et al, 2013), there was no significant heterogeneity between the two groups ($\chi^2 = 0.04$, $P = 0.84$; $I^2 = 0\%$) for the primary end point. The OR was 0.39 (95% CI: 0.23-0.66, $P < 0.001$), with a significant difference. Other outcomes lacked low-risk studies; consequently, it was difficult to apply the sensitivity analysis. (Fig. 12)

![Fig. 12 Meta-analysis of the primary end point in PPCM and conventional medicine groups](image)

### 4. Discussion

#### 4.1 summary of evidence

Recently, an increasing number of studies have confirmed the efficacy of TCM for treating UA, including case reports, case series, and RCTs, especially an herbal active ingredient, PNS. An advantage of PNS is low incidence of adverse events.

In total, 17 studies with a total of 2315 UA patients were included in this systemic review. The results from the included studies indicated that PNS has promising therapeutic effects with respect to reduction of the primary end point, improvement of ECG, symptoms including the frequency and duration of angina attacks, and the dosage of nitroglycerin. The primary end point appeared differently as 21 of 680 patients (3.0%) from oral PPCM compared with 53 of 680 patients (7.8%) treated with conventional medicine alone. PPCM exhibited significant lowering effects on duration of angina attacks (decreased by 1.88 min), dosage of nitroglycerin (decreased by 1.13 mg), TC (decreased by 0.79mmol/l), TG (decreased by 0.23mmol/l), LDL (decreased by 0.77mmol/l), HDL (increased by 0.30mmol/l) compared with conventional medicine alone.
Compared with the conventional medicine group, rare adverse reactions occur with oral PNS. However, as significant heterogeneity and low quality of the studies exists, the results should be treated with caution.

The meta-analysis showed that PNS had beneficial effects on UA. In RCTs with the outcome of the primary end point, the rate of end point was decreased by 0.37 and the heterogeneity is zero. The sensitivity analysis results also suggested that, for the primary end point, exclusion of high-risk studies did not affect the results significantly. By close comparison, we found that in the studies focusing on the end point, the medication cycle was longer, namely, 24 w, 52 w, and 12 w. However, the study which the medication cycle was 4 w observed the outcomes such as the ECG, clinical symptoms (including the frequency and duration of angina attacks), and dosage of nitroglycerin. Thus, longer administration of PNS and conventional medicine probably reduced the end point, while shorter administration preferred to improve clinical symptoms of UA patients. Several mechanisms of PNS can alter end point and symptoms, such as anti-inflammation, regulation of lipid metabolism, anti-platelet, anti-apoptosis, anti-atherosclerosis and protection against myocardial ischemia (Dou et al, 2012; Wang et al, 2016; Wang et al, 2016).

The meta-analysis has suggested that the administration of PNS could decrease the symptoms of UA from several aspects of frequency of angina attack, duration of angina attack and dosage of nitroglycerin. The data of 7 included trials demonstrated the effects to reduce the frequency of angina attack (2.07 times/week). The data of 4 included trials demonstrated the effects to reduce the duration of angina attack (1.88min/time). The meta-analysis of 2 trials referred the reduction of nitroglycerin dosage (1.13mg/week). The results indicated that PNS was beneficial for alleviate the symptoms of UA.

PPCM can also improve the ECG of UA patients. Improvement of ECG was defined as an elevation of the ST segment more than 0.05 mv. Eight RCTs reported improvement of ECG. The ECG improvement appeared differently as 281 of 349 patients (80.5%) from PPCM compared with 205 of 349 patients (58.7%) treated with conventional medicine alone. This phenomenon occurred with the alleviation of UA symptoms. The mechanisms could be related to anti-inflammation and protection against myocardial ischemia of PNS.

In our systematic review, another valuable finding was the influence on the lipid-lowering
effect of PPCM. Conventional medicine includes statin, however, PNS as a complementary medicine could strengthen its effects. Analysis of four studies showed significant lowering effects on TC (decreased by 0.21-1.50 mmol/l), TG (decreased by 0.01-0.86 mmol/l), LDL (decreased by -0.06-1.24 mmol/l). However, the effects on HDL were so different that in two studies combination treatment reduced HDL and in one study combination treatment increased HDL. In general, PNS could lower the lipids. A meta-analysis of 14 randomized trials in 2005 showed that a decrease of 1 mmol /L in plasma LDL levels generates a 20% reduction in major coronary events, coronary revascularization and stroke within 5 years (Baigent et al, 2005). The decrease of end point probably was related to the reduction of LDL. However, the heterogeneity was high in several studies. A possible explanation was the variation in the baseline data for blood lipids among participants of UA.

Moreover, no studies mentioned severe adverse events such as aspirin-associated haemorrhage, station-associated myalgia or abnormalities of liver and kidney function. The safety of PNS was likely one of the critical reasons for its popularity. However, PNS as a natural product doesn’t mean absolutely safe. In this systematic review, 9 included RCTs described slight adverse events, such as subcutaneous haemorrhage (1/28), faecal occult blood positive (1/28), rash (1/50). Although the recorded adverse reactions were slight and tolerant for CAD patients, the absolutely safety of PNS cannot be concluded in the basement of inaccurate and inadequate studies.

Published studies have not yet addressed the efficacy and safety of oral PNS for treating unstable angina pectoris. In this study, adequate studies were considered after a comprehensive search, and a sensitivity analysis was performed. Oral PNS for treating CAD was comprehensively evaluated and analysed. The sensitivity analysis showed that low-risk literatures were combined close to the total value, suggesting that the results were more stable.

4.2 Limitations

The investigators cautioned that confirmatory evidence was needed before the conclusion could be adopted into clinical practice, as we must take into consideration the limitation in this systematic review. Firstly, the quality of included RCTs was generally low according to Cochrane’s
risks of bias tool. Of the 17 studies, only 3 describe the specific random and blind program, while the rest did not show any details with only the sentence “the patients were randomized into two groups”. In addition, several trials’ author was only one (Feng et al. 2016; Song et al. 2005; Teng et al. 2014; Wei et al. 2010; Yan et al. 2015; Yu et al. 2010) except two dissertations (Du et al. 2009; Meng et al. 2013), which looked impossible in methodology. So, we have to suspect the facticity of these claimed RCTs. The lack of high-quality studies means it is difficult to make data relevant and able to be generalized.

Secondly, the limitation of this review was that the diagnostic criteria for evaluating efficacy was not uniform. Diagnosis standard of 5 trials was unstable angina pectoris diagnostic criteria, but not clear (Du et al. 2009; Kong et al. 2006; Hou et al. 2016; Kuang et al. 2011; Wan et al. 2011). Five trials adopted standards of 1979 WHO (Han et al. 2008; Song et al. 2005; Wei et al. 2010; Zhang et al. 2014; Zhou et al. 2009). One trial used AHA/ACC by Coronary angiography (Feng et al, 2016), one ACC/AHA 2011 (Teng et al. 2014), one Angina pectoris diagnostic criteria, one ACS or stable angina pectoris diagnostic criteria (unclear), one CAD diagnostic criteria (unclear) and one 1993 "diagnostic criteria for coronary heart disease angina" in China. The criteria were so different that the heterogeneity appeared high in lipids.

In addition, of 17 included trials, all of them were written in Chinese and no English article was involved. No negative studies were generated at all. Publication biases could affect the results probably. We had tried to take all measure to contact the authors to learn more information. Unfortunately, we didn’t get their reply.

5. Conclusion

In conclusion, oral PNS could reduce all-cause mortality, myocardial infarction (MI), revascularization, rehospitalization for unstable angina, and improve the ECG, the frequency and duration of angina pectoris, dosage of nitroglycerin and lipids. But taking into account the quality of the original studies, we need more multi-centre, large-sample, high-quality RCTs to provide high-quality evidence.

Contributors DL, HJY and XXJ contributed to the conception of the study. The protocol of the
manuscript was drafted by DL and HJU and was revised by XXJ. The search strategy was developed by all authors and run by DL and HJY. XXJ and LX assessed the risk of bias and completed the data synthesis. WJ arbitrated disagreements and ensured that no errors occurred during the study.

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**Conflicts of Interest**

None of the authors declare a conflict of interest.

**Financial Disclosure**

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