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Effectiveness and safety of Hwangryunhaedok-Tang (Huang-Lian-Jie-Du-Tang, Oren-Gedoku-to) for dyslipidemia

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Recent experimental and clinical studies have suggested that Hwangryunhaedok-tang (HHT), an herbal formula, could improve the lipid profiles in patients with dyslipidemia. This systematic review aimed to evaluate the effectiveness and safety of HHT monotherapy or adjunctive HHT therapy with conventional lipid-lowering drugs in managing dyslipidemia.

Methods: Twelve English, Korean, Chinese, and Japanese databases were comprehensively searched from their inception to January 2020. Randomized controlled trials (RCTs) using HHT monotherapy or adjunctive HHT therapy for dyslipidemic patients were included. The primary outcome was the low-density lipoprotein cholesterol (LDL-C) level. Descriptive analyses of participant details, interventions, and outcomes were conducted and where appropriate data were available, a meta-analysis was performed and presented as a risk ratio (RR) or mean difference (MD) with 95% confidence intervals (CIs). The risk of bias was assessed using the Cochrane risk of bias tool and the quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: Nine RCTs with 536 participants were included. In comparison with lipid-lowering drugs alone, HHT as an adjunctive therapy to lipid-lowering drugs or as a monotherapy showed significantly superior (MD -1.15 mmol/L, 95% CI -1.25 to -1.05) or inferior results (MD 0.23 mmol/L, 95% CI 0.09 to 0.38), respectively, for LDL-C levels. The incidence of adverse events was significantly lower when HHT was used in addition to lipid-lowering drugs, in comparison to that with lipid-lowering drugs alone. No serious adverse events were reported in the HHT group. Most included studies showed a high risk of performance bias and the quality of evidence was rated generally "low" because of the high risk of bias and inconsistency or imprecision of the meta-analysis results.

Conclusion: Current evidence suggests that HHT may be beneficial for patients with dyslipidemia and may reduce the adverse events associated with lipid-lowering drugs. However, due to the high risk of bias of the included studies and low quality of evidence for the main findings, no definitive conclusion could be reached. Further rigorous, high-quality, and placebo-controlled RCTs should be conducted to assess the efficacy of HHT.

Trial registration number: PROSPERO CRD42020164563

Abbreviations: ALT = alanine aminotransferase, AMED = the Allied and Complementary Medicine Database, CENTRAL = the Cochrane Central Register of Controlled Trials, CINAHL = the Cumulative Index to Nursing and Allied Health Literature, CIs = confidence intervals, CNKI = China National Knowledge Infrastructure, CRP = C-reactive protein, EATM = East Asian Traditional Medicine, GRADE = grading of recommendations assessment, development, and evaluation, HDL-C = high-density lipoprotein cholesterol, HHT = Hwangryunhaedok-tang, HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A, IL = interleukin, KISS = Koreanstudies Information Service System, KMbase = Korean Medical Database, LDL-C = low-density lipoprotein cholesterol, MD = mean difference, OASIS = Oriental Medicine Advanced Searching Integrated System, PWV = pulse wave velocity, RCTs =

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randomized controlled trials, RR = risk ratio, TC = total cholesterol, TCM = traditional Chinese medicine, TER = total effective rate, TG = triglyceride, TNF-α = tumor necrosis factor-alpha.

Keywords: dyslipidemia, herbal medicine, hwangryunhaedok-tang (Huang-lian-jie-du-tang, Korean traditional medicine, Oren-gedoku-to), systematic review

1. Introduction

Dyslipidemia is characterized by elevation of low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), or total cholesterol (TC) levels or a decline in high-density lipoprotein cholesterol (HDL-C) levels. The prevalence of dyslipidemia is reported to range from 30% to 60% worldwide, and it has been increasing consistently.[1–3] Dyslipidemia itself usually causes no symptoms but is known to be an independent and prominent risk factor for cardiovascular disease. In particular, reducing LDL-C levels can prevent atherosclerosis and reduce the mortality rate due to cardiovascular disease.[4] The primary treatment for dyslipidemia is therapeutic lifestyle modification, which includes diet therapy, exercise, and smoking cessation, while pharmacotherapy can be initiated on the basis of cardiovascular disease risk and LDL-C levels.[5] Although statins are the first-line pharmacotherapeutic agents for the management of high LDL-C levels,[6] they are known to cause various adverse reactions, including muscular abnormalities, diabetes mellitus, transaminase and creatinine elevation, and neurological symptoms, especially with long-term use.[7–9] Therefore, development of hypolipidemic agents from natural sources that can treat dyslipidemia with a good long-term safety profile is a topic of increasing interest.[9]

Herbal remedies constitute a form of complementary, integrative medicine that has been used for thousands of years to treat various diseases in East Asia. For example, Hwangryunhaedok-tang (HHT; Huang-lian-jie-du-tang in Chinese, Oren-gedoku-to in Japanese) is an herbal prescription consisting of *Coptidis rhizoma*, *Phellodendri cortex*, *Scutellariae radix*, and *Gardeniae fructus* that clear heat, dry dampness, purge fire, and detoxify according to the East Asian Traditional Medicine (EATM) theory. Dyslipidemia is regarded as a form of phlegm-dampness and blood stasis, and treatment methods such as "dispel phlegm and eliminate dampness", "activate blood and resolve stasis", and "clear heat and purge fire" have been used for this condition.[9,10] Therefore, HHT can treat dyslipidemia according to the EATM theory. In fact, HHT has been widely used for the treatment of cardiovascular and cerebrovascular diseases such as hypertension and dyslipidemia, prevention of stroke recurrence, and improvement of cerebral blood flow.[11,12]

Experimental studies have shown that HHT can reduce LDL-C and TC levels in dyslipidemic animal models by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase.[13] One experimental study also showed that HHT significantly prevented the progression of thoracic aortic plaques through its antioxidant effects after HHT administration for 8 weeks in high cholesterol animal models.[14] In addition, many published clinical studies have shown that HHT can treat dyslipidemia by improving lipid levels without causing serious adverse events.[15,16] However, none of these studies systematically analyzed the relevant randomized controlled trials (RCTs) and evaluated the evidence level to assist in clinical decision-making. Therefore, the objective of this review was to analyze the effectiveness and safety of HHT monotherapy or adjunctive therapy in patients with dyslipidemia, and to assess the methodological quality of the included studies by performing a systematic review to help clinicians establish evidence-based treatment strategies.

2. Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17] Ethical approval was not necessary because individual patient data were not used in this systematic review, and there were no concerns regarding privacy.

2.1. Data sources and search strategy

One researcher (BL) performed comprehensive searches of the following 12 English, Korean, Chinese, and Japanese databases on January 6, 2020: Medline (via PubMed), EMBASE (via Elsevier), the Cochrane Central Register of Controlled Trials (CENTRAL), the Allied and Complementary Medicine Database (AMED; via EBSCO), the Cumulative Index to Nursing and Allied Health Literature (CINAHL; via EBSCO), Oriental Medicine Advanced Searching Integrated System (OASIS), Korean studies Information Service System (KISS), Korean Medical Database (KMbase), China National Knowledge Infrastructure (CNKI), Wanfang data, VIP, and CiNii. All studies published by the search date were considered.

The reference lists of relevant articles were reviewed and a manual search on Google Scholar was performed to identify additional eligible reports. We also included grey literature, such as degree theses and conference proceedings. No language, publication date, or publication status restrictions were imposed. The following search terms were used in Medline: (Dyslipidemias [MH] OR Dyslipidemias [MH] OR Dyslipidemia [TIAB] OR Dyslipidemia [TIAB] OR Lipemia [TIAB] OR Hypercholesterolemia [TIAB] OR Hypertriglyceridemia [TIAB] OR Hyperlipoproteinemia [TIAB] OR Dyslipoproteinemia [TIAB] OR "lipoprotein disorder" [TIAB]) AND (Hwangryunhaedok-tang [TIAB] OR Hwanglyeonhaedok-tang [TIAB] OR "Huanglian jiedu tang" [TIAB] OR Huanglianjiedu-tang [TIAB] OR Orengedoku-to [TIAB] OR "Oren gedoku to" [TIAB]). The search terms of all databases were described in Supplementary Digital Content 1, http://links.lww.com/MD/F262.

2.2. Inclusion criteria

2.2.1. Types of studies. Only RCTs were included. We also included studies using the expression "randomization" without descriptions of randomization methods. Other designs such as in vivo, in vitro, case reports, retrospective studies, and quasi-RCTs using a quasi-random method for allocation of treatment (i.e., trials using alternate allocation or allocation by birth date) were excluded.

2.2.2. Types of participants. We included studies on adult participants with dyslipidemia, who were 18 years of age and older. Dyslipidemia is defined as high LDL-C, high TC, high TG,

or low HDL-C. There was no restriction on sex, race, or comorbidity. Studies were excluded if the participants had other serious medical conditions such as cancer, liver disease, or kidney disease.

2.2.3. Types of interventions. Studies using HHT as the primary treatment intervention were included. Since herbal medicines are also administered in the form of "modified herbal medicines," in which some modifications are made to the drug composition to achieve increased efficacy,[18–20] we also included studies using modified HHT, which was defined in this review as a herbal medicine designated as "modified HHT" and showing more than 50% similarity with the original composition of HHT. We included studies using only oral administration of HHT. Control interventions included placebo, no treatment, and active controls such as lipid-lowering drugs and other herbal medicines. Studies involving HHT combined with other therapies as treatment interventions were also included if the other therapies were equally used in both the treatment and control groups. There was no restriction related to the duration of treatment.

2.2.4. Types of outcome measures. The primary outcome measure was the post-treatment serum LDL-C level, which is the main outcome indicator of dyslipidemia. The secondary outcome measures included (1) other blood lipid parameters such as post-treatment TC, HDL-C, and TG levels, (2) the incidence of adverse events during the treatment period, and (3) total effective rate (TER), an outcome measure that is processed secondarily according to certain evaluation criteria, such as clinical symptom improvement or improvement rates in other quantified outcomes.

2.3. Study selection

After removing duplicates, two researchers (BL and CYK) independently screened the titles and abstracts of all searched studies from the databases and additional sources for first inclusion using EndNote X8 and then evaluated the full texts of the eligible studies for final inclusion. Any disagreement was resolved through discussion between the researchers.

2.4. Data extraction

One researcher (CYK) performed data extraction from all included studies using a standardized data collection form (Excel 2016, Microsoft, Redmond, WA), and another researcher (BL) cross-checked the extracted data. Discrepancies were resolved through discussions between the researchers. The extracted information included study characteristics (author, publication year, country, and study design); approval from institutional review boards; informed consent; sample size and the number of dropouts; details about the participants, interventions, and comparisons; duration of the intervention and follow-up; outcome measures; results; and adverse events. Specifically, we extracted data regarding the components, dosage forms, and administration durations of HHT and requested missing or insufficient data from the corresponding authors of the included studies.

2.5. Quality assessment

One researcher (CYK) assessed the risk of bias of all included studies and the quality of evidence for the main findings, and another researcher (BL) cross-checked the assessments. Discrepancies were resolved through discussions between the two researchers. The methodological quality of the included studies was evaluated using the Cochrane Collaboration's risk of bias tool. The following domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, completeness of outcome data, selective reporting, and other potential biases. In particular, we assessed other potential bias domains with an emphasis on possible baseline imbalances of treatment and control groups, such as mean participant age or baseline lipid level. We categorized each domain into one of 3 groups: "low risk," "unclear," or "high risk."

The quality of evidence for the major findings was assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[21] using the online program GRADEpro (https://gradepro.org/). The risk of bias, inconsistency, indirectness, and imprecision of the results, and the probability of publication bias were evaluated as "very low," "low," "moderate," or "high."

2.6. Data synthesis and analysis

Qualitative analyses of the details regarding the participants, interventions, comparators, and outcomes for all included studies were conducted. When at least two studies used the same type of intervention and comparator, with the outcome measure being our primary or secondary outcome measure, we performed meta-analysis using Review Manager software, version 5.3 (Cochrane, London, UK). We pooled continuous outcomes using mean differences (MDs) with 95% confidence intervals (CIs) and binary outcomes using a risk ratio (RR) with 95% CIs. Heterogeneity between the studies included in each meta-analysis was assessed using both the χ^2 test and the I^2 statistic. We considered I^2 values $\geq$ 50% and $\geq$75% indicative of substantial and considerable heterogeneity and used a random-effects model if the included studies had significant heterogeneity (I^2 value $\geq$ 50%). In contrast, we used a fixed-effect model when the heterogeneity was not significant or the number of studies included in the meta-analysis was very small, since estimates of between-study variance would show poor precision in such cases.[22,23] Subgroup analysis was performed to explain significant heterogeneity depending on whether participants were recruited according to specific identification patterns in the included study. In addition, we performed sensitivity analyses to identify the robustness of the meta-analysis results by excluding (1) studies with high risks of bias and (2) outliers that were numerically distant from the rest of the data. Two researchers (BL and CYK) independently conducted data synthesis and analysis, and disagreements between them were resolved by discussions. If there were enough studies, we assessed the possibility of publication bias using a funnel plot.

3. Results

3.1. Study selection

Of the 95 citations searched, 53 remained after excluding duplicates. The titles and abstracts of the 53 articles were screened, and 40 were excluded. By carefully reviewing the remaining 13 full-texts, one study that used duplicated data, one review article, and two non-RCTs were excluded. Finally, 9 RCTs[24–32] in seven studies including 536 participants were included in this review. Among these, six studies (eight RCTs)[24–26,28–32] including 476 participants were included in the meta-analysis. Three studies by

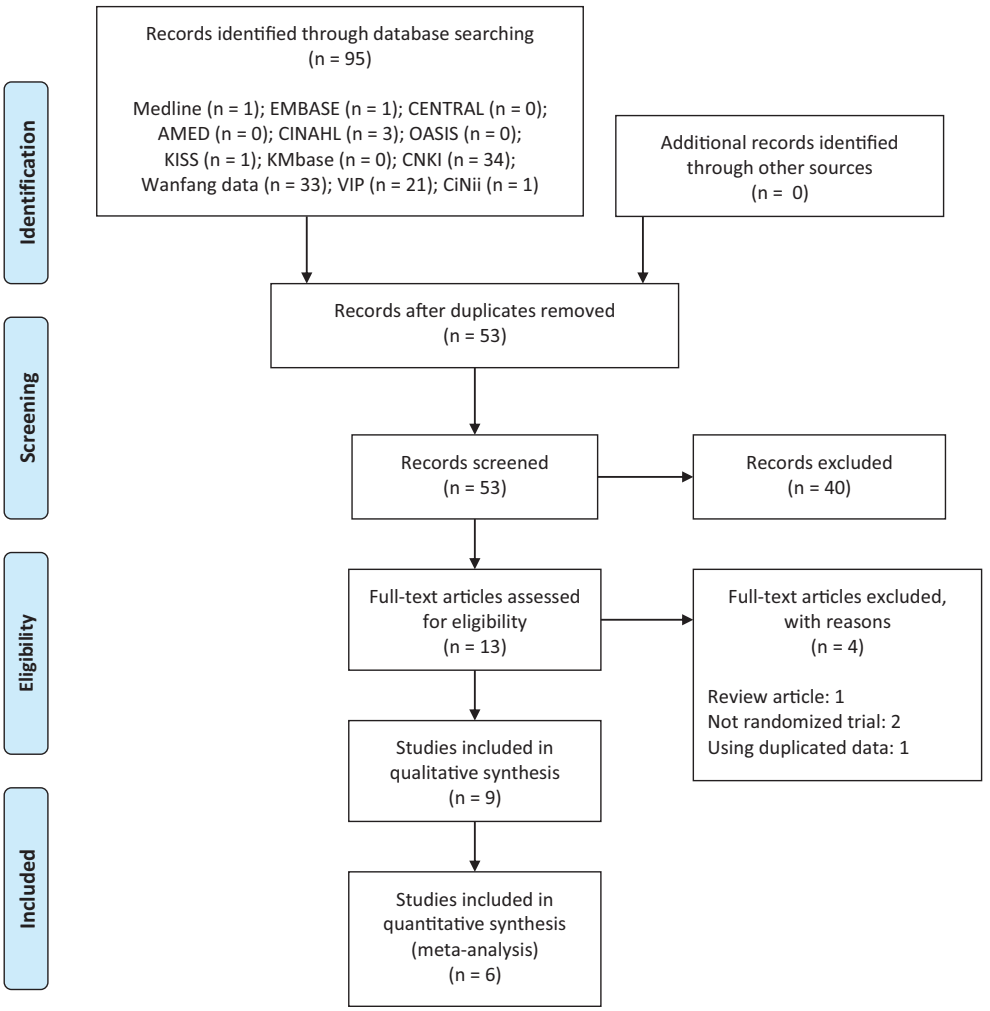

Figure 1. A PRISMA flow diagram of the literature screening and selection process. AMED = Allied and Complementary Medicine Database, CENTRAL = Cochrane Central Register of Controlled Trials, CINAHL = Cumulative Index to Nursing and Allied Health Literature, CNKI = China National Knowledge Infrastructure, KISS = Koreanstudies Information Service System, KMbase = Korean Medical Database, OASIS = Oriental Medicine Advanced Searching Integrated System.

Xue et al[29,30,31] were same studies with only differences in the reported outcomes. Therefore, these 3 articles[29–31] were considered as 1 study (Fig. 1).

3.2. Characteristics of studies

All studies were conducted in China. Two articles[27,28] were theses and 7[24–26,29–32] were journal articles. Ouyang et al[24] and Huang[28] included dyslipidemia participants with hypertension and/or diabetes. Xue et al[29–31] and Bai[32] included dyslipidemia participants with hypertension. Yang et al[26] included participants with arterial disease due to dyslipidemia. Four studies[24,27,28,32] recruited participants according to specific identification patterns: 3[24,28,32] evaluated dampness-heat and the fourth[27] assessed phlegm turbidity. Two studies[24,28] compared HHT and lipid-lowering drugs, while four studies (six RCTs)[25,26,29–32] compared HHT combined with lipid-lowering drugs and lipid-lowering drugs alone. One study[27] compared HHT and the herbal medicine product Xue Zhi Kang capsules, another herbal medicine well-known for its therapeutic effect on lipid profiles. There were no placebo-controlled trials. All studies used an HHT decoction. Two studies used modified HHT,[27,28] in which 2 of the basic components of HHT, the herbs *Phellodendri cortex* and *Gardeniae fructus*, were excluded. In addition, the herbs *Alismatis rhizoma*, *Typhae pollen*, *Poria sclerotium*, and *Polygoni multiflori radix* were added in one study[27] and the herbs *Alismatis rhizoma*, *Poria sclerotium*, and *Astragali radix* were added in in the other study.[28] The main family of pharmaceutical agents used to lower lipid profiles was the statins, including simvastatin,[24] atorvastatin,[25,28] and rosuvastatin.[29–32] Yang et al.[26] did not describe details regarding the lipid regulator. The duration of treatment in the included studies was usually similar, ranging from 1 to 2 months. All included studies reported the lipid profiles as their outcomes, including the levels of LDL-C, TC, TG, and/or HDL-C. Three studies[27–29] reported TER, of which two[27,28] calculated the TER on the basis of the traditional Chinese medicine (TCM) syndrome score and one[29] calculated it on the basis of blood lipid levels. Six RCTs[27–32] reported they had received consent from the participants, but no study reported approval by an institutional review board (Table 1).

Table 1

Characteristics of included studies.

Study ID	Sample size (included →analyzed)	Mean age (range) (years)	Population	Pattern identification#	(A) Treatment group	(B) Control group	Duration of treatment / F/U	Outcome measures	Results
Ouyang 2015	80(50:30) →80(50:30)	(A) 55.10±10.88 (NR) (B) 57.23±10.22 (NR)	Dyslipidemia with hypertension or diabetes	triple energizers fire toxin, dampness-heat, excess heat	1. HHT 2. usual care	1. Simvastatin 20 mg hs 2. usual care	4 wks / NR	1. LDL-C (mmol/L) 2. TC (mmol/L) 3. TG (mmol/L) 4. HDL-C (mmol/L) 5. fasting blood glucose (mmol/L) 6. uric acid (umol/L) 7. BUN (mmol/L) 8. creatinine (umol/L) 9. ALT (U/L)	1. N.S 2. N.S 3. N.S 4. N.S 5. (A)<(B)* 6. N.S 7. N.S 8. N.S 9. N.S
Xiao 2015	68(34:34) →68(34:34)	(A) 54.69±9.87 (37–72) (B) 55.15±8.76 (35–74)	Dyslipidemia	NA	HHT + (B)	Atorvastatin 10 mg qd	8 wks / NR	1. LDL-C (mmol/L) 1. TC (mmol/L) 2. TG (mmol/L) 4. HDL-C (mmol/L) 5. hs-CRP (mg/L) 6. TNF-α (ng/ml) 7. IL-6 (pg/ml)	1. N.S 2. (A)<(B)* 3. N.S 4. N.S 5. (A)<(B)* 6. N.S 7. N.S
Yang 2016	60(30:30) →60(30:30)	(A) 59.5±8.1 (35–75) (B) 59.4±8.2 (36–75)	Arterial disease due to dyslipidemia	NA	HHT + (B)	Conventional medication mainly for adjusting blood lipids and thrombolytic anticoagulation (the details were not reported)	4 wks / NR	1. LDL-C (mmol/L) 2. TC (mmol/L) 3. TG (mmol/L) 4. lipoprotein(a) (mmol/L) 5. femoral-ankle PWV (cm/s) 6. carotid-brachial PWV (cm/s) 7. carotid-femoral PWV (cm/s) 8. pressure-strain elastic modulus (kPa) 9. stiffness parameter (β) 10. distensibility coefficient (10^{-3}/kPa) 11. compliance coefficient (10^{-7}/kPa)	1. (A)<(B)* 2. (A)<(B)* 3. (A)<(B)* 4. (A)<(B)* 5. (A)<(B)* 6. (A)<(B)* 7. (A)<(B)* 8. (A)<(B)* 9. (A)<(B)* 10. (A)>(B)* 11. (A)>(B)*
Chai 2017	60(30:30) →60(30:30)	(A) 63.00±8.28 (47–75) (B) 66.97±5.87 (51–75)	Dyslipidemia	phlegm turbidity	HHT	Xue zhi kang capsule 0.6 g	12 wks / NR	1. LDL-C (mmol/L) 2. TC (mmol/L) 3. TG (mmol/L) 4. HDL-C (mmol/L) 5. CRP (mmol/L) 6. TCM syndrome score 7. TER (TCM syndrome score)	1. (A)<(B)* 2. (A)<(B)* 3. (A)<(B)* 4. (A)<(B)* 5. (A)<(B)* 6. (A)<(B)* 7. (A)>(B)*
Huang 2017	60(30:30) →60(30:30)	(A) 59.57±9.04 (45–75) (B) 57.43±8.24 (45–72)	Dyslipidemia with hypertension or diabetes	dampness-heat	1. HHT 2. Lifestyle modification	1. Atorvastatin calcium 10 mg hs 2. Lifestyle modification	8 wks / NR	1. LDL-C (mmol/L) 2. TC (mmol/L) 3. TG (mmol/L) 4. HDL-C (mmol/L) 5. CRP (mg/L) 6. TCM syndrome score 7. TER (TCM syndrome score)	1. N.S 2. N.S 3. N.S 4. N.S 5. (A)<(B)* 6. (A)<(B)* 7. (A)>(B)*
Xue 2018a	90(45:45) →90(45:45)	(A) 51.00±7.25 (51–77) (B) 62.14±5.56 (48–75)	Dyslipidemia with essential hypertension	NA	HHT + (B)	1. Rosuvastatin 10 mg qd 2. usual care	8 wks / NR	1. LDL-C (mmol/L) 2. TC (mmol/L) 3. TG (mmol/L) 4. HDL-C (mmol/L) 5. TER (blood lipid) 6. TER (BP) 7. SBP (mmHg) 8. DBP (mmHg)	1. (A)<(B)* 2. (A)<(B)* 3. (A)<(B)* 4. (A)>(B)* 5. (A)>(B)* 6. (A)>(B)* 7. (A)<(B)* 8. (A)<(B)*

(*continued*)

Table 1

(continued).

Study ID	Sample size (included →analyzed)	Mean age (range) (years)	Population	Pattern identification#	(A) Treatment group	(B) Control group	Duration of treatment / F/U	Outcome measures	Results
								9. pulse pressure (mmHg) 10. low-cut whole blood viscosity (mPa) 11. high-cut whole blood viscosity (mPa) 12. plasma viscosity (mPa) 13. number of plaques (n) 14. plaque of area (mm^2) 15. intima-media thickness (mm) 16. brachial-ankle PWV (cm/s) 17. ABI	9. (A)<(B)* 10. (A)<(B)* 11. (A)<(B)* 12. (A)<(B)* 13. (A)<(B)* 14. (A)<(B)* 15. (A)<(B)* 16. (A)<(B)* 17. (A)<(B)*
Xue 2018b	90(45:45) →90(45:45)	(A) 51.00 ± 7.25 (51–77) (B) 62.14 ± 5.56 (48–75)	Dyslipidemia with essential hypertension	NA	HHT + (B)	1. Rosuvastatin 10 mg qd 2. usual care	8 wks / NR	1. IL-6 (ng/L) 2. IL-10 (pg/L) 3. TNF-α (ng/L) 4. hs-CRP (mg/L) 5. MCP-1 (ng/L) 6. ICAM-1 (ng/L) 7. BUN (ng/ml) 8. adiponectin (ng/ml) 9. vaspin (ng/L) 10. PMBC NF-κB mRNA expression 11. PMBC NF-κB protein expression	1. (A)<(B)* 2. (A)>(B)* 3. (A)<(B)* 4. (A)<(B)* 5. (A)<(B)* 6. (A)<(B)* 7. (A)<(B)* 8. (A)>(B)* 9. (A)>(B)* 10. (A)<(B)* 11. (A)<(B)*
Xue 2018c	90(45:45) →90(45:45)	(A) 51.00 ± 7.25 (51–77) (B) 62.14 ± 5.56 (48–75)	Dyslipidemia with essential hypertension	NA	HHT + (B)	1. Rosuvastatin 10 mg qd 2. usual care	8 wks / NR	1. MDA (nmol/L) 2. SOD (ng/ml) 3. GSH-Px (U/L) 4. AOPP (umol/ml) 5. TAOP (U/L) 6. vWF (%) 7. NO (umol/L) 8. ET-1 (pg/L) 9. TXB2 (ng/L) 10. 6-Keto-PGF-1a (ng/L) 11. CD62p (%) 12. CD63 (%) 13. FWD (%) 14. NMD (%)	1. (A)<(B)* 2. (A)>(B)* 3. (A)>(B)* 4. (A)<(B)* 5. (A)>(B)* 6. (A)<(B)* 7. (A)>(B)* 8. (A)<(B)* 9. (A)<(B)* 10. (A)>(B)* 11. (A)<(B)* 12. (A)<(B)* 13. (A)>(B)* 14. (A)>(B)*
Bai 2019	118(59:59) →118(59:59)	(A) 71.22 ± 8.63 (54–85) (B) 72.82 ± 9.05 (55–87)	Dyslipidemia with hypertension	dampness-heat	HHT + (B)	1. Rosuvastatin 10–40 mg qd 2. ultrasound therapy, 20–40 min/day, daily 3. usual care	2 mon / NR	1. TC (mmol/L) 2. TG (mmol/L) 3. TER (BP) 4. SBP (mmHg) 5. DBP (mmHg)	1. (A)<(B)* 2. (A)<(B)* 3. (A)>(B)* 4. (A)<(B)* 5. (A)<(B)*

an approach of some East Asian traditional medicines, including TCM, which enables individual treatment by categorizing the signs and symptoms of patients into a series of syndrome concepts.

'*' means significant differences between two groups, $P < .05$. 'N.S' means no significant difference between two groups, $p > 0.05$.

ABI = ankle-brachial index, ALT = alanine aminotransferase, AOPP = advanced oxidation protein products, BP = blood pressure, BUN = blood urea nitrogen, CRP = C reactive protein, DBP = diastolic blood pressure, ET-1 = endothelin 1, FMD = flow-mediated diastolic function, GSH-Px = Glutathione peroxidase, HDL-C = high density lipoprotein cholesterol, HHT = Hwangryunhaedok-tang, hs-CRP = high-sensitivity C reactive protein, ICAM = intercellular adhesion molecule, IL = interleukin, LDL-C = low density lipoprotein cholesterol, MCP = monocyte chemoattractant protein, MDA = malondialdehyde, NA = not applicable, NF-κB = nuclear factor kappa B, NMD = nitroglycerin-mediated diastolic function, NO = nitric oxide, NR = not reported, PMBC = peripheral blood mononuclear cell, PWV = pulse wave velocity, SBP = systolic blood pressure, SOD = superoxide dismutase, TAOP = total antioxidant power, TC = total cholesterol, TCM = traditional Chinese medicine, TER = total effective rate, TG = triglyceride, TNF-α = tumor necrosis factor-α, TXB2 = thromboxane B2, vWF = von Willebrand factor.

3.3. Risk of bias assessment

Except for one study[27] that used simple randomization and two[28,32] that used a random number table, the remaining studies did not mention the method used for random sequence generation. None of the studies reported the method used for allocation concealment. With the exception of 2 articles[27,28] that described single-blinding, the rest did not describe the blinding of participants and personnel. However, the risk of performance bias was rated high in all studies, given the nature of the interventions used. None of the studies reported blinding for outcome assessment; therefore, the risk of bias was rated unclear. The included studies reported no withdrawal or drop-out cases. Since all studies reported blood lipid profiles as the outcome of interest, the risk of bias for selective reporting was rated low. Moreover, because all studies described demographic and clinical homogeneity at baseline between treatment and control groups, the other sources of bias categories were rated low (Fig. 2).

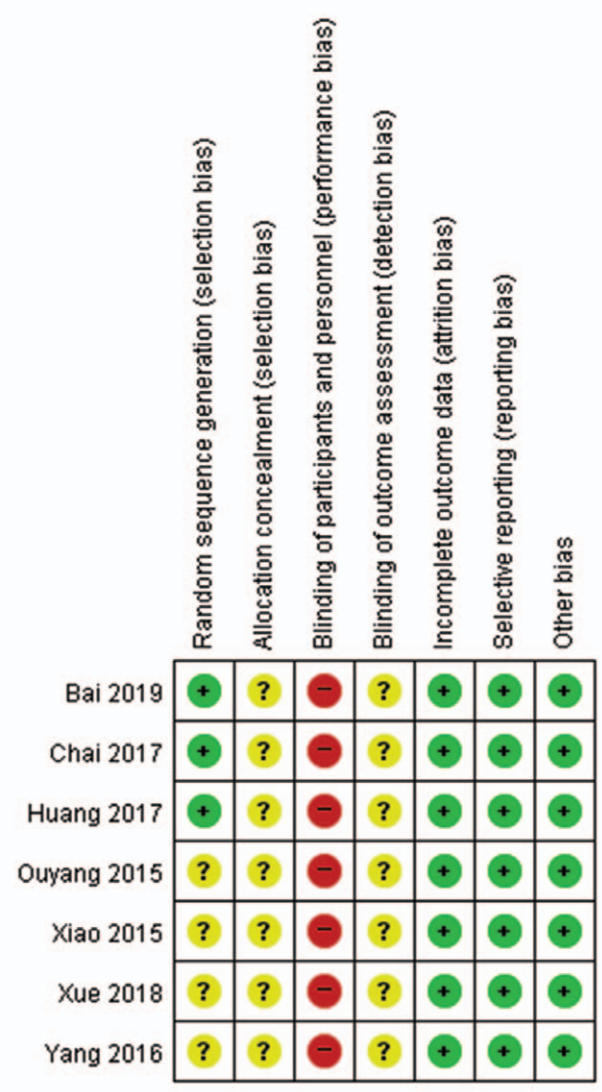

Figure 2. Risk of bias summary for all included studies. Low, unclear, and high risk, respectively, are represented with the following symbols: "+", "?", and "−".

3.4. Effectiveness

Two studies[24,28] comparing HHT and lipid-lowering drugs and 4[25,26,29,32] studies comparing HHT in combination with lipid-lowering drugs and lipid-lowering drugs alone were included in the meta-analysis.

3.4.1. HHT combined with lipid-lowering drugs vs lipid-lowering drugs alone. In comparison with lipid-lowering drugs alone, the combination of HHT with lipid-lowering drugs was associated with significantly lower levels of LDL-C (3 studies,[25,26,29] n = 218; MD, −1.15 mmol/L, 95% CI, -1.25 to -1.05; $I^2 = 90\%$), TC (4 studies,[25,26,29,32] n = 336; MD, −1.32 mmol/L, 95% CI, -1.43 to -1.21; $I^2 = 84\%$), and TG (4 studies,[25,26,29,32], n = 336; MD -0.48 mmol/L, 95% CI -0.53 to -0.43; $I^2 = 98\%$), and with significantly higher levels of HDL-C (2 studies[25,29], n = 158; MD 0.43 mmol/L, 95% CI 0.33 to 0.52; $I^2 = 95\%$). In order to interpret the significant heterogeneity, subgroup analysis was performed depending on whether pattern identification, which is a patient classification system in TCM, was used. As a result, the I^2 value reflecting heterogeneity in TC decreased from 84% to 36% and the I^2 value in TG decreased from 98% to 95% without affecting the effect size in favor of the HHT group. TER based on post-treatment blood lipid profiles was significantly higher in the group that received HHT plus lipid-lowering drugs than in the group that received only lipid-lowering drugs (1 study,[29] n = 90; RR 1.19, 95% CI 1.02 to 1.40) (Table 2).

3.4.2. HHT versus lipid-lowering drugs. In comparison with treatment with lipid-lowering drugs, HHT monotherapy was associated with significantly higher levels of LDL-C (2 studies,[24,28] n = 140; MD, 0.23 mmol/L, 95% CI,0.09 to 0.38; $I^2 = 45\%$) and TC (2 studies,[24,28] n = 140; MD, 0.46 mmol/L, 95% CI, 0.31 to 0.62; $I^2 = 85\%$), while there were no significant differences between the two groups in the levels of TG (2 studies,[24,28] n = 140; MD, 0.11 mmol/L, 95% CI, -0.05 to 0.26; $I^2 = 0\%$) and HDL-C (2 studies,[24,28] n = 140; MD, 0.05 mmol/L, 95% CI,-0.08 to 0.19; $I^2 = 32\%$). TER based on the TCM syndrome score was significantly higher in the HHT group than that in the lipid-lowering drugs only group (1 study,[28] n = 60; RR 1.59, 95% CI, 1.14 to 2.22) (Table 2).

3.4.3. Other results. In one study,[27] HHT and Xue Zhi Kang capsules were compared. HHT was associated with significantly lower levels of LDL-C, TC, TG, and HDL-C (all, $P < .05$). Interestingly, in the study by Ouyang et al[24] that included dyslipidemia participants with hypertension and/or diabetes, fasting blood glucose levels were significantly lower in the HHT group than lipid-lowering drugs group after 4 weeks of treatment ($P < .05$). Moreover, in the study by Yang et al,[26] which includes participants with arterial disease due to dyslipidemia, several parameters related to vascular stiffness (femoral-ankle pulse wave velocity [PWV], carotid-brachial PWV, carotid-femoral PWV, pressure-strain elastic modulus, stiffness parameter [β], distensibility coefficient, and compliance coefficients) were significantly improved in the HHT combined with lipid-lowering drugs group than in the lipid-lowering drugs only group after 4 weeks of treatment (all, $P < .05$). In the studies by Xue et al[29] and Bai,[32] which included dyslipidemic participants with hypertension, HHT combined with lipid-lowering drugs was associated with significantly lower systolic and diastolic blood pressure when compared with the lipid-lowering drugs only group, after 8 weeks or 2 months of treatment (all, $P < .05$).

Table 2

Summary of findings.

Outcomes		No. participants (RCTs)	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	I^2 value	Quality of evidence (GRADE)	Comments
			Risk with control group	Risk with HHT group				
HHT combined with lipid-lowering drugs *versus* lipid-lowering drugs alone								
LDL-C (mmol/L)	Total (No pattern identification)	218 (3)	-	MD 1.15 lower (1.25 to 1.05 lower)	-	90%	⊕◯◯◯ VERY LOW	Risk of bias (-1) Inconsistency (-2)
TC (mmol/L)	Total	336 (4)	-	MD 1.32 lower (1.43 to 1.21 lower)	-	84%	⊕◯◯◯ VERY LOW	Risk of bias (-1) Inconsistency (-2)
	Pattern identification	118 (1)	-	MD 0.92 lower (1.15 to 0.69 lower)	-	Not applicable	⊕⊕⊕◯ MODERATE	Risk of bias (-1)
	No pattern identification	218 (3)	-	MD 1.45 lower (1.57 to 1.32 lower)	-	36%	⊕⊕⊕◯ MODERATE	Risk of bias (-1)
TG (mmol/L)	Total	336 (4)	-	MD 0.48 lower (0.53 to 0.43 lower)	-	98%	⊕◯◯◯ VERY LOW	Risk of bias (-1) Inconsistency (-2)
	Pattern identification	118 (1)	-	MD 0.12 lower (0.2 to 0.04 lower)	-	Not applicable	⊕⊕⊕◯ MODERATE	Risk of bias (-1)
	No pattern identification	218 (3)	-	MD 0.69 lower (0.75 to 0.63 lower)	-	95%	⊕◯◯◯ VERY LOW	Risk of bias (-1) Inconsistency (-2)
HDL-C (mmol/L)	Total (No pattern identification)	158 (2)	-	MD 0.43 higher (0.33 to 0.52 higher)	-	95%	⊕◯◯◯ VERY LOW	Risk of bias (-1) Inconsistency (-2)
TER (blood lipid)	Total (No pattern identification)	90 (1)	800 per 1,000	952 per 1,000 (816 to 1,000)	RR 1.29 (1.20 to 1.40)	Not applicable	⊕◯◯◯ VERY LOW	Risk of bias (-1) Indirectness (-1) Imprecision (-1)
Adverse event	Total (No pattern identification)	90 (1)	267 per 1,000	67 per 1,000 (21 to 221)	RR 0.25 (0.08 to 0.83)	Not applicable	⊕⊕◯◯ LOW	Risk of bias (-1) Imprecision (-1)
HHT vs lipid-lowering drugs								
LDL-C (mmol/L)	Total (Pattern identification)	140 (2)	-	MD 0.23 higher (0.09 to 0.38 higher)	-	45%	⊕⊕⊕◯ MODERATE	Risk of bias (-1)
TC (mmol/L)	Total (Pattern identification)	140 (2)	-	MD 0.46 higher (0.31 to 0.62 higher)	-	85%	⊕◯◯◯ VERY LOW	Risk of bias (-1) Inconsistency (-2)
TG (mmol/L)	Total (Pattern identification)	140 (2)	-	MD 0.11 higher (0.05 lower to 0.26 higher)	-	0%	⊕⊕◯◯ LOW	Risk of bias (-1) Imprecision (-1)
HDL-C (mmol/L)	Total (Pattern identification)	140 (2)	-	MD 0.05 higher (0.08 lower to 0.19 higher)	-	32%	⊕⊕◯◯ LOW	Risk of bias (-1) Imprecision (-1)
TER (TCM syndrome score)	Total (Pattern identification)	60 (1)	567 per 1,000	901 per 1,000 (646 to 1,000)	RR 1.59 (1.14 to 2.22)	Not applicable	⊕◯◯◯ VERY LOW	Risk of bias (-1) Indirectness (-1) Imprecision (-1)
Adverse event	Total (Pattern identification)	60 (1)	100 per 1,000	14 per 1,000 (1 to 265)	RR 0.14 (0.01 to 2.65)	Not applicable	⊕◯◯◯ VERY LOW	Risk of bias (-1) Imprecision (-2)

CI = confidence interval, HDL-C = high density lipoprotein cholesterol, HHT = Hwangryunhaedok-tang, LDL-C = low density lipoprotein cholesterol, MD = mean difference, RCT = randomized controlled trial, RR = risk ratio, TC = total cholesterol, TCM = traditional Chinese medicine, TER = total effective rate, TG = triglyceride.

Lastly, some studies reported the potential anti-inflammatory and immunomodulatory effects of HHT or HHT combined with lipid-lowering drugs, and suggested decreased levels of C-reactive protein (CRP),[25,27,28,30] interleukin (IL)-6,[30] and tumor necrosis factor-alpha (TNF-α),[30] as well as a concomitantly increased level of IL-10[30] (all, $P < .05$). Because all studies had a high risk of bias, a sensitivity analysis excluding studies with a high risk of bias was not performed.

3.5. Safety

Only three studies reported safety data. Chai[27] compared HHT with capsules of the herbal medicine product Xue Zhi Kang, stating that there were no adverse events and no abnormal findings in routine safety tests. However, Xue et al[29] assessed HHT combined with lipid-lowering drugs, as well as lipid-lowering drugs alone, finding one case of dizziness and two instances of nausea and vomiting in the HHT groups, while five cases presented with an increase in alanine aminotransferase (ALT) level, two cases of dizziness, three instances of nausea and vomiting, and two episodes of fatigue were observed in the lipid-lowering drug group (RR 0.25, 95% CI, 0.08 to 0.83). Huang[28] similarly compared HHT and lipid-lowering drugs, finding no adverse events and no abnormal data in the HHT group, while there was one case of a slight increase in ALT level, one instance of mild itching, and a single episode of mild abdominal distension in the lipid-lowering drugs group (RR 0.14, 95% CI, 0.01 to 2.65).

3.6. Quality of evidence

In the comparison of HHT with lipid-lowering drugs *versus* lipid-lowering drugs alone, and in the comparison of HHT vs lipid-lowering drug monotherapy, the quality of evidence was graded as "Very Low" to "Moderate" (Table 2). The main reason for downgrading was the high risk of bias of the included RCTs and inconsistencies due to the unexplained heterogeneity of the meta-analysis. Furthermore, we judged some findings to have low precision because they did not satisfy the optimal sample size or had wide CIs. Especially for TER, the indirectness of the outcome measure also lowered the precision.

3.7. Publication bias

Since the number of studies included in each analysis was less than 10, evaluation of publication bias through the funnel plot was not conducted.

4. Discussion

4.1. Summary of findings

The findings of the present study show that HHT was significantly inferior to lipid-lowering drugs for regulation of LDL-C and TC levels when compared with all statins, and that the two groups showed no significant difference in TG and HDL-C regulation. However, HHT combined with lipid-lowering drugs (mainly statins) was significantly superior in all four lipid parameters, including LDL-C, TC, TG, and HDL-C regulation, when compared with lipid-lowering drugs only (mainly statins). In a few studies, HHT also improved comorbid hypertension,[29,32] diabetes,[24] and arterial disease.[26] Lastly, some studies[25,27,28,30] have shown the potential anti-inflammatory and immunomodulatory effects of HHT in comparison with lipid-lowering drugs. Furthermore, a few studies[27–29] have reported the drug's safety profiles, and HHT treatment appears to be generally less likely to result in adverse events or abnormal findings in safety tests in comparison with treatment using lipid-lowering agents alone. However, the risk of bias of the included studies was generally high and the quality of evidence for the major findings was generally low.

4.2. Clinical implications

These data suggest that the combination of HHT with lipid-lowering drugs, especially statins, may yield synergistic effects on lipid profile improvement. HHT is a well-known anti-inflammatory herbal agent, and inflammation is known to be related to various metabolic diseases and cardiovascular risks such as dyslipidemia, hypertension, obesity, and diabetes. Therefore, the use of HHT along with lipid-lowering drugs for lipid regulation may have a secondary effect of reducing metabolic burdens and cardiovascular risks without any serious adverse events. In addition, given the increased demand for natural products that can regulate lipids due to the many adverse effects of statins, the results of this study suggest the possibility of using HHT alone, especially for regulation of TG and HDL-C levels.

4.3. Strengths and limitations

To the best of our knowledge, this is the first systematic review that evaluated the effectiveness and safety of HHT monotherapy or adjunctive HHT therapy with lipid-lowering drugs, especially statins, for dyslipidemia patients. We tried to collect as much of the latest evidence as possible through a comprehensive search of English, Korean, Japanese, and Chinese databases.

However, there are some limitations to consider when interpreting the results. Although the subgroup analysis was conducted depending on whether the study recruited participants according to specific pattern identification, there were some unresolved heterogeneities in our findings. These might be due to the clinical heterogeneity, such as the presence of comorbidities, including hypertension and diabetes, and the composition and dose of HHT used in each included study. In particular, the heterogeneities in HHT, such as type and dose of each herb in the studies included, may reflect the characteristics of TCM prescription for herbal medicines that are tailored to the patient's characteristics and disease state. However, efforts are still needed to identify the optimal ratio of the four key herbs in HHT for dyslipidemia control. Additionally, there were no placebo-controlled studies, which resulted in a high risk of performance and detection bias. In addition, none of the included studies performed follow-up observations, and we could not know how the lipid level changed after HHT administration was finished. Furthermore, because few studies have reported whether the adverse events or abnormal laboratory findings occurred after HHT administration, the safety profile of HHT is still unclear. In particular, long-term monitoring is necessary because long-term use of *Gardeniae Fructus*, one of the HHT components, may cause mesenteric phlebosclerosis.[33]

4.4. Suggestions for further studies

Higher methodological quality RCTs addressing the use of HHT for dyslipidemia should be conducted to support decision-making

in the clinical setting. In particular, placebo-controlled trials are needed to prevent potential performance and detection bias. Although LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management and therefore,[34] we set LDL-C as the primary outcome, dyslipidemia does not cause problems on its own and increases the risk of cardiovascular events. In the future, long-term clinical trials or large-scale cohort studies are needed to evaluate the effects of HHT on cardiovascular events or mortality in dyslipidemic patients. The subgroup analysis revealed no significant differences in lipid levels between studies recruiting patients according to specific pattern identification and studies that did not. However, HHT requires a typical heat-clearing and detoxifying prescription,[35] and it is necessary to confirm whether there is a difference according to pattern identification on a larger sample size. There is also a need for further experimental studies on the mechanism of HHT related to lipid-lowering. In addition, in order to generalize the potential benefits of using HHT as an adjuvant therapy identified in the findings, research on the herb-drug interactions of HHT and statins is essential.

5. Conclusion

Current evidence suggests that the herbal medicine HHT may have positive effects on dyslipidemia, especially when used along with lipid-lowering drugs without serious adverse events. However, due to the high risk of bias of the included studies and the low quality of evidence for the main findings, no definite conclusion could be reached. Further rigorous, high-quality, and placebo-controlled RCTs and research on the herb-drug interaction of HHT and conventional lipid-lowering drugs are needed.

Author contributions

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