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Original Research Article

Efficacy and safety of Qishen Yiqi drop pill for coronary heart disease: An overview of systematic review and meta-analysis

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Abstract

Purpose: *To investigate current pieces of evidence on Qishen Yiqi drop pill (QSYQ) in coronary heart disease (CHD).*
Methods: *All systematic reviews (SRs) and meta-analyses (Mas) on QSYQ for CHD were collected by searching six databases and evaluated using the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2). The grading of recommendations assessment, development, and evaluation (GRADE) system was applied to assess the quality of outcomes.*
Results: *Five SRs/MAs were analyzed and twenty-four outcome indicators were reported. The AMSTAR 2 revealed that 3 (12.5 %) of the outcome indicators were of moderate quality, 6 (25 %) were of low quality, and 15 (62.5 %) were of deficient quality. Five SRs/MAs (80 %) described adverse reactions, with two reporting no significant adverse reactions and two reporting minor adverse reactions ($p > 0.05$).*
Conclusion: *Combining QSYQ with conventional therapy improves CHD patients' electrocardiogram and overall health outcomes. Future high-quality clinical trials and standardized study methods are needed to further investigate the safety of QSYQ.*

Keywords: *Qishen Yiqi Drop Pill, Coronary heart disease, Systematic reviews, Meta-analysis, Overview*

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INTRODUCTION

Coronary heart disease (CHD) is a significant health concern for the global population [1]. Approximately 20.5 million individuals aged 20

and above in the United States are diagnosed with CHD [2]. It remains the primary cause of death, responsible for approximately one-third of all deaths in individuals aged 35 and above [3]. Coronary heart disease (CHD) is associated with various risk factors such as hypertension, hyperlipidemia, obesity/overweight, and diabetes [4].

Currently, treatment guidelines recommend thrombolysis, blood pressure lowering, platelet lowering, blood cholesterol-lowering therapy and cardiac intervention [1]. However, conventional monotherapy is still not sufficient to reduce CHD incidence and is often accompanied by complications [5], therefore, better treatment options are required to treat CHD. Qishen Yiqi Drop Pill (QSYQ) is a Chinese herbal preparation containing four traditional Chinese herbal medicines: Astragalus, Salvia, *Panax notoginseng*, and Radix et Rhizoma. It obtained approval from the State Food and Drug Administration in 2003 (Approval number of CFDA: Z20030139) for treating cardiac dysfunction. Clinical trials have demonstrated that QSYQ elicited a comparable effect with aspirin in the secondary prevention of myocardial infarction [6]. As a result, QSYQ has been applied as an adjunct therapy in CHD.

Systematic reviews (SRs) and meta-analyses (MAs) serve as vital instruments for informing evidence-based clinical practice. With the development of evidence-based Chinese medicine in recent years, SRs/MAs of QSYQ for CHD have been increasing to assess effectiveness and safety. A higher-level overview of SRs/MAs may comprehensively synthesize and provide more information resulting in a more focused and easier use of evidence, as well as improved clinical applications [7]. Therefore, this study is an overview of the SRs/MAs of QSYQ for CHD to assess the quality and level of evidence for outcome indicators, and provide evidence for clinical studies.

METHODS

Search strategy

The China National Knowledge Infrastructure, Wan Fang, China Science and Technology Journal Database, Embase, Pubmed, and Cochrane Library were systematically explored for all SRs/MAs related to QSYQ for Coronary Heart Disease (CHD) from the inception of each database until May 3, 2022. Search terms included Qishen Yiqi Drop Pill, coronary heart disease, coronary atherosclerotic heart disease, angina pectoris, systematic review, and meta-analysis. The Supplementary file contained the detailed search strategy. The study protocol was registered on the OSF website with Registration DOI: 10.17605/OSF.IO/S6JBK.

Inclusion criteria

Systematic reviews and meta-analyses (SRs/Mas) of randomized controlled trials (RCTs) on QSYQ for CHD were included to evaluate the effectiveness and safety of QSYQ. The assessment was conducted exclusively in both Chinese and English.

Exclusion criteria

Repeatedly published articles, full text not available, and articles with incomplete data were excluded.

Study selection and data extraction

Two reviewers (JY1 and CZ) independently conducted the identification and screening of SRs/Mas. They evaluated titles and abstracts to exclude potentially irrelevant articles and then assessed the full texts to determine eligibility. Any discrepancies were resolved through discussion between the reviewers, and if needed, a third reviewer (WY) was consulted to reach a consensus. The collected and recorded data included details such as first author, publication year, country, number of trials and cases involved, interventions in both the QSYQ and control groups, funding sources, quality assessment tools for the enrolled Randomized Controlled Trials (RCTs), funding information, and conclusion.

Quality assessment

Two reviewers (XC and JY2) independently assessed the methodological quality of the Systematic reviews (SRs) and meta-analysis (MAs) using the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2), which consists of 16 items scored as "Y" (Yes), "PY" (Partial Yes), and "N" (No). The specific quality criteria were as follows: if there was no or only one non-critical item not meeting the criteria, the evaluation was considered high quality; if more than one non-critical item did not meet the criteria, it was deemed moderate quality; if one critical item did not meet the criteria with or without a non-critical item not meeting the criteria, it was evaluated as low quality; and if more than one critical item did not meet the criteria with or without a non-critical item not meeting them, it was assessed as very low quality. Any disagreement in the evaluation was

resolved through discussion between the two reviewers (XC and JY2) or was subject to adjudication by a third reviewer (LJ).

Two reviewers (XC and JY2) independently utilized the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool to evaluate the level of evidence for the outcome indicators. This tool [8] appraised the quality grade of the outcome indicators across five dimensions namely; limitations, inconsistency, indirectness, imprecision, and publication bias. Quality grades were categorized as high quality, (confidence that the effect size estimate closely represented the true picture), moderate quality (confidence that the effect size estimate was likely close to the true picture but could differ substantially), low quality (limited confidence in the effect size estimate and likely to differ substantially from the true picture), and very low quality (little confidence in effect size estimates, likely to be significantly different from the true picture). Any discrepancy was resolved through discussion between the two reviewers (XC and JY2) or was subject to adjudication by a third reviewer (LJ).

Participants

Patients diagnosed with CHD according to the following criteria, irrespective of age, gender, race, or duration of disease. Guidelines for clinical studies of drugs in the cardiovascular system [9], Nomenclature and criteria for diagnosis of ischemic heart disease [10], 2013 Internal Medicine in Chinese Medicine [11], nomenclature and diagnostic criteria of ischemic heart disease [12], Guiding Principles for Clinical Study of New Chinese Medicines [13], Recommendations on the Nomenclature and Diagnostic Criteria of Coronary Artery Disease [14], American College of Cardiology and American Heart Association (ACC/AHA) 2004 Revised Guidelines for the Treatment of ST-Segment Elevation Acute Myocardial Infarction (STEMI) [15], 2007 ACC/AHA Updated Guidelines for Treatment of Unstable Angina/Non-ST Segment Elevation Myocardial Infarction (UA/NSTEMI) [16].

Interventions

According to CHD diagnosis protocol, control group was treated with conventional therapy (nitrates, β-blockers, calcium channel blockers, antiplatelet agents, cholesterol-lowering drugs, etc.) or placebo in addition to conventional therapy and study group was treated with QSYQ in addition to conventional therapy.

Evaluation of parameters/indices

Outcome indicators

Outcome indicators were anginal efficacy, electrocardiogram (ECG) efficacy, Traditional Chinese Medicine (TCM) symptom efficacy, left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), left ventricular end-diastolic dimensions (LVEDD), left ventricular end-systolic volume (LVESV), nitroglycerin reduction rate, cardiac output, and endpoint event rate.

Angina efficacy

Angina efficacy was classified as significantly effective (absence of chest tightness, shortness of breath, or breath-holding symptoms after general activities, and no angina or decrease in frequency of angina attacks at same level of exertion), effective (reduction in frequency of angina attacks or alleviation of chest tightness), ineffective (no noticeable improvement in angina attacks despite medication usage. Efficacy was calculated as the sum of significantly effective rate and effective rate.

Electrocardiogram efficacy

Electrocardiogram efficacy was classified as significantly effective (restoration of ECG ischemic indicators), effective (restoration of ECG ischemic ST-segment depression by more than 1 mm after treatment, and transformation of inverted T-wave to hypotonic), ineffective (no apparent improvement in ECG alterations despite medication usage or no alteration in the ECG pattern). Efficacy was calculated as the sum of significantly effective rate and effective rate.

Symptom efficacy

The TCM symptom efficacy such as chest pain, chest tightness, shortness of breath, weakness, palpitations, spontaneous sweating, and less flushed face were judged based on the integral method, mainly referring to the Guidelines for Clinical Research on New Chinese Medicines. Symptom efficacy was classified as significant efficacy ($n \geq 66.67$ %), effective ($66.67\ \% > n \geq 33.33$ %), ineffective ($0 \leq n < 33.33$ %), and aggravation ($n < 0$). Efficacy index (n) was calculated using Eq 1.

$$n = (Pre\text{-}Pos/Pre)100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

where Pre is the pre-treatment score, Pos is the post-treatment score.

RESULTS

A total of 37 articles were obtained from six databases. After eliminating 18 duplicate studies, the titles and abstracts of 19 studies were reviewed, and seven full texts were examined. Among these, 5 studies were not SRs/MAs, 4 studies did not pertain to CHD, and 5 studies did not involve QSYQ. Eventually, five studies [17-21] that satisfied the criteria were included (Figure 1).

Description of the included reviews

The five studies [17-21] were all published in Chinese journals between 2013 and 2019. The first and corresponding authors were from China and none mentioned funding support. The studies were all RCTs and meta-analyses. The number of studies included in each SR/MA was between 9 and 25 with sample sizes ranging from 750 to 6246 participants. The interventions in 3 studies [18,20,21] were QSYQ (0.5 g po tid) combined with conventional therapy (QSYQ group) and conventional therapy or conventional therapy with placebo (control group). Specific QSYQ dose and usage were not specified in the two studies [17,19]. Three studies [17-19] used the Jadad Scale and two studies [20,21] used the Cochrane Risk of Bias Assessment Tool. All studies concluded that combination of conventional therapy with QSYQ improves clinical efficacy and safety compared to conventional therapy for CHD treatment but the quality evidence was insufficient and needed to be validated in larger, high-quality clinical trials (Table 1).

Quality assessment

The methodological quality of all five SRs/MAs was assessed as very low using the AMSTAR 2 evaluation tool due to inadequate reporting of key items. Only two SRs/MAs [17,20] (40 %) reported 62.5 % of the 16 items, while the remaining three SRs/MAs [18,19,21] (60 %) reported only 56.25 % of the 16 items. Regarding critical items, none of the five SRs/MAs (100 %) had a registered or developed protocol in advance (item 2). Only three SRs/MAs [19-21] (60 %) employed a comprehensive literature search strategy, while the others [17,18] (40 %) did not conduct supplementary searches. None of the SRs/MAs provided a list of excluded studies and reasons for their exclusion (item 7). One SR/MA [19] (20 %) did not assess publication bias (Item 15).

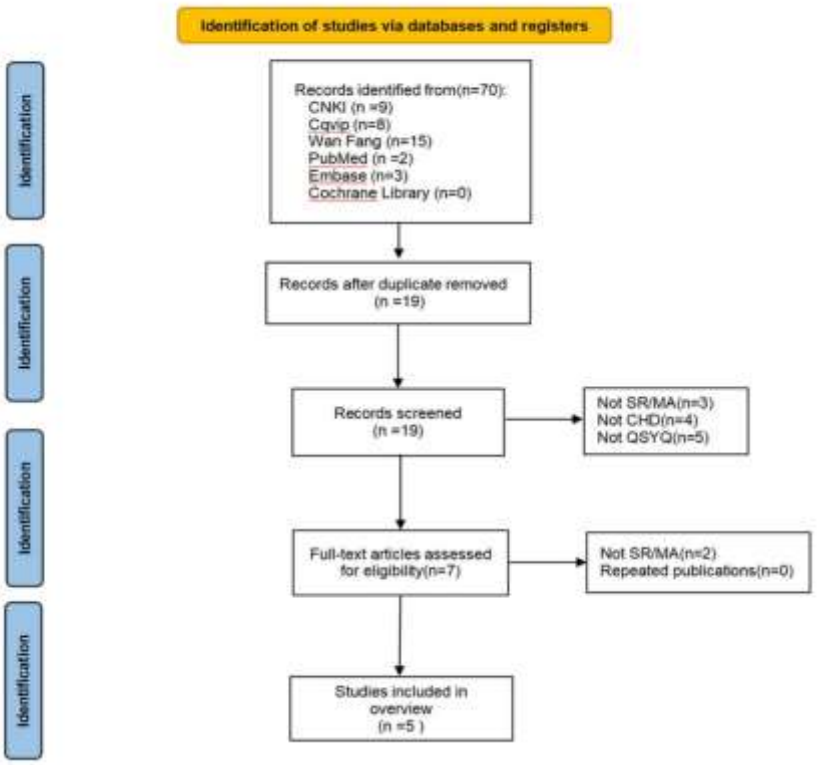

Figure 1: Flow chart of the study selection process**.** CHD, coronary heart disease; CNKI, China National Knowledge Infrastructure database; Cqvip, China Science and Technology Journal Database; Embase, Excerpta Medica database; QSYQ, Qishen Yiqi Drop Pill; SR, Systematic review; MA, Meta-analysis

Table 1: Main characteristics of included studies in China

Author(s), year	Trials (subjects)	Treatment intervention	Control intervention	Quality assessment	Main results	Funds	GRADE
Yang Ye 2014	9 (750)	QSYQ (0.5g po tid)+CM	CM	Cochrane	The addition of QSYQ to conventional treatment improves rate of improvement of angina symptoms and ECG recovery in patients with coronary artery disease.	N	N
Yang Qiaoning 2013	25 (6246)	QSYQ+CM	CM/CM+Placebo	Jadad	Combination of QSYQ with conventional treatment further improves clinical symptoms, ECG efficacy, nitroglycerin dosage and cardiac function index of CHD compared to conventional treatment alone with good safety.	N	N
Rong Jie 2015	11(1035)	QSYQ+CM	CM/CM+Placebo	Jadad	Combination of conventional Western medicine with QSYQ is better than conventional Western medicine alone or with placebo in the treatment of CHD.	N	N
Li Liping 2013	12 (1090)	QSYQ (0.5g po tid)+CM	CM/CM+Placebo	Jadad	QSYQ is safe and effective in the treatment of angina pectoris in CHD.	N	N
Chen Yalu 2019	13 (1293)	QSYQ (0.5g po tid)+CM	CM/CM+Placebo	Cochrane	Combination of Western medicine with QSYQ further improves clinical efficacy and safety compared to Western medicine alone	N	N

Note: QSYQ, Qishen Yiqi Drop Pill; CM, conventional western medicine; CHD, coronary heart disease

Table 2: Methodological quality assessment of the included reviews using the AMSTAR 2 tool

Author(s), year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Quality
Yang Ye 2014	Y	PY	N	Y	N	N	N	Y	Y	N	Y	Y	Y	Y	Y	N	VL
Yang Qiaoning 2013	Y	PY	N	Y	Y	Y	N	N	Y	N	Y	Y	Y	Y	N	N	VL
Rong Jie 2015	Y	PY	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N	VL
Li Liping 2013	Y	PY	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	N	VL
Chen Yalu 2019	Y	PY	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	N	VL

Note: Q: question, Y: yes, N: no, PY: partial yes, VL: very low

Concerning non-critical items, none of the five SRs/MAs explained the rationale behind their study designs (item 3), one SR/MA [21] (20 %) employed a single reviewer for screening the literature and extracting data (items 5 and 6); one SR/MA [19] (20 %) did not adequately describe the essential characteristics of the included studies (item 8); and all SRs/MAs failed to report funding sources (item 10) and potential conflicts of interest (item 16). Also, two SRs/MAs [18,20] (40 %) did not address heterogeneity in their results (item 14, Table 2).

Evidence quality

All SRs/MAs included a total of 24 outcome indices on the efficacy of QSYQ for CHD. According to GRADE results, none of the 24 outcome indices were supported by high-quality evidence. Only three outcome indices [17,20] (12.50 %) were deemed to have moderate-quality evidence, six outcome indices [19] (25 %) were categorized as low-quality evidence, and the remaining 15 outcome indices [17-21] (62.50 %) were all classified as very low-quality evidence. The results showed that randomized controlled trials (RCTs) were of low quality, and biases related to blinding, randomization, and allocation concealment limited the reliability of outcome indices. Also, high heterogeneity was observed in eight outcome indices (33.33 %) obtained through meta-analysis, leading to inconsistency, 11 outcome indices (45.83 %) lacked consistency due to either small sample sizes of included RCTs (less than 300) or asymmetry observed in the funnel plot, indicating imprecision. Furthermore, 21 outcome indices (87.5 %) were not assessed for publication bias using the funnel plot or showed evidence of publication bias, resulting in further downgrading of the results (Table 3 and Table 4).

Outcomes

Angina pectoris treatment effect

The five SRs/MAs examined the effectiveness of QSYQ in treating angina pectoris in CHD. Among them, one study [19] was further divided into two subgroups based on the diagnostic criteria and efficacy criteria. In one subgroup, diagnostic criteria followed the nomenclature and diagnostic criteria of ischemic heart disease [11], and the efficacy evaluation criteria were based on angina pectoris and electrocardiogram of coronary heart disease. Diagnostic criteria for the other subgroup were not specified, and efficacy evaluation followed the Guiding Principles for Clinical Study of New Chinese Medicines [12]. The results indicated a significant difference in the efficacy of QSYQ for angina pectoris in CHD compared to the control group. Two outcome indices [17,20] were assessed as having a moderate-quality grade (12 RCTs [20], OR = 3.85, 95 % CI 2.70 to 5.50, $p < 0.05$, I2 = 0 %; 7 RCTs [17], OR = 3.48, 95 % CI 2.23 to 5.43, $p < 0.05$, $I^2 = 0$ %), and two outcome indices [19] were of low quality (7 RCTs [19], RR = 1.18, 95 % CI 1.10 to 1.26, $p < 0.05$, $I^2 = 0$ %; 5 RCTs [19], RR = 1.20, 95 % CI 1.09 to 1.32, $p < 0.05$, $I^2 = 0$ %). The remaining studies [18,21] were rated as very low quality (9 RCTs [21], RR = 1.27, 95 % CI 1.18 to 1.36, $p < 0.05$, $I^2 = 0$ %; 12 RCTs [18], OR = 3.10, 95 % CI 1.80 to 5.33, $p < 0.05$, $I^2 = 45$ %).

Electrocardiogram efficacy

All SRs/MAs examined the electrocardiographic efficacy of QSYQ in CHD. One study [19] was further divided into two subgroups based on the diagnostic and efficacy criteria of the included studies. Four reviews [17,18,20,21] and a subgroup of one SR [19] reported that QSYQ exhibited superior efficacy compared to control group in terms of overall improvement rate of electrocardiographic indices. However, results of another subgroup within the same SR [19] indicated that there was no significant difference in overall improvement rate of ECG indices between QSYQ and control group. One outcome indicator was assessed as having a moderate-quality grade (6 RCTs [17], OR = 2.74, 95 % CI 1.86 to 4.03, $p < 0.05$, $I^2 = 0$ %), while the remaining four outcome indicators were rated as very low quality (6 RCTs [21], RR = 1.30, 95 % CI 1.18 to 1.43, $p < 0.05$, $I^2 = 0$ %; 2 RCTs [19], RR = 1.31, 95 % CI 1.08 to 1.60, $p < 0.05$, $I^2 = 0$ %; 2 RCTs [19], RR = 1.15, 95 % CI 0.89 to 1.50, $p > 0.05$, $I^2 = 0$ %; 12 RCTs [18], OR = 2.86, 95 % CI 1.67 to 4.88, $p < 0.05$, $I^2 = 61$ %; 2 RCTs [20], OR = 2.879, 95 % CI 1.58 to 5.20, $p < 0.05$, $I^2 = 0$ %).

Left ventricular ejection fraction (LVEF)

Three SRs/Mas [17,19,31] reported that combination of conventional therapy with QSYQ significantly improves LVEF in patients with CHD. Three outcome indicators were very low-quality evidence (6RCTs [19], MD = 5.58, 95 % CI 3.53 to 7.62, $p < 0.05$, $I^2 = 78$ %; 4RCTs [20], WMD = 0.98, 95 % CI 0.58 to 1.38, $p < 0.05$, $I^2 = 68$ %; 5RCTs [17], MD = 6.71, 95 % CI 3.90 to 9.53, $p < 0.05$, $I^2 = 86$ %).

Table 3: Quality of evidence in the included systematic reviews based on GRADE

Author(s), year	Intervention	Outcome	Trials (subject)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality	I^2 (%)
Yang Ye 2014	QSYQ+CM VS CM	Angina pectoris treatment effect	9 (750)	-1[a]	0	0	-1[d]	-1[f]	very low	0
		ECG efficacy	6 (569)	-1[a]	0	0	-1[d]	-1[f]	very low	0
		Incidence of endpoint events	2 (3138)	-1[a]	0	0	0	-1[f]	low	64
Yang Qiaoning 2013	QSYQ+CM VS CM/CM+Placebo	Angina pectoris treatment effect	A 7 (813)	-1[a]	0	0	0	-1[f]	low	0
			B 5 (502)	-1[a]	0	0	0	-1[f]	low	0
		ECG efficacy	A 2 (125)	-1[a]	0	0	-1[e]	-1[f]	very low	0
			B 2 (275)	-1[a]	0	0	-1[e]	-1[f]	very low	0
	QSYQ+Nitroglycerin vs Nitroglycerin	Nitroglycerin stopping reduction rate	4 (408)	-1[a]	0	0	0	-1[f]	low	0
	QSYQ+CM VS CM/CM+Placebo	LVDD	6 (685)	-1[a]	-2[c]	0	0	-1[f]	very low	91
		LVEDV	6(685)	-1[a]	0	0	0	-1[f]	low	22
		LVESV	6 (685)	-1[a]	0	0	0	-1[f]	low	34
		LVEF	6 (685)	-1[a]	-2[c]	0	0	-1[f]	very low	78

Note: CO, Cardiac output; CM, conventional western medicine; ECG, Electrocardiogram; LVEDD: left ventricular end-diastolic dimensions; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; QSYQ, Qishen Yiqi Drop Pill; TCM, Traditional Chinese Medicine. [a]The included study had an unclear risk of selection, performance, detection, and reporting biases. [b]50 ≤ I 2 < 75 %.[c]I^2 ≥ 75. [d]Funnel plot indicated asymmetry. [e]Sample size < 300. [f]There may be publication bias

Table 4: Quality of evidence in the included systematic reviews based on GRADE *(continued)*

Author(s), year	Intervention	Outcome	Trials (subject)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality	I^2 (%)
Li Liping 2013	QSYQ+CM VS CM/CM+Placebo	Angina pectoris treatment effect	12 (1090)	-1[a]	0	0	-1[d]	-1[f]	very low	45
		ECG efficacy	12 (1090)	-1[a]	-1[b]	0	-1[d]	-1[f]	very low	61
Chen Yalu 2019	QSYQ+CM VS CM/CM+Placebo	Angina pectoris treatment effect	12 (1167)	-1[a]	0	0	0	0	moderate	0
		ECG efficacy	2 (280)	-1[a]	0	0	-1[e]	-1[f]	very low	0
		Nitroglycerin stopping reduction rate	2 (159)	-1[a]	0	0	-1[e]	-1[f]	very low	0
		TCM Symptom Treatment	2 (159)	-1[a]	-2[c]	0	-1[e]	-1[f]	very low	82
		LVEF	4 (351)	-1[a]	-1[b]	0	0	-1[f]	very low	68
		CO	3 (233)	-1[a]	-2[c]	0	-1[e]	-1[f]	very low	88
Rong Jie 2015	QSYQ+CM VS CM/CM+Placebo	Angina pectoris treatment effect	7 (650)	-1[a]	0	0	0	0	moderate	0
		ECG efficacy	6 (591)	-1[a]	0	0	0	0	moderate	0
		TCM Symptom Treatment	3 (201)	-1[a]	-1[b]	0	-1[e]	-1[f]	very low	56
		LVEF	5 (432)	-1[a]	-2[c]	0	0	-1[f]	very low	86

Note: CO, Cardiac output; CM, conventional western medicine; ECG, Electrocardiogram; LVEDD: left ventricular end-diastolic dimensions; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; QSYQ, Qishen Yiqi Drop Pill; TCM, Traditional Chinese Medicine. [a]The included study had an unclear risk of selection, performance, detection, and reporting biases. [b]50 ≤ I 2 < 75 %.[c]I^2 ≥ 75. [d]Funnel plot indicated asymmetry. [e]Sample size < 300. [f]There may be publication bias

Nitroglycerin reduction

Two SRs/MAs [19,20] examined nitroglycerin reduction associated with QSYQ in CHD, and the results revealed that QSYQ group exhibited higher rate of nitroglycerin discontinuation compared to control group. One outcome indicator was considered low-quality evidence (4 RCTs [19], RR = 1.12, 95 % CI 1.02 to 1.23, $P < 0.05$, $I^2 = 0$ %), while another outcome indicator was rated as very low-quality evidence (2 RCTs [20], OR = 1.97, 95 % CI 0.76 to 5.09, $P < 0.05$, $I^2 = 0$ %).

Traditional Chinese medicine symptom treatment

Two SRs/Mas [17,20] reported the efficacy of QSYQ in CHD treatment of TCM symptoms and the results revealed that combination of conventional therapy with QSYQ significantly improves TCM symptoms in patients with CHD. Two outcome indicators were both very low-quality evidence (2RCTs [20], OR = 29.48, 95 % CI 0.81 to 1075.20, $P < 0.05$, $I^2 = 82$ %; 3RCTs [17], OR = 4.26, 95 % CI 1.44 to 12.57, $P < 0.05$, $I^2 = 56$ %).

Adverse effects

Two SRs/Mas [20,21] mentioned adverse effects during CHD treatment with QSYQ (Table 5). There were 38 cases of gastric pain, 14 cases of acid reflux, 11 cases of allergy, and 2 cases of bleeding reported in one SR/MA [19]. Also, there were 9 cases of dizziness and light-headedness, 7 cases of flushing, 16 cases of nausea and vomiting, 2 cases of rapid heartbeat, and 2 cases of transient transaminase elevation reported in another study [20]. Differences between QSYQ and control groups were not mentioned. Two SRs/Mas [17,18] mentioned no significant adverse reactions.

DISCUSSION

This review provides a systematic summary of the effectiveness and safety of QSYQ for CHD and represents the first published systematic review on this subject. Five SRs/MAs were included for analysis, and their methodological quality and evidence were evaluated using AMSTAR 2 tool and the GRADE system to offer clinicians higher-quality evidence. The results suggest that combining QSYQ with conventional therapy for CHD may enhance clinical efficacy and pharmacologic safety, although the quality of evidence supporting these conclusions is generally low. According to the AMSTAR 2 results, all five SRs/MAs exhibited very low methodological quality primarily due to incomplete reporting of key items. None of the included SRs/MAs had pre-registered or published study plans, diminishing the credibility and transparency of the studies, and 40 % of them did not provide a comprehensive search strategy despite searching more than two databases. This lack of inclusion of grey literature and failure to search study registries increased the risk of search bias and publication bias. Additionally, none of the five SRs/MAs provided a list of excluded studies and reasons for exclusion during the full-text reading stage, which is crucial for ensuring transparency. A high-quality systematic review should provide such a list to consider exclusion and ensure transparency [22]. Furthermore, 20 % of the SRs/MAs did not adequately investigate publication bias, which undermined the veracity and credibility of the findings. Reporting of non-key items was also deficient: none of the SRs/MAs explained the basis for selecting the study design, making the type of included studies unjustified. Moreover, none of them reported information on grant funding, potentially influencing the results.

Table 5: Details of adverse events among included systematic reviews

Author, year	Adverse events		Number of RCTs reporting AEs
	Intervention	Control	
Yang Ye 2014	NR	NR	9RCTs
Yang Qiaoning 2013	Stomach pain (n=38), Acid reflux (n=14), Allergies (n=11), Hemorrhage (n=2)		25RCTs -Reporting AEs:1
Rong Jie 2015	None	None	11RCTs -No AEs:8 -NR:3
Li Liping 2013	None	None	12RCTs -No AEs:12
Chen Yalu 2019	Transient transaminase elevation (n=2), Dizziness (n=9), flushed face (n=7), Nausea and vomiting (n=16), Accelerated heartbeat (n=2)		13RCTs -NR:7 -No AEs:2 -Reporting AEs:4

AE, adverse event; NR, no reporting

None of the five SRs/MAs disclosed any potential conflict of interest, leaving readers unable to assess whether conflicts of interest might affect the objectivity of the results.

In one study, only one researcher screened the studies and extracted the information, raising concerns about screening omissions and selection bias. Other SRs/MAs did not provide detailed descriptions of included studies, ignoring the impact of heterogeneity on the results. Additionally, 40 % of SRs/MAs failed to adequately explain and discuss the presence of heterogeneity, undermining the credibility of the results. Future relevant studies are advised to consult the AMSTAR 2 checklist to ensure comprehensiveness and scientific validity of each item, thereby enhancing the methodological quality of SRs/MAs. The SRs/MAs suggested that combining conventional therapy with QSYQ may enhance efficacy in treating angina pectoris, electrocardiographic parameters, TCM symptom efficacy, improve LVEF, and decrease nitroglycerin usage. However, these findings lacked robust supporting evidence. Among the five factors contributing to downgrading; limitations, publication bias, and inconsistency were the most prevalent. Clinical researchers are encouraged to focus on refining research design details, while future studies should aim to increase sample sizes and conduct comprehensive and scientific analyses of outcome indicators.

Chinese herbal medicine preparations have multi-component and multi-target characteristics, as well as good therapeutic or adjuvant effects on complex cardiovascular diseases such as CHD [23]. The QSYQ has certain advantages in CHD treatment and a network pharmacological study [24] showed that the important active ingredients in QSYQ are astragaloside, tanshinone IIA, salvia polyphenolic acid, and panaxoside. Tanshinone IIA and Tanshin polyphenolic acid inhibit platelet agglutination and improve the anti-hypoxia ability of cardiac myocytes [26]. Panax ginseng saponin fights against atherosclerosis, anticoagulation, coronary artery dilation and hypoxic damage to vascular endothelial cells, thus protecting cardiomyocytes [27]. He *et al* [28] created a model of myocardial ischemia-reperfusion injury by ligating the left anterior descending branch of the coronary artery in small pigs. Their findings indicated that QSYQ improved myocardial function, reduced the incidence of ventricular fibrillation, and activated the PI3K/AKT signaling pathway, thereby mitigating myocardial injury caused by ischemia-reperfusion and safeguarding myocardial cells. A recent pharmacological study [29] showed that QSYQ prevents ischemia or reperfusion-induced cardiac microvascular hyperpermeability by modulating signaling mechanisms of Src/caveolin-1 and RhoA/ROCK/MLC and attenuating myocardial damage caused by ischemia-reperfusion. Also, a clinical trial [30] demonstrated that QSYQ significantly regulates lipid metabolism and improves myocardial ischemia in elderly patients with stable angina pectoris of CHD, thus relieving stable angina pectoris of CHD. In summary, QSYQ improves symptoms of CHD in a multi-session, multi-pathway, multi-targeted manner.

Limitations

This study presents several limitations. Firstly, our search was limited to published literature in Chinese and English, potentially introducing a language bias since reviews in other languages were not considered. Secondly, QSYQ, being a Chinese herbal medicine unique to China, was the focus of our analysis. Consequently, all included studies were conducted in China with Chinese CHD patients, thereby limiting the generalizability of our findings to other populations. Lastly, none of the selected studies included lipid levels as an outcome indicator, which may have influenced the accuracy of the results to some extent.

CONCLUSION

The review shows that QSYQ in combination with conventional therapy improves clinical efficacy compared to conventional therapy alone with comparable safety. Future high-quality clinical trials and standardized study methods are needed to further investigate the safety of QSYQ. Relevant systematic evaluations should also be conducted under the guidance of international unified standards such as AMSTAR 2 and GRADE to provide a higher level of evidence to support QSYQ for CHD treatment.

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Ethical approval

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Weiqing Yu and Lili Jin conceptualized this research. Jingwen Yan, Chaorong Zhang, Xiaohui Chen and Jiaqi Yan, conducted this overview. Jingwen Yan and Chaorong Zhang drafted the original manuscript and Wanwen Zhu and Lili Jin revised this manuscript.

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