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Review

Lipid-lowering Effect of Danshen, Fufang Danshen, Shuxuening and Shuxuetong Injections: A Systematic Review and Meta-Analysis of Controlled Clinical Trials

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Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections, four traditional Chinese medicine prescriptions, have been widely explored regarding their lipid-lowering property, but the findings were inconsistent and inconclusive. This meta-analysis was to clarify the lipid-lowering effect of the four injections. PubMed, Scopus, Embase, Web of Science, Google Scholar, Cochrane Library and CNKI databases were searched, and data including age, sex, ethnicity, disease type, dose, duration, sample size and blood lipids were extracted from each eligible study. The alterations in lipids from pre- to post-treatment were calculated and compared between control and treatment groups, and standardized mean differences (SMDs) with 95% confidence intervals (CIs) were used to assess the lipid-lowering effect of the injections. Twenty-eight studies (2,624 subjects), 31 studies (3,023 subjects), 17 studies (1,507 subjects) and 54 studies (4,435 subjects) were respectively identified for Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections. All of the four injections could effectively and significantly reduce serum levels of triglycerides ($p < 0.001$ for all), total cholesterol ($p < 0.001$ for all) and low-density lipoprotein cholesterol ($p < 0.001$ for all), and elevate high-density lipoprotein cholesterol level ($p \leq 0.02$ for all). Shuxuening injection had the strongest lipid-lowering effect with almost twice that of the other three injections. Danshen, Fufang Danshen and Shuxuening injections showed a good lipid-lowering effect on patients with heart disease, while Shuxuetong injection displayed a powerful lipid-lowering effect among diabetic patients. Unfortunately, all of these injections had a poor lipid-lowering effect in patients with renal disease. The meta-analysis demonstrates that Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections all can effectively reduce blood lipids. Among them, Shuxuening injection has the strongest lipid-lowering effect with almost twice that of the other three injections. In terms of reducing blood lipid levels, Danshen, Fufang Danshen and Shuxuening injections are suitable for patients with cardiovascular disease, Shuxuetong injection is suitable for patients with diabetes, but none of them is suitable for patients with renal disease.

Keywords: Danshen; Fufang Danshen; lipid; injection; Shuxuening; Shuxuetong
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Introduction

Cerebrovascular and cardiovascular diseases are currently one of the leading causes of death around the world (Alanaeme et al. 2022; Pál et al. 2023; Tsao et al. 2023). Multiple risk factors are implicated in the pathogenesis of cerebrovascular and cardiovascular diseases, such as hyperlipidemia, hypertension, hyperuricemia, hyperhomocystein-

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emia, diabetes, obesity, old age, male gender, smoking, etc. (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2002; Grundy et al. 2019). Hyperlipidemia is probably the most important modifiable risk factor for cardiovascular and cerebrovascular diseases, and accounts for approximately fifty percent of the population-attributable risk (Yusuf et al. 2004; O'Donnell et al. 2016). Hyperlipidemia is a severe lipid disorder mainly involving abnormal elevation of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and triglycerides (TG), and/or reduction of high-density lipoprotein cholesterol (HDL-C) in circulation, although apolipoproteins AI and B and lipoprotein (a) are sometimes also included in clinical testing (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2002, Grundy et al. 2019). A systematic review of 23 randomized controlled trials demonstrated that a 40% reduction in LDL-C along with a 30% elevation in HDL-C is able to lower the risk of cardiovascular disease by nearly 70% (Brown et al. 2006). There are several classes of lipid-lowering drugs currently available in pharmacy for patients to use, such as statins, fibrates, bile acid sequestrants, PCSK9 inhibitors, etc., but none of these drugs are suitable for all patients (Tsu et al. 2021; Chen and Chen 2023; Zivkovic et al. 2023). Statins, as the most widely used lipid-lowering drugs in the world, have muscle symptoms of rhabdomyolysis with a prevalence estimated at 10% (Iatan et al. 2023). The use of fibrates in patients with end-stage renal disease did not reduce cardiovascular risk and events regardless of being used alone or in combination with other drugs (Ho et al. 2022). PCSK9 inhibitors were recently reported to be less effective in women compared to men, and there were about 30% incidence of side effects such as neurological and gastrointestinal symptoms in both genders (Galema-Boers et al. 2023). Based on these concerns, there have been increasing attempts to use traditional Chinese medicines as alternatives to Western lipid-lowering medicines in some specific patient populations, and traditional Chinese medicines are sometimes more acceptable to Chinese patients.

Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections are four Chinese patent drugs which are widely used in hospitals and clinics around China. Danshen injection, also known as Salvia miltiorrhiza injection, is made from the extracts of a famous Chinese herbal medicine Danshen (Radix Salviae Miltiorrhizae), and contains a variety of active ingredients such as salvianolic acids, protocatechuic aldehyde, rosmarinic acid and caffeic acid. A number of clinical studies indicated that Danshen injection has a good therapeutic effect on cerebrovascular disease (Yu et al. 2000; Ren et al. 2022), cardiovascular disease (Liu et al. 2014; Shao et al. 2018; Li et al. 2022a), pneumonia (Guo et al. 2022) and ulcerative colitis (Zhou et al. 2022). Fufang Danshen injection, also named as compound Danshen injection or Xiangdan injection, is made from the extracts of two Chinese herbs Danshen and Jiangxiang (Lignum Dalbergiae Odoriferae). The main active ingredients of Fufang Danshen injection include not only the active ingredients of Danshen, but also the active ingredients from Jiangxiang, such as flavonoids, caryophyllene oxide and nerolidol. Clinical researches have shown that Fufang Danshen injection was effective in treating cerebrovascular disease (Huang et al. 2015; Li et al. 2015; Bian et al. 2021), cardiovascular disease (Geng et al. 2004; Wu et al. 2004; Li et al. 2022a), ulcerative colitis (Zhou et al. 2022) and nephrotic syndrome (Yu et al. 2020). Shuxuening injection, made from the extracts of another Chinese herb gingko leaf (Ginkgo biloba L.), has its main active ingredients such as flavonol glycosides, ginkgolides and bilobalide. Clinical studies have suggested that Shuxuening injection has a good efficacy in treating cerebrovascular disease (Jiang et al. 2016; Ren et al. 2022; Li et al. 2023a), cardiovascular disease (Tan et al. 2018; Fan et al. 2022; Shen et al. 2022), diabetes (Shen et al. 2022) and idiopathic pulmonary fibrosis (Huang et al. 2022). The above-mentioned three types of injections are all from Chinese herbal medicines, while Shuxuetong injection is made from the extracts of two worms, leech (Whitmania pigra whitman) and earthworm (Pheretima). The chemical composition of Shuxuetong injection is complex, and its active ingredients are not yet clear (Chai et al. 2023). The use of Danshen, Jiangxiang, gingko leaf, leech and earthworm for the treatment of human diseases was initially recorded in the Chinese ancient medical books such as *Shennong's Classic of Materia Medica* and *Compendium of Materia Medica*, and all of these traditional Chinese medicines are currently officially listed in *Chinese Pharmacopoeia*.

A series of clinical researches have examined the lipid-lowering effect of Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections, but the results were inconsistent and inconclusive. Some studies suggested that the four injections can effectively and significantly reduce serum levels of LDL-C, TC and TG, and elevate HDL-C level (Xie and Yang 2004; Pu 2009; Wang 2013; Chen 2015; Zhou 2017; Liu and Wang 2021), while data from other laboratories did not support these findings (Gong 2011; Tong et al. 2012; He et al. 2014). Herein, a systematic review and meta-analysis is performed to clarify the effects of Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections on serum lipid levels, and the research results can provide a reference for physicians in clinical practice and help doctors better diagnose and treat patients.

Methods

Literature Search

The systematic review and meta-analysis was registered in PROSPERO (CRD42023429674) and performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. Comprehensive searches of the electronic databases such as PubMed, Google Scholar, Cochrane Library, Embase,

CNKI, Wanfang and VIP were conducted to identify eligible studies published before May 2023. All researches that investigated the effects of Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections on serum lipid levels were reviewed and identified. The languages of the articles were limited to Chinese and English. The keywords employed for literature searches included "Danshen or Fufang Danshen or Shuxuening or Shuxuetong or Danshen injection or Fufang Danshen injection or Shuxuening injection or Shuxuetong injection" and "low-density lipoprotein cholesterol or total cholesterol or high-density lipoprotein cholesterol or triglyceride or LDL-C or TC or HDL-C or TG" and "cerebral infarction or coronary heart disease or type 2 diabetes mellitus or nephrotic syndrome or hyperlipidemia or hypertension or hyperlipidemic acute pancreatitis or non-alcoholic fatty liver disease". The indicators examined in this systematic review and meta-analysis were limited to LDL-C, TC, HDL-C, and TG. All of the following criteria should be fulfilled: 1) a study pattern of "A vs. A + B", i.e., basic treatment vs. basic treatment + injection; 2) the study that was designed as a controlled clinical trial; 3) the publication that reported the effects of Danshen, Fufang Danshen, Shuxuening or Shuxuetong injection on one or more of the four serum lipid parameters (LDL-C, TC, HDL-C, and TG); 4) the publication that presented the serum lipid variables as mean ± standard deviation (SD) or mean ± standard error (SE), and 5) the lipid data before and after treatment available. Publications with invalid data, review article, abstract, case report, animal and *in vivo* studies were excluded from the systematic review and meta-analysis.

Data Extraction

The researches that did not fully meet the inclusion criteria were excluded after being carefully reviewed by at least two reviewers. A structured data collection form was developed, and the data extracted from each of the enrolled studies were as follows: first author, sex, age, ethnicity, disease type, treatment duration, treatment dose, sample size, lipid variables before and after the treatment of Danshen, Fufang Danshen, Shuxuening or Shuxuetong injections. Data were carefully checked to ensure accuracy, and any uncertainty was discussed and solved in the whole group. Regarding the overlapping publications, only those with the most detailed information were included in the present meta-analysis.

Statistical Analysis

The STATA software package version 11 (Stata Corp., College Station, TX, USA) was used for this systematic review and meta-analysis. Data were shown in the form of mean ± SD, and SE was converted to SD by the formula: SD = SE*SQRT(n). The unit of all four lipid indicators was shown as mmol/L, and unit conversion was performed if other units were used. Standardized mean difference (SMD) in net change of the lipid parameters as well as 95% confidence interval (95% CI) was employed to estimate the effects of Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections on serum levels of LDL-C, TC, HDL-C and TG. Net change of lipid parameters upon treatment was calculated by using the following formulas: mean change = $mean_{post\text{-}treatment}$ - $mean_{pre\text{-}treatment}$; SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - 2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment}]$, assuming a correlation coefficient (R) = 0.5 (Yu et al. 2018). Subgroup analyses were performed based on disease type, duration and dose of treatment. The systematic review and meta-analysis used the random effects model as this model provides a more conservative evaluation of the significance of the associations than the fixed effects model (Li et al. 2023b). Cochran's χ^2-based Q-statistic test was conducted to evaluate heterogeneity among studies at a significance level of $p < 0.05$, and Galbraith plot was used to detect the potential sources of heterogeneity (Li et al. 2022b). Begg's rank correlation test was performed to assess the publication bias at a significance level of $p < 0.05$, and funnel plot was used to suggest the presence of a potential publication bias (Su et al. 2021).

Results

Characteristics of the Enrolled Studies

Flow diagram of the literature searches is displayed in Fig. 1. Twenty-eight studies (2,624 subjects), 31 studies (3,023 subjects), 17 studies (1,507 subjects) and 54 studies (4,435 subjects) were respectively identified for Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections, and the reference list of these studies is presented in Supplementary Table S1. Characteristics of the included studies are shown in Supplementary Tables S2-S5. The enrolled studies were published from 2009 to 2022, and written exclusively in Chinese. All research subjects were Chinese people. Two studies in which Fufang Danshen injection was used to treat early onset severe preeclampsia only included women, and the other studies included both men and women. Twenty-seven studies, 28 studies, 19 studies and 20 studies respectively presented data for TG, TC, HDL-C and LDL-C for Danshen injection (Supplementary Table S2). Thirty-one studies, 28 studies, 21 studies and 18 studies respectively presented data for TG, TC, HDL-C and LDL-C for Fufang Danshen injection (Supplementary Table S3). Sixteen studies, 15 studies, 7 studies and 7 studies respectively presented data for TG, TC, HDL-C and LDL-C for Shuxuening injection (Supplementary Table S4). Fifty-three studies, 54 studies, 36 studies and 32 studies respectively presented data for TG, TC, HDL-C and LDL-C for Shuxuetong injection (Supplementary Table S5). The original lipid data and lipid changes from pre- to post-treatment are shown in Supplementary Tables S6-S9 for Danshen, Fufang Danshen, Shuxuening, and Shuxuetong injections, respectively. Danshen injection was mainly used to treat diabetic nephropathy (16 studies), heart disease (12 studies), stroke (6 studies) and fatty liver disease (4 studies). Fufang Danshen injection was mainly used to treat heart disease (22

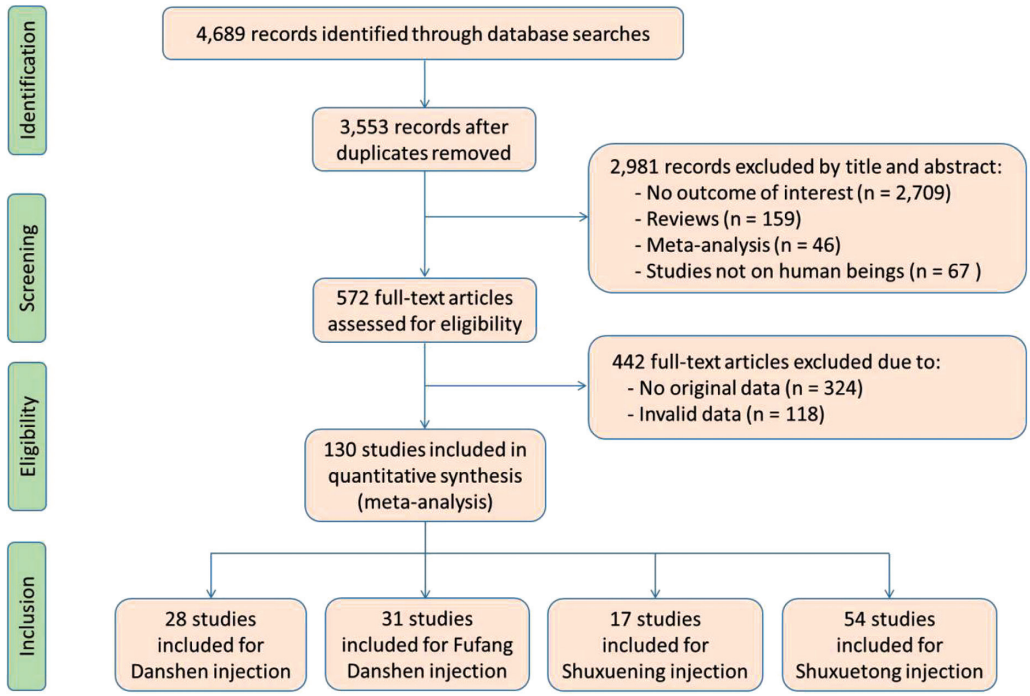

Fig. 1. The flow diagram of the literature searches.

studies), diabetes (14 studies), nephrotic syndrome (6 studies) and hyperlipidemic acute pancreatitis (4 studies). Shuxuening injection was mainly used to treat heart disease (20 studies), nephrotic syndrome (6 studies) and stroke (4 studies). Shuxuetong injection was mainly used to treat heart disease (40 studies), stroke (26 studies), diabetic nephropathy (10 studies), nephrotic syndrome (10 studies) and hypertension (6 studies). The treatment dose and duration of Danshen injection were 20-30 mL and 2-16 weeks, respectively. The treatment dose and duration of Fufang Danshen injection were 10-60 mL and 1-12 weeks, respectively. The treatment dose and duration of Shuxuening injection were 10-30 mL and 1-12 weeks, respectively. The treatment dose and duration of Shuxuetong injection were 4-6 mL and 1-6 weeks, respectively.

Associations of Danshen Injection with Plasma Lipid Levels

The meta-analysis of all eligible studies showed that Danshen injection can effectively decrease serum levels of TG (SMD = −0.88 mmol/L, 95% CI = −1.04 to −0.71 mmol/L, $p < 0.001$) (Supplementary Fig. S1), TC (SMD = −0.80 mmol/L, 95% CI = −1.10 to −0.49 mmol/L, $p < 0.001$) (Supplementary Fig. S2) and LDL-C (SMD = −0.71 mmol/L, 95% CI = −1.00 to −0.42 mmol/L, $p < 0.001$) (Supplementary Fig. S3), and increase HDL-C level (SMD = 0.78 mmol/L, 95% CI = 0.47 to 1.08 mmol/L, $p < 0.001$) (Supplementary Fig. S4) (Table 1).

Stratification analysis by disease type displayed that the lipid-lowering effect of Danshen injection is robust in patients with heart disease or stroke, while it is uncertain in patients with diabetes or renal disease since the reduction of LDL-C did not reach a significant level among these patients after treatment (diabetes: SMD = −0.29 mmol/L, 95% CI = −0.65 to 0.06 mmol/L, $p = 0.11$; renal disease: SMD = −0.50 mmol/L, 95% CI = −1.03 to 0.03 mmol/L, $p = 0.06$). Stratification analysis by treatment dose showed that Danshen injection decreased serum lipid levels in a dose-dependent manner, and lipid reduction in high-dose treatment group (30 mL) was apparently greater than that in low-dose treatment group (20 mL) (TG: −1.12 vs. −0.81 mmol/L; TC: −1.49 vs. −0.74 mmol/L; LDL-C: −0.94 vs. −0.69 mmol/L; HDL-C: 0.94 vs. 0.84 mmol/L). Reduction in serum TG and TC levels by Danshen injection was also found to be in a time-dependent manner, and the reduction magnitude of TG and TC increased with the prolongation of treatment time (TG: 2 vs. 4 vs. 8 weeks = −0.65 vs. −0.91 vs. −1.17 mmol/L; TC: 2 vs. 4 vs. 8 weeks = −0.49 vs. −0.97 vs. −1.39 mmol/L).

Associations of Fufang Danshen Injection with Serum Lipid Levels

The meta-analysis of all eligible studies showed that Fufang Danshen injection can effectively decrease serum levels of TG (SMD = −0.77 mmol/L, 95% CI = −0.97 to −0.57 mmol/L, $p < 0.001$) (Supplementary Fig. S5), TC (SMD = −0.77 mmol/L, 95% CI = −1.01 to −0.53 mmol/L, $p < 0.001$) (Supplementary Fig. S6) and LDL-C (SMD = −0.64 mmol/L, 95% CI = −0.85 to −0.42 mmol/L, $p < 0.001$) (Supplementary Fig. S7), and increase HDL-C level (SMD = 0.63 mmol/L, 95% CI = 0.31 to 0.95 mmol/L, $p < 0.001$) (Supplementary Fig. S8) (Table 2).

Stratification analysis by disease type displayed that the lipid-lowering effect of Fufang Danshen injection is robust in patients with heart disease or dyslipidemia, while

Table 1. Meta-analysis for Danshen injection and blood lipids.

Groups or subgroups	Studies (Subjects)	$P_{Heterogeneity}$	SMD (95% CI)	P_{SMD}
TG				
All	27 (2556)	< 0.001	–0.88 (–1.04, –0.71)	< 0.001
Diabetes	13 (1360)	< 0.001	–0.81 (–1.04, –0.57)	< 0.001
Renal disease	9 (1120)	< 0.001	–0.91 (–1.18, –0.63)	< 0.001
Heart disease	6 (524)	< 0.001	–1.01 (–1.43, –0.60)	< 0.001
Stroke	3 (236)	0.52	–0.82 (–1.08, –0.55)	< 0.001
Low dose (20 mL)	15 (1692)	< 0.001	–0.81 (–1.02, –0.60)	< 0.001
High dose (30 mL)	9 (680)	0.07	–1.12 (–1.34, –0.89)	< 0.001
Short duration (2 weeks)	5 (560)	< 0.001	–0.65 (–1.13, –0.18)	0.007
Medium duration (4 weeks)	12 (1300)	< 0.001	–0.91 (–1.12, –0.69)	< 0.001
Long duration (8 weeks)	6 (432)	0.35	–1.17 (–1.39, –0.95)	< 0.001
TC				
All	28 (2624)	< 0.001	–0.80 (–1.10, –0.49)	< 0.001
Diabetes	13 (1360)	< 0.001	–0.83 (–1.25, –0.42)	< 0.001
Renal disease	10 (1188)	< 0.001	–0.94 (–1.45, –0.44)	< 0.001
Heart disease	6 (524)	< 0.001	–0.93 (–1.39, –0.46)	< 0.001
Stroke	3 (236)	0.001	–1.05 (–1.82, –0.28)	0.007
Low dose (20 mL)	16 (1760)	< 0.001	–0.74 (–0.98, –0.51)	< 0.001
High dose (30 mL)	9 (680)	< 0.001	–1.49 (–2.22, –0.77)	< 0.001
Short duration (2 weeks)	5 (560)	0.23	–0.49 (–0.69, –0.28)	< 0.001
Medium duration (4 weeks)	13 (1368)	< 0.001	–0.97 (–1.40, –0.53)	< 0.001
Long duration (8 weeks)	6 (432)	< 0.001	–1.39 (–2.00, –0.79)	< 0.001
LDL-C				
All	19 (1658)	< 0.001	–0.71 (–1.00, –0.42)	< 0.001
Diabetes	8 (642)	< 0.001	–0.29 (–0.65, 0.06)	0.11
Renal disease	6 (536)	< 0.001	–0.50 (–1.03, 0.03)	0.06
Heart disease	6 (524)	< 0.001	–1.24 (–1.85, –0.63)	< 0.001
Low dose (20 mL)	13 (1226)	< 0.001	–0.69 (–1.07, –0.30)	0.001
High dose (30 mL)	4 (320)	0.01	–0.94 (–1.39, –0.49)	< 0.001
Short duration (2 weeks)	4 (470)	0.17	–0.61 (–0.86, –0.36)	< 0.001
Medium duration (4 weeks)	7 (582)	0.001	–0.37 (–0.70, –0.05)	0.025
Long duration (8 weeks)	5 (382)	0.002	–1.64 (–2.14, –1.15)	< 0.001
HDL-C				
All	20 (1772)	< 0.001	0.78 (0.47, 1.08)	< 0.001
Diabetes	10 (812)	< 0.001	1.02 (0.60, 1.44)	< 0.001
Renal disease	7 (634)	< 0.001	1.12 (0.61, 1.64)	< 0.001
Heart disease	6 (524)	0.001	0.75 (0.38, 1.11)	< 0.001
Low dose (20 mL)	14 (1324)	< 0.001	0.84 (0.45, 1.24)	< 0.001
High dose (30 mL)	3 (264)	0.001	0.94 (0.28, 1.60)	0.005
Short duration (2 weeks)	5 (560)	< 0.001	0.30 (–0.27, 0.86)	0.30
Medium duration (4 weeks)	8 (692)	< 0.001	1.23 (0.80, 1.66)	< 0.001
Long duration (8 weeks)	4 (296)	0.004	0.94 (0.42, 1.46)	< 0.001

SMD, standardized mean difference; 95% CI, 95% confidence interval; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

it is uncertain in patients with diabetes or renal disease since the changes in LDL-C (SMD = −0.11 mmol/L, 95% CI = −0.59 to 0.38 mmol/L, $p = 0.66$) and HDL-C (SMD = 0.11 mmol/L, 95% CI = −0.42 to 0.63 mmol/L, $p = 0.69$) are not significant among patients with diabetes, and the reduction of TG (SMD = −0.75 mmol/L, 95% CI = −1.61 to 0.10 mmol/L, $p = 0.08$) and TC (SMD = −1.15 mmol/L, 95% CI = −2.31 to 0.008 mmol/L, $p = 0.052$) did not reach

Table 2. Meta-analysis for Fufang Danshen injection and blood lipids.

Groups or subgroups	Studies (Subjects)	$P_{Heterogeneity}$	SMD (95% CI)	P_{SMD}
TG				
All	31 (3023)	< 0.001	–0.77 (–0.97, –0.57)	< 0.001
Diabetes	7 (603)	0.30	–0.43 (–0.61, –0.26)	< 0.001
Renal disease	3 (148)	0.002	–0.75 (–1.61, 0.10)	0.08
Heart disease	10 (1160)	<0.001	–1.06 (–1.40, –0.71)	< 0.001
Dyslipidemia	5 (407)	0.007	–0.71 (–1.10, –0.31)	< 0.001
Low dose (10 mL)	4 (297)	< 0.001	–0.81 (–1.68, 0.06)	0.07
High dose (20 mL)	18 (1911)	< 0.001	–0.79 (–0.97, –0.61)	< 0.001
Short duration (1-2 weeks)	16 (1544)	< 0.001	–0.89 (–1.24, –0.54)	< 0.001
Medium duration (3-4 weeks)	6 (502)	< 0.001	–0.65 (–1.07, –0.24)	0.002
Long duration (> 4 weeks)	8 (890)	0.11	–0.65 (–0.83, –0.48)	< 0.001
TC				
All	28 (2776)	< 0.001	–0.77 (–1.01, –0.53)	< 0.001
Diabetes	7 (603)	0.01	–0.49 (–0.77, –0.21)	0.001
Renal disease	3 (148)	< 0.001	–1.15 (–2.31, 0.008)	0.052
Heart disease	10 (1171)	< 0.001	–0.80 (–1.23, –0.38)	< 0.001
Dyslipidemia	3 (236)	0.39	–0.33 (–0.59, –0.08)	0.01
Low dose (10 mL)	4 (297)	< 0.001	–0.76 (–1.69,0.17)	0.11
High dose (20 mL)	16 (1751)	< 0.001	–0.82 (–1.07, –0.57)	< 0.001
Short duration (1-2 weeks)	14 (1384)	< 0.001	–0.81 (–1.15, –0.47)	< 0.001
Medium duration (3-4 weeks)	6 (502)	< 0.001	–0.65 (–1.31, 0.01)	0.054
Long duration (> 4 weeks)	8 (890)	< 0.001	–0.80 (–1.20, –0.39)	< 0.001
LDL-C				
All	21 (2282)	< 0.001	–0.64 (–0.85, –0.42)	< 0.001
Diabetes	5 (441)	< 0.001	–0.11 (–0.59, 0.38)	0.66
Heart disease	9 (1051)	< 0.001	–0.86 (–1.13, –0.59)	< 0.001
Low dose (10 mL)	4 (297)	< 0.001	–0.89 (–1.61, –0.16)	0.016
High dose (20 mL)	12 (1437)	< 0.001	–0.53 (–0.82, –0.24)	< 0.001
Short duration (1-2 weeks)	14 (1264)	< 0.001	–0.81 (–1.09, –0.53)	< 0.001
Medium duration (3-4 weeks)	3 (290)	0.15	–0.26 (–0.59, 0.07)	0.12
Long duration (> 4 weeks)	6 (728)	< 0.001	–0.49 (–0.91, –0.08)	0.018
HDL-C				
All	18 (2084)	< 0.001	0.63 (0.31, 0.95)	< 0.001
Diabetes	4 (386)	< 0.001	0.11 (–0.42, 0.63)	0.69
Heart disease	8 (964)	< 0.001	0.72 (0.16, 1.28)	0.01
Low dose (10 mL)	3 (242)	0.55	1.41 (1.13, 1.69)	< 0.001
High dose (20 mL)	10 (1294)	< 0.001	0.65 (0.26, 1.04)	0.001
Short duration (1-2 weeks)	9 (1066)	< 0.001	0.73 (0.19, 1.27)	0.008
Medium duration (3-4 weeks)	3 (290)	< 0.001	0.22 (–0.50, 0.94)	0.55
Long duration (> 4 weeks)	6 (728)	< 0.001	0.68 (0.23, 1.14)	0.003

SMD, standardized mean difference; 95% CI, 95% confidence interval; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

a significant level among patients with renal disease after treatment. Reduction in serum lipid levels by Fufang Danshen injection was not found to be in a dose- and time-dependent manner.

Associations of Shuxuening Injection with Serum Lipid Levels

The meta-analysis of all eligible studies showed that Shuxuening injection can effectively decrease serum levels of TG (SMD = −1.51 mmol/L, 95% CI = −2.04 to −0.99 mmol/L, $p < 0.001$) (Supplementary Fig. S9), TC (SMD =

Table 3. Meta-analysis for Shuxuening injection and blood lipids.

Groups or subgroups	Studies (Subjects)	$P_{Heterogeneity}$	SMD (95% CI)	P_{SMD}
TG				
All	16 (1467)	< 0.001	–1.51 (–2.04, –0.99)	< 0.001
Diabetes	3 (277)	0.32	–0.31 (–0.56, –0.05)	0.02
Heart disease	10 (1005)	< 0.001	–1.49 (–2.09, –0.90)	< 0.001
Short duration (1-2 weeks)	7 (618)	< 0.001	–0.86 (–1.33, –0.40)	< 0.001
Long duration (3-4 weeks)	7 (679)	< 0.001	–1.60 (–2.41, –0.78)	< 0.001
TC				
All	15 (1397)	< 0.001	–1.35 (–1.78, –0.92)	< 0.001
Diabetes	3 (277)	< 0.001	–0.52 (–1.25, 0.22)	0.17
Heart disease	10 (1005)	< 0.001	–1.61 (–2.17, –1.05)	< 0.001
Short duration (1-2 weeks)	7 (618)	< 0.001	–1.08 (–1.71, –0.45)	0.001
Long duration (3-4 weeks)	6 (609)	< 0.001	–1.34 (–1.97, –0.71)	< 0.001
LDL-C				
All	7 (612)	< 0.001	–1.26 (–1.90, –0.63)	< 0.001
Heart disease	5 (480)	< 0.001	–1.31(–2.20, –0.43)	0.004
Long duration (3-4 weeks)	4 (382)	< 0.001	–0.97 (–1.78, –0.15)	0.02
HDL-C				
All	7 (612)	< 0.001	1.10 (0.16, 2.05)	0.02
Heart disease	5 (480)	< 0.001	1.53 (0.24, 2.83)	0.02
Long duration (3-4 weeks)	4 (382)	< 0.001	0.43 (–0.34, 1.19)	0.27

SMD, standardized mean difference; 95% CI, 95% confidence interval; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

−1.35 mmol/L, 95% CI = −1.78 to −0.92 mmol/L, p < 0.001) (Supplementary Fig. S10) and LDL-C (SMD = −1.26 mmol/L, 95% CI = −1.90 to −0.63 mmol/L, p < 0.001) (Supplementary Fig. S11), and increase HDL-C level (SMD = 1.10 mmol/L, 95% CI = 0.16 to 2.05 mmol/L, p < 0.001) (Supplementary Fig. S12) (Table 3).

Stratification analysis by disease type displayed that the lipid-lowering effect of Shuxuening injection is robust in patients with heart disease, while it is uncertain in patients with diabetes since TC reduction did not reach a significant level among such patients after treatment (SMD = −0.52 mmol/L, 95% CI = −1.25 to 0.22 mmol/L, p = 0.17). Reduction in serum TG and TC levels by Shuxuening injection was found to be in a time-dependent manner, and 3 to 4 weeks of treatment had a larger magnitude of reduction in TG and TC levels than 1 to 2 weeks of treatment (TG: −1.60 vs. −0.86 mmol/L; TC: −1.34 vs. −1.08 mmol/L).

Associations of Shuxuetong Injection with Serum Lipid Levels

The meta-analysis of all eligible studies showed that Shuxuetong injection can significantly decrease serum levels of TG (SMD = −0.68 mmol/L, 95% CI = −0.86 to −0.50 mmol/L, p < 0.001) (Supplementary Fig. S13), TC (SMD = −0.83 mmol/L, 95% CI = −1.05 to −0.60 mmol/L, p < 0.001) (Supplementary Fig. S14) and LDL-C (SMD = −0.82 mmol/L, 95% CI = −1.05 to −0.58 mmol/L, p < 0.001) (Supplementary Fig. S15), and increase HDL-C level (SMD = 0.33 mmol/L, 95% CI = 0.13 to 0.53 mmol/L, p = 0.001) (Supplementary Fig. S16) (Table 4).

Stratification analysis by disease type displayed that the lipid-lowering effect of Shuxuetong injection is robust in patients with diabetes, stroke or hypertension, while it is uncertain in patients with renal disease, heart disease and atherosclerosis. TG reduction in patients with renal disease (SMD = −0.54 mmol/L, 95% CI = −1.17 to 0.10 mmol/L, p = 0.10), LDL-C reduction in patients with atherosclerosis (SMD = −1.40 mmol/L, 95% CI = −4.95 to 2.15 mmol/L, p = 0.44), and HDL-C elevation in patients with heart disease (SMD = 0.17 mmol/L, 95% CI = −0.16 to 0.49 mmol/L, p = 0.31) and atherosclerosis (SMD = 0.34 mmol/L, 95% CI = −0.50 to 1.19 mmol/L, p = 0.43) did not reach a significant level. Reduction in serum lipid levels by Shuxuetong injection was not found to be in a dose- and time-dependent manner.

Heterogeneity Analysis

Significant heterogeneity was detected in the pooled meta-analyses for Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections in the whole population (Tables 1-4). Sources of heterogeneity were successfully identified by using Galbraith plots. The heterogeneity was effectively removed or decreased after excluding the outlier studies,

Table 4. Meta-analysis for Shuxuetong injection and blood lipids.

Groups or subgroups	Studies (Subjects)	$P_{Heterogeneity}$	SMD (95% CI)	P_{SMD}
TG				
All	53 (4397)	< 0.001	–0.68 (–0.86, –0.50)	< 0.001
Diabetes	12 (861)	< 0.001	–0.49 (–0.88, –0.11)	0.012
Renal disease	10 (805)	< 0.001	–0.54 (–1.17, 0.10)	0.10
Heart disease	20 (1571)	< 0.001	–0.67 (–0.99, –0.35)	< 0.001
Stroke	13 (1228)	< 0.001	–0.80 (–1.04, –0.56)	< 0.001
Hypertension	4 (414)	0.006	–0.83 (–1.25, –0.41)	< 0.001
Atherosclerosis	3 (210)	0.11	–0.73 (–1.15, –0.32)	0.001
Low dose (4 mL)	4 (282)	0.31	–0.95 (–1.23, –0.68)	< 0.001
High dose (6 mL)	48 (3925)	< 0.001	–0.68 (–0.87, –0.49)	< 0.001
Short duration (1-2 weeks)	34 (2884)	< 0.001	–0.73 (–0.94, –0.52)	< 0.001
Medium duration (3-4 weeks)	14 (1030)	< 0.001	–0.66 (–1.13, –0.19)	0.006
Long duration (> 4 weeks)	5 (483)	0.053	–0.44 (–0.72, –0.16)	0.002
TC				
All	54 (4435)	< 0.001	–0.83 (–1.05, –0.60)	< 0.001
Diabetes	13 (899)	< 0.001	–0.98 (–1.57, –0.38)	0.001
Renal disease	10 (805)	< 0.001	–1.05 (–1.91, –0.20)	0.016
Heart disease	20 (1571)	< 0.001	–0.98 (–1.40, –0.57)	< 0.001
Stroke	13 (1228)	0.01	–0.65 (–0.82, –0.48)	< 0.001
Hypertension	4 (414)	0.85	–0.44 (–0.64, –0.25)	< 0.001
Atherosclerosis	3 (210)	0.01	–1.67 (–2.36, –0.99)	< 0.001
Low dose (4 mL)	4 (282)	0.007	–0.92 (–1.43, –0.41)	< 0.001
High dose (6 mL)	49 (3963)	< 0.001	–0.84 (–1.08, –0.60)	< 0.001
Short duration (1-2 weeks)	35 (2922)	< 0.001	–0.64 (–0.86, –0.42)	< 0.001
Medium duration (3-4 weeks)	14 (1030)	< 0.001	–1.26 (–1.96, –0.56)	< 0.001
Long duration (> 4 weeks)	5 (483)	< 0.001	–0.99 (–1.47, –0.51)	< 0.001
LDL-C				
All	36 (2910)	< 0.001	–0.82 (–1.05, –0.58)	< 0.001
Diabetes	6 (408)	< 0.001	–1.08 (–1.84, –0.31)	0.006
Heart disease	17 (1223)	< 0.001	–0.88 (–1.15, –0.61)	< 0.001
Stroke	10 (937)	< 0.001	–0.71 (–0.99, –0.43)	< 0.001
Hypertension	4 (414)	0.45	–0.59 (–0.79, –0.39)	< 0.001
Atherosclerosis	3 (210)	< 0.001	–1.40 (–4.95, 2.15)	0.44
High dose (6 mL)	36 (2910)	< 0.001	–0.82 (–1.05, –0.58)	< 0.001
Short duration (1-2 weeks)	28 (2295)	< 0.001	–0.69 (–0.86, –0.51)	< 0.001
Medium duration (3-4 weeks)	6 (476)	< 0.001	–1.35 (–2.67, –0.02)	0.046
HDL-C				
All	32 (2532)	< 0.001	0.33 (0.13, 0.53)	0.001
Diabetes	6 (412)	0.08	0.43 (0.14, 0.71)	0.003
Heart disease	17 (1223)	< 0.001	0.17 (–0.16, 0.49)	0.31
Stroke	9 (827)	< 0.001	0.61 (0.34, 0.88)	< 0.001
Atherosclerosis	3 (210)	< 0.001	0.34 (–0.50, 1.19)	0.43
High dose (6 mL)	32 (2532)	< 0.001	0.33 (0.13, 0.53)	0.001
Short duration (1-2 weeks)	24 (1913)	< 0.001	0.42 (0.26, 0.57)	< 0.001
Medium duration (3-4 weeks)	5 (356)	< 0.001	–0.21 (–1.47, 1.05)	0.74
Long duration (> 4 weeks)	3 (263)	0.01	0.36 (–0.16, 0.89)	0.17

SMD, standardized mean difference; 95% CI, 95% confidence interval; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

while the results of the pooled meta-analysis were not altered significantly except the association of Shuxuening injection with HDL-C, which became insignificant when the outlier studies were excluded (SMD = 0.05 mmol/L, 95% CI = −0.17 to 0.27 mmol/L, $P_{\text{Heterogeneity}} = 0.99$, $P_{\text{SMD}} = 0.68$).

Publication Bias

Publication bias was observed in the association analysis between Shuxuening injection and TG or TC, and between Shuxuetong injection and TG, TC or LDL-C. However, no significant changes were found for all after adjustment by trim-and-fill method.

Discussion

As clinical therapeutic drugs, traditional Chinese medicine injections are subject to strict supervision by China Food and Drug Administration (CFDA). CFDA has a set of strict guidelines for traditional Chinese medicine injections such as new drug approval process, adverse drug reaction monitoring and drug instruction supervision. In the process of clinical use, the government and relevant functional departments will follow up on safety, efficacy, rational drug use and combined drug use. Danshen and Fufang Danshen injections in the present meta-analysis were mainly made by Chiatai Qingchunbao Pharmaceutical Co., Ltd., Hangzhou, China. The national medicine permission number (NMPN) of Danshen is Z33020176, and its national quality standard is 1.5 g of Danshen per mL. Fufang Danshen's NMPN is Z33020055, and its national quality standard is 1 g each of Danshen and Jiangxiang per mL. Shuxuening injection (NMPN Z23022004) was mainly made by Hei Long Jiang ZBD Pharmaceutical Co., Ltd., Hulin, China, and its national quality standard is 4.2 mg of total flavonol glycosides and 0.30 mg ginkgolide A per 5 mL. Shuxuetong injection (NMPN Z20010100) was mainly made by Mudanjiang Youbo Pharmaceutical Co., Ltd., Mudanjiang, China, and its national quality standard is ≥ 12 mg total solids per mL.

A large number of clinical studies have explored the lipid-lowering effect of Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections. Associations of the four injections with decreased levels of TG, TC and LDL-C, and/or increased level of HDL-C have been reported in some, but not all studies. Two research teams respectively from Traditional Mongolia Medicine Hospital of Ar Horqin Banner and Xiangzhou District People's Hospital of Xiangyang used Danshen injection to treat patients with angina pectoris for 8 weeks, and all blood lipid indexes significantly decreased by about 40% (Wang 2013; Chen 2015). Other researchers observed similar or even better lipid-lowering effect when using Danshen, Shuxuening and Shuxuetong injections to treat patients with angina pectoris, cerebral infarction or hyperlipidemia (Xie and Yang 2004; Pu 2009: Zhou 2017; Liu and Wang 2021). However, several studies demonstrated that these injections had a poor lipid-lowering ability in patients with coronary artery disease or early onset severe preeclampsia, and the differences did not reach a significant level (Gong 2011; Tong et al. 2012; He et al. 2014). A lack of consistency in lipid-lowering effects reflects some limitations in these studies such as small sample size and differences in disease type, dose and duration of treatment. The present meta-analysis was conducted to clarify the overall lipid-lowering effect of these injections under various conditions. To our knowledge, this is the first meta-analysis to explore the lipid-lowering effect of the four injections based on well-designed clinical studies.

The results of this meta-analysis suggested that all of the four injections can effectively and significantly decrease serum levels of TG, TC and LDL-C, and increase HDL-C level in the whole population. In subgroup analyses, it was found that different injections have different lipid-lowering effects on different disease types. Danshen, Fufang Danshen and Shuxuening injections all showed a good lipid-lowering effect on patients with heart disease, but the lipid-lowering effect of Shuxuetong injection on these patients was uncertain; the increase in HDL-C after treatment did not reach a significant level. On the other hand, the lipid-lowering effects of Danshen, Fufang Danshen and Shuxuening injections on patients with diabetes are not so well, while Shuxuetong injection has a very good effect on reducing blood lipids among these patients, and all lipid parameters have been significantly improved after treatment. In terms of lipid-lowering effect, all of these injections may not be suitable for patients with renal disease as they are unable to effectively and significantly reduce blood lipid levels among such patients. This meta-analysis showed a dose- and time-dependent relationship in the lipid-lowering effect of Danshen and Shuxuening injections, which can guide clinical doctors to choose different doses and treatment courses for different patients.

None of the included studies in the present meta-analysis mentioned toxicology of Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections. However, some side effects of the injections have been pointed out, e.g., nausea, vomiting, skin itching, edema and headache caused by Danshen injection (Xu et al. 2010; Weng and Han 2012); nausea, rash, dizziness, chest tightness and cough caused by Fufang Danshen injection (Li 2012; Pan 2020); allergic reaction, diarrhea, dizziness and gastrointestinal discomfort caused by Shuxuening injection (Yang and Xie 2014; Qu et al. 2023). Shuxuetong injection has a good safety record. Since its launch for more than 10 years, it has been used in a total of over 100 million doses and in over 10 million cases. By tracking and searching in the database of the National Adverse Drug Reaction Monitoring Center, only a few patients experienced side effects such as allergies and fever, and there were no reports of serious adverse reactions (Wang and Zhang 2012). Generally, special treatments are not required for all of these side effects which will disappear on their own within 2-4 days after discontinuation of

the medication (Dong and Dong 2016; Gong and Shang 2023). Some rare and severe adverse reactions have also been reported, e.g., anaphylactic shock and difficulty in breathing caused by Shuxuening injection and Fufang Danshen (Song et al. 2009; Yang et al. 2013).

The mechanisms by which Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections lower serum lipid levels have not been clarified yet. However, several studies (Zhang et al. 2003; Li et al. 2013; Wang et al. 2022) have made some preliminary explorations on the mechanisms by which Danshen and Shuxuening injections reduced serum lipid levels. Wang et al. (2022) established a mouse model of hyperlipidemia and found that Danshen injection exerts a lipid-lowering effect by upregulating the expression of the genes related to cholesterol conversion and excretion such as cytochrome P450 family 7 subfamily A member 1 (CYP7A1) and lecithin-cholesterol acyl transferase (LCAT), as well as downregulating the expression of 3-hydroxy-3-methylglutaryl coenzyme A Reductase (HMGCR), the only rate-limiting enzyme in cholesterol *de novo* synthesis. Li et al. (2013) confirmed this discovery in her doctoral thesis, and found that Danshen extract reduced blood lipids and hepatic lipid content by upregulating the expression of CYP7A1 and low-density lipoprotein receptor (LDLR), and downregulating the expression of HMGCR in a rat model of hyperlipidemia. The main component of Shuxuening injection is Ginkgo biloba extract. Zhang et al. (2003) found that Ginkgo biloba extract can increase transformation and excretion of cholesterol by modulating the composition of gut microbiota.

Significant heterogeneity was detected in the overall analysis for all injections and lipid indexes. Subgroup analyses stratified by disease type, dose and duration of treatment were performed to explore the potential sources of the observed heterogeneity, and the results showed that disease type, dose and duration are all responsible for the heterogeneity. Galbraith plots were drawn to figure out the studies which produced heterogeneity. The heterogeneity was effectively removed or decreased after excluding the outlier studies, and no significant changes in SMD values and 95% CIs were found after excluding the outlier studies except the association between Shuxuening injection and HDL-C, which became insignificant when the outlier studies were excluded. It suggests that the significant relationship between Shuxuening injection and HDL-C may be due to the extensive heterogeneity among studies. The results from this meta-analysis were based on the random effects model. Comparing with the fixed effects model, the random effects model is a more conservative method and less likely to produce false-positive results.

Several limitations should be acknowledged in this meta-analysis. Firstly, all of the included studies used an A versus A + B design in which each patient was randomly assigned a control treatment or a control treatment plus an experimental treatment. This kind of design is likely to generate false positive results (Yu et al. 2018). However, it was not possible to find better designed trials to evaluate the lipid-lowering effect of Danshen, Fufang Danshen, Shuxuening or Shuxuetong injection. Secondly, this meta-analysis only included the studies published in Chinese, and all of the subjects were exclusively Chinese people as there were no studies being conducted outside of China so far. Due to this limitation, the results of this study may only apply to Chinese populations, but cannot be extended to populations elsewhere.

Conclusions

In summary, the present meta-analysis demonstrated that Danshen, Fufang Danshen, Shuxuening and Shuxuetong injections all can effectively reduce blood lipids. Among them, Shuxuening injection has the strongest lipid-lowering effect, almost twice that of the other three injections. In addition, the lipid-lowering effect of these injections is influenced by the type of disease, Danshen, Fufang Danshen and Shuxuening injections are suitable for patients with cardiovascular disease, Shuxuetong injection is suitable for patients with diabetes, but none of them is suitable for patients with renal disease.

Author Contributions

Song, Y.Y., Zhang, Y.J. and Yang, J. conceived of the systematic review and meta-analysis, participated in the design, analyzed the data, and drafted the manuscript. Pang, Q.Y., Lv, Z.M., Zhu, D. and Wang, Y.H. carried out the literature searches, collected the data, and revised the manuscript critically for important intellectual content.

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Conflict of Interest

The authors declare no conflict of interest.

References

Alanaeme, C.J., Bittner, V., Brown, T.M., Colantonio, L.D., Dhalwani, N., Jones, J., Kalich, B., Exter, J., Jackson, E.A., Levitan, E.B., Poudel, B., Wang, Z., Woodward, M., Muntner, P. & Rosenson, R.S. (2022) Estimated number and percentage of US adults with atherosclerotic cardiovascular disease recommended add-on lipid-lowering therapy by the 2018 AHA/ACC multi-society cholesterol guideline. *Am. Heart J. Plus*, **21**, 100201.

Bian, F., Kang, S., Cui, H., Wang, F. & Luan, T. (2021) The clinical efficacy of compound Danshen injection on acute cerebral infarction and on the changes in the CRP, D-dimer, and IL-6 levels. *Am. J. Transl. Res.*, **13**, 8126-8133.

Brown, B.G., Stukovsky, K.H. & Zhao, X.Q. (2006) Simultaneous low-density lipoprotein-C lowering and high-density lipoprotein-C elevation for optimum cardiovascular disease prevention with various drug classes, and their combinations: a meta-analysis of 23 randomized lipid trials. *Curr. Opin. Lipidol.*,

17, 631-636.

Chai, S.W., Ge, M.L., Wu, M.X. & He, J. (2023) Study on UPLC fingerprint and content determination of 5 nucleosides in Shuxuetong Injection. *Tianjin Journal of Traditional Chinese Medicine*, **40**, 364-370. doi: 10.11656/j.issn.1672-1519.2023.03.15.

Chen, H. & Chen, X. (2023) PCSK9 inhibitors for acute coronary syndrome: the era of early implementation. *Front. Cardiovasc. Med.*, **10**, 1138787.

Chen, L.J. (2015) Evaluation of the effect of Danshen injection on treating angina pectoris. *Modern Diagnosis and Treatment*, **26**, 3868-3869. doi: CNKI: SUN: XDZD.0.2015-17-020.

Dong, C.P. & Dong, H. (2016) Analysis on the clinical safety of Shuxuetong injection. *Zhong Wai Yi XueYan Jiu*, **14**, 125-126. doi: 10.14033/j.cnki.cfmr.2016.33.067.

Fan, G., Liu, M., Liu, J., Chen, X. & Huang, Y. (2022) Systematic Review of the Efficacy and Safety of Shuxuening Injection in the Treatment of Unstable Angina. *Evid. Based Complement. Alternat. Med.*, **2022**, 6650763.

Galema-Boers, A.M.H., Mulder, J., Steward, K. & Roeters van Lennep, J.E. (2023) Sex differences in efficacy and safety of PCSK9 monoclonal antibodies: A real-world registry. *Atherosclerosis*, **384**, 117108.

Geng, Q.X., Zhu, X.L. & Zhang, X.H. (2004) Effect of combined therapy of shenmai and compound danshen injection on myocardial reperfusion injury after percutaneous coronary intervention in patients with acute myocardial infarction. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, **24**, 496-499.

Gong, T. & Shang, B. (2023) Reasonability and safety evaluation in the use of Shuxuening injection. *Hai Jun Yi Xue Za Zhi*, **44**, 524-526. doi: 10.3969/j.issn.1009-0754.2023.05.023.

Gong, Y.X. (2011) Clinical efficacy of Danshen injection in the treatment of acute coronary syndrome. *Lin Chuang He Li Yong Yao Za Zhi*, **4**, 44-45. doi: 10.15887/j.cnki.13-1389/r.2011.27.006.

Grundy, S.M., Stone, N.J., Bailey, A.L., Beam, C., Birtcher, K.K., Blumenthal, R.S., Braun, L.T., de Ferranti, S., Faiella-Tommasino, J., Forman, D.E., Goldberg, R., Heidenreich, P.A., Hlatky, M.A., Jones, D.W., Lloyd-Jones, D., et al. (2019) 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, **139**, e1082-e1143.

Guo, J.N., Bai, X., Zhang, H.X., Zhang, N., Liang, J.M., Guo, Z.Y. & Cui, X. (2022) Efficacy and safety of Chinese herbal medicine for pneumonia convalescence in children: A systematic review and meta-analysis. *Front. Pharmacol.*, **13**, 956736.

He, X.Y., Zheng, F.S. & Huang, J.Y. (2014) Clinical observation of Shuxuening injection combined with Rosuvastatin on unstable angina. *Zhong Guo Xian Dai Ying Yong Yao Xue*, **31**, 606-609. doi: 10.13748/j.cnki.issn1007-7693.2014.05.024.

Ho, W.Y., Yen, C.L., Lee, C.C., Tu, Y.R., Chen, C.Y., Hsiao, C.C., Chu, P.H., Hsu, H.H., Tian, Y.C. & Chang, C.H. (2022) Use of fibrates is not associated with reduced risks of mortality or cardiovascular events among ESRD patients: A national cohort study. *Front. Cardiovasc. Med.*, **9**, 907539.

Huang, S.Y., Cui, H.S., Lyu, M.S., Huang, G.R., Hou, D. & Yu, M.X. (2022) Efficacy of traditional Chinese medicine injections for treating idiopathic pulmonary fibrosis: A systematic review and network meta-analysis. *PLoS One*, **17**, e0272047.

Huang, X.F., Wang, J.M., Chen, Q., Wei, Y.Y. & Chen, H.W. (2015) Meta-analysis on effect of compound Danshen injection in treating neonatal hypoxic-ischemic encephalopathy. *Zhongguo Zhong Yao Za Zhi*, **40**, 141-148.

Iatan, I., Mancini, G.B.J., Yeoh, E. & Hegele, R.A. (2023) Statin associated muscle symptoms (SAMS): strategies for prevention, assessment and management. *Expert Rev. Cardiovasc. Ther.*, **21**, 423-435.

Jiang, J.J., Xie, Y.M., Zhang, Y., Zhang, Y.K., Wang, Z.M. & Han, B. (2016) Clinical medication characteristics of Shuxuening injection in treatment of cerebral infarction research based on registration. *Zhongguo Zhong Yao Za Zhi*, **41**, 4516-4520.

Li, C.M., Dong, X.L., Fan, X.D., Wu, J.H., Wang, Q.H., Tian, X.L., Guo, D.J., Wong, M.S., Qiu, T.Q. & Chan, S.W. (2013) Aqueous extract of danshen (Salvia miltiorrhiza Bunge) protects ovariectomized rats fed with high-fat diet from endothelial dysfunction. *Menopause*, **20**, 100-109.

Li, H.Q., Wei, J.J., Xia, W., Li, J.H., Liu, A.J., Yin, S.B., Wang, C., Song, L., Wang, Y., Zheng, G.Q. & Fan, J.P. (2015) Promoting blood circulation for removing blood stasis therapy for acute intracerebral hemorrhage: a systematic review and meta-analysis. *Acta. Pharmacol. Sin.*, **36**, 659-675.

Li, L.D., Zhou, Y. & Shi, S.F. (2023a) Edaravone combined with Shuxuening versus edaravone alone in the treatment of acute cerebral infarction: A systematic review and meta-analysis. *Medicine* (*Baltimore*), **102**, e32929.

Li, M., Li, H., Liu, H., Lai, X. & Xing, W. (2022a) Efficacy and safety of eight types Salvia miltiorrhiza injections in the treatment of unstable angina pectoris: A network meta-analysis. *Front. Pharmacol.*, **13**, 972738.

Li, S., He, C., Nie, H., Pang, Q., Wang, R., Zeng, Z. & Song, Y. (2022b) G Allele of the rs1801282 Polymorphism in PPAR-gamma Gene Confers an Increased Risk of Obesity and Hypercholesterolemia, While T Allele of the rs3856806 Polymorphism Displays a Protective Role Against Dyslipidemia: A Systematic Review and Meta-Analysis. *Front. Endocrinol.* (*Lausanne*), **13**, 919087.

Li, S., Zhang, Y., Xu, W., Lv, Z., Xu, L., Zhao, Z., Zhu, D. & Song, Y. (2023b) C Allele of the PPARdelta+294T>C Polymorphism Confers a Higher Risk of Hypercholesterolemia, but not Obesity and Insulin Resistance: A Systematic Review and Meta-Analysis. *Horm. Metab. Res.*, **55**, 355-366.

Li, S.Y. (2012) Re-evaluation on safety and efficacy of Xiangdan injection for treating the syndrome of qi deficiency and blood stasis. *Zhong Guo Shi Yan Fang Ji Xue Za Zhi*, **18**, 318-320. doi: 10.13422/j.cnki.syfjx.2012.21.050.

Liu, Y., Huang, Y., Zhao, C., Qin, X., Zhu, Q., Chen, S. & Qu, J. (2014) Salvia miltiorrhiza injection on pulmonary heart disease: a systematic review and meta-analysis. *Am. J. Chin. Med.*, **42**, 1315-1331.

Liu, Y. & Wang, J. (2021) Effect of rosuvastatin calcium tablets combined with Shuxuetong injection on blood lipid indexes and inflammatory factor levels in elderly patients with acute cerebral infarction. *Lin Chuang Yi Xue Yan Jiu Yu Shi Jian*, **6**, 67-69. doi: 10.19347/j.cnki.2096-1413.202136021.

National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2002) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*, **106**, 3143-3421.

O'Donnell, M.J., Chin, S.L., Rangarajan, S., Xavier, D., Liu, L., Zhang, H., Rao-Melacini, P., Zhang, X., Pais, P., Agapay, S., Lopez-Jaramillo, P., Damasceno, A., Langhorne, P., McQueen, M.J., Rosengren, A., et al. (2016) Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet*, **388**, 761-775.

Pál, E., Ungvari, Z., Benyo, Z. & Varbiro, S. (2023) Role of Vitamin D Deficiency in the Pathogenesis of Cardiovascular and Cerebrovascular Diseases. *Nutrients*, **15**, 334.

Pan, E. (2020) Safety evaluation and clinical rational use of Xiangdan injection. *Zhong Xi Yi Jie He Xin Xue Guan Bing Dian Zi Za Zhi*, **8**, 165-166. doi: 10.16282/j.cnki.cn11-9336/r.2020.17.125.

Pu, K.J. (2009) Clinical observation of Xiangdan injection

combined with Lovastatin in the treatment of impaired glucose tolerance with Dyslipidemia. *Lin Chuang He Li Yong Yao Za Zhi*, **2**, 46- 47. doi: 10.15887/j.cnki.13-1389/r.2009.22.069.

Qu, Y., Ma, X.J., Li, Q.H., Li, H.L., Zhao, X.C., Sun, X.H., Zhang, M. & Chen, H. (2023) Intensive hospital monitoring study on safety of 9735 cases of Shuxuening injection. *Zhong Cao Yao*, **54**, 3253-3260. doi: 10.7501/j.issn.0253-2670.2023.10.022.

Ren, P., Cao, L., Zhao, X.K., Zhu, B.B. & Liu, K. (2022) Network Meta-analysis of Chinese medicine injections in treatment of hypertensive intracerebral hemorrhage. *Zhongguo Zhong Yao Za Zhi*, **47**, 3637-3647.

Shao, H., Li, M., Chen, F., Chen, L., Jiang, Z. & Zhao, L. (2018) The Efficacy of Danshen Injection as Adjunctive Therapy in Treating Angina Pectoris: A Systematic Review and Meta-Analysis. *Heart Lung Circ.*, **27**, 433-442.

Shen, H., Zhou, P., Shen, L., Ju, C., Du, H. & Qu, X. (2022) Effectiveness and safety of selected traditional Chinese medicine injections in patients with combined diabetes mellitus and coronary heart disease: A systematic review and network meta-analysis of randomized clinical trials. *Front. Pharmacol.*, **13**, 1060956.

Song, L.G., Wang, Q. & Bai, H.P. (2009) Safety evaluation and rational use of Xiangdan injection. *Zhong Guo Shi Ping Yao Ping Jian Guan*, **12**, 72-73. doi: CNKI: SUN: YPJD.0.2009-06-043.

Su, M., Jia, A., He, Y. & Song, Y. (2021) Associations of the Polymorphisms in ADIPOQ with Circulating Levels of Adiponectin and Lipids: A Meta-Analysis. *Horm. Metab. Res.*, **53**, 541-561.

Tan, D., Wu, J., Liu, S., Zhang, D., Cui, Y., Zhang, X. & Zhang, B. (2018) Injections of ginkgo in the treatment of cerebral infarction: a systematic review and network Meta-analysis. *J. Tradit. Chin. Med.*, **38**, 1-11.

Tong, C.X., Xing, X.F. & Qiao, S.H. (2012) Clinical effectiveness assessment of compound danshen injection on early onset severe preeclampsia patients. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, **32**, 482-485. doi: CNKI: SUN: ZZXJ.0.2012-04-018.

Tsao, C.W., Aday, A.W., Almarzooq, Z.I., Anderson, C.A.M., Arora, P., Avery, C.L., Baker-Smith, C.M., Beaton, A.Z., Boehme, A.K., Buxton, A.E., Commodore-Mensah, Y., Elkind, M.S.V., Evenson, K.R., Eze-Nliam, C., Fugar, S., et al. (2023) Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation*, **147**, e93-e621.

Tsu, L.V., Carroll, K., Kindler, K. & Early, N. (2021) Pharmacological Management of Hyperlipidemia in Older individuals. *Sr. Care Pharm.*, **36**, 284-303.

Wang, M. & Zhang, J. (2012) The correlation between the quality process and medication safety of Shuxuetong injection. *Zhong Guo Zhong Yao Za Zhi*, **37**, 2818-2819. doi: 10.4268/cjcmm20121837.

Wang, Y.Q., Guo, W.Q., Liu, X.X., Xiao, H.B., Niu, W.Y. & Li, F.J. (2022) Effect of Danshen injection on lipid metabolism in hyperlipidemia model mice. *Hu Nan Zhong Yi Yao Xue Bao*, **42**, 911-916. doi: 10.3969/j.issn.1674-070X.2022.06.007.

Wang, Z.Q. (2013) Analysis of the therapeutic effect of Danshen injection on 50 cases with angina pectoris. *Da Jia Jian Kang*, **7**, 15. doi: CNKI: SUN: JKXS.0.2013-05-014.

Weng, M.L. & Han, Y. (2012) Safe application of Danshen Injection. *Zhong Guo Shi Yan Fang Ji Xue Za Zhi,* **18**, 322-324. doi: 10.13422/j.cnki.syfjx.2012.22.048.

Wu, S.D., Wang, J., Chen, S.C., Xu, J.B., Zheng, Q., Yan, Y.F., Wen, T.M. & Tang, Y.R. (2004) Effect of Xiangdan Injection on mRNA expression of endothelial vaso-active factors of patients with coronary heart disease and blood stasis. *Zhong Xi Yi Jie He Xue Bao*, **2**, 94-96.

Xie, Y.Q. & Yang, X.S. (2004) Clinical evaluation of Shuxuening injection in the treatment of acute cerebral infarction. *Yi Xue Lin Chuang Yan Jiu*, **21**, 185-187. doi: 10.3969/j.issn.1671-7171.2004.02.035.

Xu, X.M., Lai, S.Z., Tan, B.R., Xu, W.G., Fang, P.S. & Guo, J.Y. (2010) Preliminary safety evaluation of Salvia Miltiorrhiza injection in its clinical application. *Zhong Guo Xian Dai Ying Yong Yao Xue*, **27**, 753-756. doi: CNKI: SUN: XDYD.0.2010-08-029.

Yang, L., Wang, Y.C., Du, X.X., Ren, J.T., Song, H.B. & Liu, X.D. (2013) Post-marketing safety literature analysis and risk control recommendations of Shuxuening injection. *Zhong Guo Yao Wu Jing Jie*, **10**, 553-556. doi: 10.3969/j.issn.1672-8629.2013.09.012.

Yang, W. & Xie, Y.M. (2014) Safety researches and risk minimization action plan of Shu xue ning injection. *Shi Jie Zhong Yi Yao*, **9**, 1128-1132. doi: 10.3969/j.issn.1673-7202.2014.09.005.

Yu, H., Han, M., Lin, W., Wang, L., Liu, P., Yang, K., Pei, M. & Yang, H. (2020) Efficacy of Chinese Herbal Injections for the Treatment of Primary Nephrotic Syndrome: A Bayesian Network Meta-Analysis of Randomized Controlled Trials. *Front. Pharmacol.*, **11**, 579241.

Yu, L., Zhou, C., Luo, Z., Zeng, W., Lai, F., Han, G. & Song, Y. (2018) The lipid-lowering effects of Danhong and Huangqi injections: a meta-analysis of clinical controlled trials. *Lipids Health Dis.*, **17**, 106.

Yu, W., Shen, F. & Ma, Z. (2000) Observation of therapeutic effect of Salviae miltiorrhiza and cytosine diphosphate-choline injection on patients with hypertensive cerebral hemorrhage. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, **20**, 94-96.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J., Lisheng, L. & INTERHEART Study Investigators (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*, **364**, 937-952.

Zhang, L.Y., Wang, X.X. & Yang, J.Y. (2003) New exploration in the mechanism of Ginkgo leaf extract regulating lipid. *Zhong Guo Wei Sheng Tai Xue Za Zhi,* **15**, 342-344. doi: 10.3969/j.issn.1005-376X.2003.06.014.

Zhou, X.F. (2017) Effects of Xiang dan injection combined with Trimetazidine tablets for angina pectoris and influences on the levels of inflammatory factors. *Ji Lin Zhong Yi Yao*, **37**, 788-791. doi: 10.13463/j.cnki.jlzyy.2017.08.009.

Zhou, Z., Chen, H., Shen, Y. & Huang, H. (2022) Chinese Herb Injections in the Adjuvant Treatment for Ulcerative Colitis: A Network Meta-Analysis of Randomized Controlled Trials. *Evid. Based Complement. Alternat. Med.*, **2022**, 3166416.

Zivkovic, S., Maric, G., Cvetinovic, N., Lepojevic-Stefanovic, D. & Bozic Cvijan, B. (2023) Anti-Inflammatory Effects of Lipid-Lowering Drugs and Supplements-A Narrative Review. *Nutrients*, **15**, 1517.