Complementary Therapies in Medicine 43 (2019) 218–226

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

The efficacy of Xue Fu Zhu Yu prescription for hyperlipidemia: A meta-analysis of randomized controlled trials

Sheng Wang[a,b], Xin-jian Qiu[a,*]

[a] Xiangya Hospital, Xiangya Street No.87, Changsha, 410008, China
[b] The Second Clinical Medical College, Zhejiang Chinese Medicine University, Hangzhou, 310053, China

ARTICLE INFO

Keywords:
Hyperlipidemia
Xue Fu Zhu Yu prescription
Meta-analysis

ABSTRACT

Hyperlipidemia is rampant as a crucial risk factor for cardiovascular diseases. Xue Fu Zhu Yu (XFZY), a prescription formula in traditional Chinese medicine, is well-known for treating hyperlipidemia. Herein we conducted meta-analysis and assessed the efficacy of XFZY prescription as mono or adjunctive therapy in patients with hyperlipidemia. Databases including Medline, Cochrane Library, Embase, CNKI, Wanfang Data and VIP Information were comprehensively investigated via searching keywords "Xuefuzhuyu", "Xuefu Zhuyu", "Xue Fu Zhu Yu", "Xuefu-Zhuyu" or "XFZY" in combination with "hyperlipidemia" and "dyslipidemia". Efficacy, methodological quality, and publication bias of recruited trials on XFZY prescription were also assessed. Review Manager version 5.3 software was used for statistical analysis. Twelve trials involving 1305 participants all reported in Chinese were enrolled and, based on our analysis, significant increase of efficacy in XFZY prescription groups compared to control groups was observed, and there was either significance or non-significance of differences in regulating the levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C). This meta-analysis preliminarily demonstrated that XFZY prescription is effective for treating hyperlipidemia, but due to the poor methodological quality of most analyzed trials, conclusion should be cautiously summarized. Thoroughly designed, large-scale and multicenter trials are needed to estimate efficacy and safety of XFZY prescription for hyperlipidemia in the future.

1. Introduction

Hyperlipidemia is featured by hypercholesterolemia, hypertriglyceridemia and mixed hyperlipidemia[1] associated with the escalation of single or multiple lipid components (total cholesterol (TC), triglycerides (TG)) and/or lipoproteins (very low-density lipoproteins (VLDL), low-density lipoprotein cholesterol (LDL-C)), and/or decreased levels of high density lipoprotein cholesterol (HDL-C). It is usually categorized into primary and secondary hyperlipidemia.[2,3] With the elevating incidence and prevalence, hyperlipidemia becomes a global issue for public health. As such, hyperlipidemia is one of the most crucial risk factors for cardiovascular diseases (CVD).[4] It was reported that the newly addressed lipid measures, such as TC/HDL-C, TG/ HDL-C, and LDL-C/HDL-C ratios, are significantly associated with severity of CVD risk.[5]

It is necessary to prevent CVDs with lipid-lowering treatment, and statins is considered as the first choice to date.[6] Statins restrains the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is responsible for cholesterol synthesis.[7] Statins were reported beneficial in reducing the levels of TC and LDL-C.[8] However, those patients suffering from adverse events failed to respond to statins-based treatment.[9,10] Statin-fibrate combination was recommended for hyperlipidemia treatment by the National Cholesterol Education Program Adult Treatment Panel III.[11] However, the clinical benefit of statin-fibrate combination appeared to be limited[12] and raised kidney-related side effects.[13,14]

Xue Fu Zhu Yu (XFZY) prescription, a famous traditional Chinese medicine (TCM) formula, refers to a combination of 11 crude drugs, including Angelica sinensis (Oliv.) Diels (root, Apiaceae), Rehmannia glutinosa (Gaertn.) DC. (root, Plantaginaceae), Prunus persica (L.) Batsch (seed, Rosaceae), Carthamus tinctorius L. (flower, Compositae), Citrus aurantium L. (fruit, Rutaceae), Paeonia veitchii Lynch (root, Paeoniaceae), Bupleurum chinense DC. (root, Apiaceae), Glycyrrhiza uralensis Fisch. (root, Leguminosae), Platycodon grandiflorum (Jacq.) A. DC. (root, Campanulaceae), Ligusticum striatum DC. (root, Apiaceae) and Achyranthes bidentata Blume. (root, Amaranthaceae).

* Corresponding author.
E-mail address: qiuxjxy@126.com (X.-j. Qiu).

https://doi.org/10.1016/j.ctim.2019.02.008
Received 17 March 2018; Received in revised form 12 January 2019; Accepted 7 February 2019
Available online 08 February 2019
0965-2299/

Additionally, hydroxysafflor yellow A, amygdalin, albiflorin, paeoniflorin, liquiritin, ferulic acid, naringin, hesperidin, neohesperidin, naringenin, isoliquiritigenin, glycyrrhizic acid, marmin, senkyunolide A, dehydrosafynol, safynol and ferric acid are reported as effective compounds within XFZY prescription.[15–17] XFZY prescription is originally applied to the treatment of blood-stasis syndrome in the chest for centuries. In recent decades, beneficial effects of XFZY prescription for hyperlipidemia have been confirmed in the forms of decoction, capsule and oral liquid.[18] It has been regularly used alone or in conjunction with hypolipidemic drugs, similar as those prescriptions for treating other TCMs. XFZY prescription functions through multi-targets and pathways. A metabolomics study in rats indicated that XFZY prescription improves global lipid profiles by affecting several metabolic pathways, such as ketone body metabolism, acetyl-glycoprotein metabolism and glutathione biosynthesis.[19] Pharmacological studies suggested the major active constituents such as auraptene, naringin, hesperetin, saponins and ferulic acid demonstrate promising effects on anti-hyperlipidemia, anti-oxidative and anti-inflammatory.[20],[21] Hyperlipidemia with complex pathogenesis is more likely to respond well to those multi-pathway treatments.

It is believed that different dosage forms may induce changes in proportion of active compounds within a formula[22] and then influence its efficacy. Particularly, the potential interactions between TCM and western medicines is an unavoidable safety issue.[23] Here in current meta-analysis, we aimed to assess the efficacy and safety of XFZY prescription including different dosage forms, as mono- or adjunctive therapy in patients with hyperlipidemia.

2. Materials and methods

2.1. Search strategy

We systematically investigated the published reports on randomized controlled trials (RCTs) of XFZY prescription treatments in patients with hyperlipidemia throughout six databases (Medline, Cochrane Library, Embase through Ovid, CNKI, Wan fang Data, and VIP Information) inclusive to June 15, 2017, by searching the terms "Xuefuzhuyu", "Xuefu Zhuyu", "Xue Fu Zhu Yu", "Xuefu-Zhuyu", "XFZY" in combination with "hyperlipidemia", "dyslipidemia". There was no limitation to languages and formulation of XFZY prescription.

2.2. Study selection

Two reviewers (L.L.Z and S.W) independently decided which literature fit the inclusion criteria of the meta-analysis. Inclusion criteria was described as below: (1) the experiments were conducted with randomized and controlled design; (2) hyperlipidemia diagnosis should accomplished based on strict criteria: TC > 5.7 mmol/L and (or) TG > 1.7 mmol/L. (Focus group of prevention and treatment of dyslipidemia, 1997); (3) the experiments should include the comparison of the efficacy of XFZY (monotherapy or concomitant therapy with lipid-lowering drugs) to lipid-lowering drugs or placebo; (4) sample size should be more than 30 in each group, and the therapy duration should be at least 4 weeks; (5) outcomes assessments should include the effective rate based on "Guiding principle of clinical research on cardiovascular drugs (Trial)"[24] or lipid levels (TC, TG, LDL-C and HDL-C).

In addition, the exclusion criteria include: (1) studies involved patients with secondary hyperlipidemia (2) studies which can't be extract the original information.

2.3. Data extraction

Detailed information including the authors, year of publication, methodological information, baseline data of subjects, (age, gender, severity, duration of disease), diagnostic instruments, outcome measurements were independently extracted by two authors, (L.L.Z, S.W). Discrepancies were solved by discussing with a third reviewer. Methodological quality was evaluated primarily by Jadad's validated score[25] which includes the evaluation of randomization, (D. S. Wang), blinding, description of lost cases. In addition, allocation concealment was also assessed.

2.4. Quality appraisal

Methodological quality was evaluated using the Jadad's validated score,[25] and allocation concealment was also assessed by two authors.[26] Disagreements were resolved by discussing with a third reviewer.

2.5. Sensitivity analyses

Sensitivity analyses were performed to examine the robustness of the results. Each of the trials with poor methodological quality (JADAD score ≤ 2) was removed in turn from the analysis to investigate the influence on heterogeneity and the changes of effect size.[27]

2.6. Publication bias

The likelihood of publication bias in this meta-analysis was evaluated by asymmetry funnel plot and examined by Egger's and Begg's test statistic.[28],[29]

2.7. Statistical analysis

Review Manager version 5.3 software (Cochrane Collaboration) and STATA software version 14.0 (STATA Corporation, College Station, TX, US) were employed for statistical analysis. For dichotomous data, risk ratios (RRs) were calculated using mantel-haenszel ((M-H)) method, while for continuous data, weighted mean difference (WMD) were calculated using inverse variance (IV) method, both with 95% confidence interval (95% CI). Heterogeneity was tested by chi-squared test and I squared statistic. A fixed-effect model was applied when statistical homogeneity existed (p value > 0.1 or $I^2 < 50\%$), while a random-effect model was applied when statistical heterogeneity appeared (P value < 0.1 or $I^2 > 50\%$).

3. Results

3.1. Studies selection

A total of 113 studies, including 108 trials reported in Chinese and five trials reported in English, were comprehensively investigated. Amongst 12 studies involving 1305 participants reported in Chinese were recruited. The selection process and exclusion reasons were summarized in Fig. 1. Characteristics of the included studies were detailed in Table 1. The publishing time period ranged from February 2000 to June 2015. The ages of patients ranged from 18 to 80 years, and course of diseases ranged from 5 months to 49 years. Severe diseases and secondary hyperlipidemia were excluded in most of the recruited trials.[30–41]

3.2. Interventions

Patients in four trials[32,33,37,38] employed XFZY prescription in combination of lipid-lowering drugs in the treatment groups, in comparison to lipid-lowering drugs alone for those in control groups. Patients in three trials[31–36,38,40] received XFZY prescription in treatment groups comparing to lipid-lowering drugs in control groups. Patients in four trials[30,34,39,41] used XFZY prescription in treatment groups in contrast to Chinese medicine in control groups. Patients in one trial[40] employed XFZY prescription in the treatment groups comparing to placebo in the control group. The treatment duration ranged from 4 weeks to 12 weeks. Detailed information was summarized in Table 1,

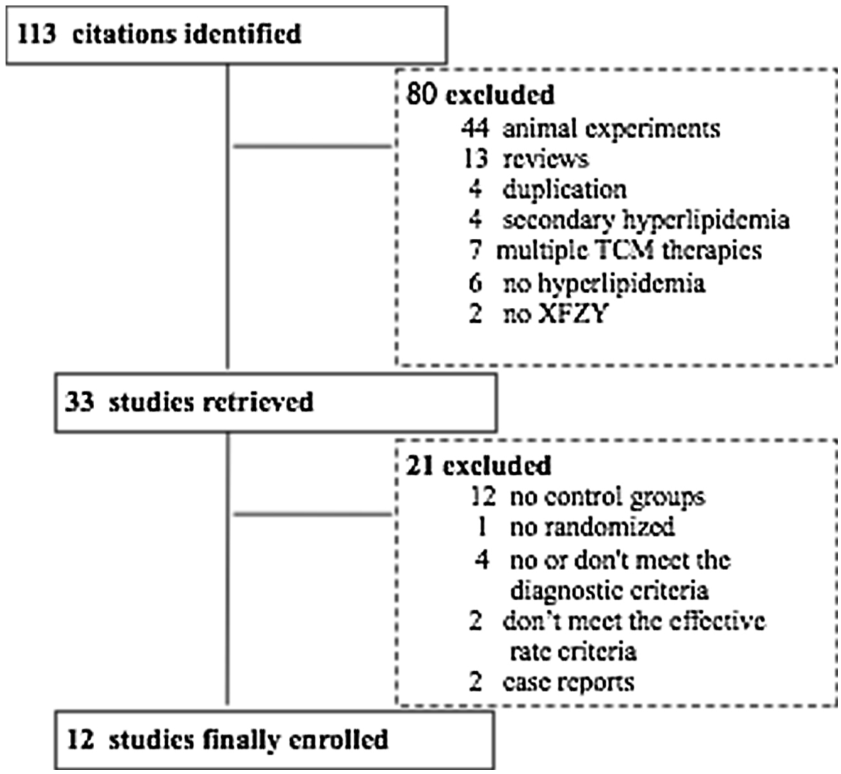

Fig. 1. Studies selection process.

and the ingredients and dosages of the formulas were listed in Table 2. However, none of the included trials reported the authorities and family of the botanical drugs. The voucher specimens were also missing.

3.3. Adverse events

Three trials described the adverse events by XFZY prescription, including the mild gastrointestinal discomfort, fatigue and headache in the treatment groups.[31,33,37] It is noteworthy that among these trials, concomitant therapy with lipid-lowering drugs was utilized in two trials.[33,37] Thus, we could not identify the potential source of adverse events. Two trials stated that there was no adverse event in XFZY prescription group.[30,32] The rest did not describe any information about adverse events potentially due to XFZY prescription.

3.4. Methodological quality

Most of the trials were designed with randomization and included suitable control groups. However, there was no report mentioning the method of sequence generation. Only one trial[40] set up blinding of participants and investigators to treatment allocation. Majority of trials except one[31] stated that there was no significant differences between the treatment and control groups in terms of the backgrounds of participants, including ages, genders and other conditions. No study described the information about the strategy for allocation concealment. One trial[40] described the withdrawal and dropout without defined reason. Multi-center study and data analysis based on FAS (full analysis set) were conducted in one single report[40] (shown in Table 1).

3.5. Outcomes measurements

3.5.1. Effective rate assessments

A total of 11 RCTs compared effective rates between the two random groups after intervention periods. All trials presented significantly increased effective rates in treatment groups, comparing to those in control groups. XFZY prescription were applied in four trials[32,33,37,38] in combination with lipid-lowering drugs and compared with lipid-lowering drugs only (risk ratios 1.18, 95% CI: 1.08–1.28; $Z = 3.93$, $p < 0.0001$), and used XFZY prescription was compared with lipid-lowering drugs in three trails (risk ratios 1.24, 95% CI: 1.11–1.39; $Z = 3.83$, $p = 0.0001$). [30,35,36] XFZY prescription, versus placebo, was employed in one multicenter clinical trial,[40] and the data in four centers were jointly analyzed (risk ratios 1.31, 95% CI: 1.06–1.62; $Z = 2.48$, $p = 0.01$). The fixed-effects model was applied for the statistical evaluation of heterogeneity, and the results were $P = 0.30/I^2 = 18\%$, $P = 0.29/I^2 = 20\%$ and $P = 0.18/I^2 = 39\%$, respectively corresponding to the subgroups mentioned above (Fig. 2.1). Application of XFZY prescription versus Chinese medicine were performed in 3 trials[34,39,41] (risk ratios 1.33, 95% CI: 1.11–1.60; $Z = 3.14$, $p = 0.002$) and we employed the random-effect model (Fig. 2.2) according to the statistical test of heterogeneity ($P = 0.09$, $I^2 = 58\%$).

Results of sensitivity analysis displayed one trial[39] seems to markedly influence the pooled risk ratios. By removing this trial from the analysis, the risk ratios for XFZY prescription versus Chinese medicine was 1.44 (95% CI: 1.25–1.66; $Z = 5.09$, $p < 0.00001$), and heterogeneity was reduced to $P = 0.37$, $I^2 = 0\%$.

3.5.2. Outcome: total cholesterol (TC)

A total of nine RCTs paralleled the efficacy of lowering TC between the two random groups. Both trials revealed that XFZY prescription was significantly more effective than controls in lowering TC. Three trials[33,37,38] exerted XFZY prescription plus lipid-lowering drugs comparing to lipid-lowering drugs (WMD = 0.92, 95% CI: 0.48–1.37; $Z = 4.07$, $p = 0.0003$). XFZY prescription was compared with lipid-lowering drugs in three trials[31,35,36] (WMD = 0.66, 95% CI: 0.22–1.11; $Z = 2.94$, $p = 0.003$), and three trials[31,39,41] reported the application of XFZY prescription in comparison with Chinese medicine (WMD = 1.18, 95% CI: 0.71–1.65; $Z = 4.95$, $p < 0.00001$). We completed the analysis via random-effects model due to the statistical tests of heterogeneity ($P = 0.0003/I^2 = 87\%$, $P = 0.03/I^2 = 71\%$ and $P = 0.002/I^2 = 84\%$,

Table 1
Characteristics of the included 11 RCTs for XFZY prescription in the treatment of hyperlipidemia. XFZYC: Xue Fu Zhu Yu capsule; XFZYT: Xue Fu Zhu Yu Tang; T: treatment group; C: control group.

Study	Sample Size		Age (Years)		Percentage of Men		Therapy Duration	Interventions		Response Definition
	T	C	T	C	T	C		T	C	
Lei (2006)	43	43	62.4 ± 9.4	63.1 ± 8.7	77	72	8w	XFZYT +, simvastatin, 30mg/d	simvastatin 30mg/d	TC,TG,HDL-C,LDL-C effective rate
Zeng (2011)	36	36	57.2 ± 11.5	58.2 ± 10.8	72	75	4w	XFZYT +, simvastatin, 10mg/d	simvastatin 10mg/d	TC,TG,HDL-C,LDL-C effective rate
Qiu (2012)	67	50	46.4 ± 7.1	43.3 ± 9.7	46	46	8w	XFZYT +, simvastatin, 20mg/d	simvastatin 20mg/d	TC,TG,HDL-C, effective rate
Dong (2007)	53	53	52.6 ± 9.3	50.8 ± 12.1	60	57	4w	XFZYT	hexanicit 1.2g/d	TC,TG, effective rate
Zhang (2008)	58	43	55.4 ± 8.3	53.2 ± 9.8	53.4	58	4w	XFZYT	gemfibrozil 0.9g/d	TC,TG,HDL-C effective rate
Xu (2010)	48	48	50 ± 15	52 ± 12	50	50	8w	XFZYC, 4.8g/d	simvastatin10mg/d	TC,TG, effective rate
Xu (2000)	32	30	38-59	38-59			8w	XFZYC, 4.8g/d	Polysaccharide sulfate, 150mg/d	TC, TG
Liu (2003)	43	37	53.0 ± 10.9	51.0 ± 9.0	60	59	8w	XFZYC, 4.8g/d	Zhibituo, 2.16g/d	TC,TG,HDL-C,LDL-C, effective rate
Wang (2009)	82	82	54 ± 11.6	54 ± 11.6	68	68	4w	XFZYT	Xuezhikang 1.2g/d	effective rate
Liu et al. (2010)	60	60	64.5 ± 6.8	65.4 ± 7.2	62	57	12w	XFZYT	Zhibituo, 1.05g/d	TC,TG,HDL-C,LDL-C, effective rate
Xu, -2015	31	31	51.0 ± 5.7	48.5 ± 7.2	48	55	4w	XFZYT +, simvastatin, 20mg/d	simvastatin 20mg/d	effective rate
Zhu et al. (2010), 1	27	33	18-70	18-70			6w	XFZYC, 4.8g/d	placebo 4.8g/d	effective rate
2	31	29	18-70	18-70			6w	XFZYC, 4.8g/d	placebo 4.8g/d	effective rate
3	31	28	18-70	18-70			6w	XFZYC, 4.8g/d	placebo 4.8g/d	effective rate
4	30	30	18-70	18-70			6w	XFZYC, 4.8g/d	placebo 4.8g/d	effective rate

respectively) (Fig. 3).

Sensitivity analysis revealed that two trials[30,39] seemed to significantly influence the pooled WMD. By excluding the trial[30] from analysis, the pooled WMD for XFZY prescription versus chemotherapy was 0.43 (95% CI: 0.11 to 0.75; Z = 2.62, p = 0.009), and the heterogeneity was reduced to P = 0.37, I^2 = 0%. By excluding the trial,[39] the pooled WMD for XFZY prescription versus Chinese medicine was 1.44 (95% CI: 1.36 to 1.52; Z = 35.90, p < 0.00001), and the heterogeneity was reduced to P = 0.96, I^2 = 0%.

3.5.3. Outcome: triglyceride (TG)

A total of nine RCTs were incorporated in the analysis. Amongst three[33,37,38] reported the use of XFZY prescription plus lipid-lowering drugs in contrast to lipid-lowering drugs (WMD = 0.36, 95% CI: 0.15-0.56), showing significant differences between treatment and control groups in TG lowing levels (Z = 3.42, p = 0.0006) under fixed-effects model (P = 0.26, I2 = 27%) (Fig. 4.1). Three trails[31,35,36] stated the comparisons of XFZY prescription versus lipid-lowering drugs (WMD = 0.85, 95% CI: -0.10-1.80), and showed no significant differences in TG lowing levels between treatment and control groups (Z = 1.75, p = 0.08) under random-effect models (P < 0.0001, I2 = 91%) (Fig. 4.2). Three trails[30,39,41] described the comparison between XFZY prescription and Chinese medicine (WMD = 0.39, 95% CI: 0.08-0.69), which showed significant differences in TG lowing levels (Z = 2.48, p = 0.01) under random-effects model (P = 0.001, I2 = 85%) (Fig. 4.2).

Sensitivity analysis indicated that two trials[30,36] seemed to markedly influence the pooled WMD. Not including trial[36] from analysis, the pooled WMD for XFZY prescription versus chemotherapy was 1.27 (95% CI: 0.80 to 1.3; Z = 5.33, p < 0.00001), and the heterogeneity was decreased to P = 0.41, I2 = 0%. By excluding the trial[30] from analysis, the pooled WMD for XFZY prescription versus Chinese medicine was 0.22 (95% CI: 0.18 to 0.27; Z = 9.41, p < 0.00001), and the heterogeneity was reduced to P = 0.72, I2 = 0%.

3.5.4. Outcome: LDL-C

Four RCTs contributed to the analysis. Two trails[33,37] presented the comparisons of XFZY prescription plus lipid-lowering drugs versus lipid-lowering drugs (WMD = 0.60, 95% CI: 0.38-0.82), showing significant differences between treatment and control groups in LDL-C lowing levels (Z = 5.25, p < 0.00001) under fixed-effects model (P = 0.70, I2 = 0%). two trails[39,41] paralleled the XFZY prescription to Chinese medicine (WMD = 0.06, 95% CI: -0.02-0.15), and presented no significant differences in LDL-C lowing levels (Z = 1.43, p = 0.15) within the fixed-effects model (P = 0.57, I2 = 0%) (Fig. 5).

3.5.5. Outcome: HDL-C

Six RCTs were applied to the analysis. Three RCTs[33,37,38] listed the comparisons of XFZY prescription plus lipid-lowering drugs to lipid-lowering drugs (WMD = 0.13, 95% CI: -0.05-0.31) and exhibited no significance between treatment and control groups in regulation of HDL-C levels (Z = 1.37, p = 0.17) based on random-effects model (p = 0.03, I2 = 73%). One single trail[35] stated the comparison of XFZY prescription with lipid-lowering drugs (WMD = 0.24, 95% CI: 0.13-0.35), which presented significant differences between treatment and control group in HDL-C level regulation (Z = 4.28, p < 0.0001). Two trials[39,41] compared the XFZY prescription to Chinese medicine (WMD = 0.26, 95% CI: -0.05-0.57) and showed no significant differences in HDL-C level regulation (Z = 1.63, p = 0.10) under random-effects model (p = 0.0003, I2 = 93%) (Fig. 6).

Sensitivity analysis revealed that one trial[37] appeared to markedly influence the pooled WMD. By removing the trial from the analysis, pooled WMD for XFZY prescription plus chemotherapy versus chemotherapy was 0.03 (95% CI: -0.10 to 0.16; Z = 0.46, p = 0.64), and the heterogeneity was reduced to P = 0.83, I2 = 0%.

Table 2
The key herbal composition of XFZY prescription.

Study	Formulation	Dose	Botanical Material Rating*	Major Herbal Composition
Lei (2006)	Decoction	1 dose/d	C	Angelica sinensis (Oliv.) Diels 10g, Ligusticum striatum DC. 10 g, Rehmannia glutinosa (Gaertn.) DC. 10g, Prunus persica (L.) Batsch 10g, Carthamus tinctorius L 6g, Citrus aurantium L 12g, Paeonia veitchii Lynch 12g, Bupleurum chinense DC 10g, Glycyrrhiza uralensis Fisch 6g, Platycodon grandiflorum (Jacq.) A. DC 6 g, Achyranthes bidentata Blume. 15g
Zeng (2011)	Decoction	1 dose/d	C	Astragalus membranaceus (Fisch.) Bunge 15g, Prunus persica (L.) Batsch 10g, Carthamus tinctorius L 10g, Angelica sinensis (Oliv.) Diels 10 g, Rehmannia glutinosa (Gaertn.) DC. 10g, Ligusticum striatum DC. 10g, Paeonia veitchii Lynch 10g, Achyranthes bidentata Blume 15g, Platycodon grandiflorum (Jacq.) A. DC 15g, Bupleurum chinense DC 10g, Citrus aurantium L 10g, Alisma orientale (Sam.) Juz. 10g, Pinellia ternata (Thunb.) Ten. ex Breitenb. 10g, Glycyrrhiza uralensis Fisch. 6g
Qiu (2012)	Decoction	1 dose/d	C	Prunus persica (L.) Batsch 10g, Carthamus tinctorius L 10g, Paeonia veitchii Lynch 10g, Bupleurum chinense DC 10g, Ligusticum striatum DC. (root, Apiaceae) 10g, Achyranthes bidentata Blume. 10g, Crataegus pinnatifida Bunge 10g, Rehmannia glutinosa (Gaertn.) DC 10g, Ligusticum striatum DC. 10g, Citrus aurantium L 10g, Glycyrrhiza uralensis Fisch 10g, Platycodon grandiflorum (Jacq.) A. DC 10g
Dong (2007)	Decoction	1 dose/d	C	Prunus persica (L.) Batsch 15g, Angelica sinensis (Oliv.) Diels
Zhang (2008)	Decoction	1 dose/d	C	Prunus persica (L.) Batsch 10g, Carthamus tinctorius L 5g, Angelica sinensis (Oliv.) Diels 10g, Citrus aurantium L 10g Achyranthes bidentata Blume 10g Ligusticum striatum DC. 10g Bupleurum chinense DC 10g, Platycodon grandiflorum (Jacq.) A. DC 10g Rehmannia glutinosa (Gaertn.) DC. 15g Cassia obtusifolia L.15g Crataegus pinnatifida Bunge 15g, Salvia miltiorrhiza Bunge 15g Nelumbo nucifera Gaertn. 10g, Glycyrrhiza uralensis Fisch 3g
Xu (2010)	capsule, Tianjin Hong Ren Tang Pharmaceutical Co., Ltd. Batch no. 081025	4.8g/d	A	Standardized
Xu (2000)	Capsule	4.8g/d	C	Standardized
Liu (2003)	Capsule	4.8g/d	C	Standardized
Wang (2009)	Decoction	NR	C	Prunus persica (L.) Batsch, Carthamus tinctorius L, Angelica sinensis (Oliv.) Diels, Rehmannia glutinosa (Gaertn.) DC. Ligusticum striatum DC. Paeonia veitchii Lynch, Platycodon grandiflorum (Jacq.) A. DC, Bupleurum chinense DC, Glycyrrhiza uralensis Fisch
Liu et al. (2010)	Decoction	1 dose/d	C	Angelica sinensis (Oliv.) Diels 10g, Ligusticum striatum DC. 10 g, Rehmannia glutinosa (Gaertn.) DC. 10g, Prunus persica (L.) Batsch 10g, Carthamus tinctorius L 6g, Prunus persica (L.) Batsch 10g, Carthamus tinctorius L 6g,Citrus aurantium L 12g, Achyranthes bidentata Blume 12g, Bupleurum chinense DC 10g, Glycyrrhiza uralensis Fisch 6g, Platycodon grandiflorum (Jacq.) A. DC, 6g, Paeonia veitchii Lynch 15g
Xu-2015	Decoction	1 dose/d	C	Prunus persica (L.) Batsch 12g, Angelica sinensis (Oliv.) Diels 10g, Carthamus tinctorius L 9g, Rehmannia glutinosa (Gaertn.) DC 15g, Bupleurum chinense DC 10g, Citrus aurantium L 10g, Ligusticum striatum DC. 10g, Paeonia veitchii Lynch 10g, Platycodon grandiflorum (Jacq.) A. DC 10g, Glycyrrhiza uralensis Fisch. 6g, Achyranthes bidentata Blume 15g
Zhu et al. (2010)	Capsule	4.8g/d	A	Standardized

* A, Full information about the botanical material is provided including a voucher specimen; B, Only partial information about the botanical material is provided, but a voucher specimen is missing and there are taxonomic inaccuracies; C, Inadequate information and overall taxonomicically inadequate.

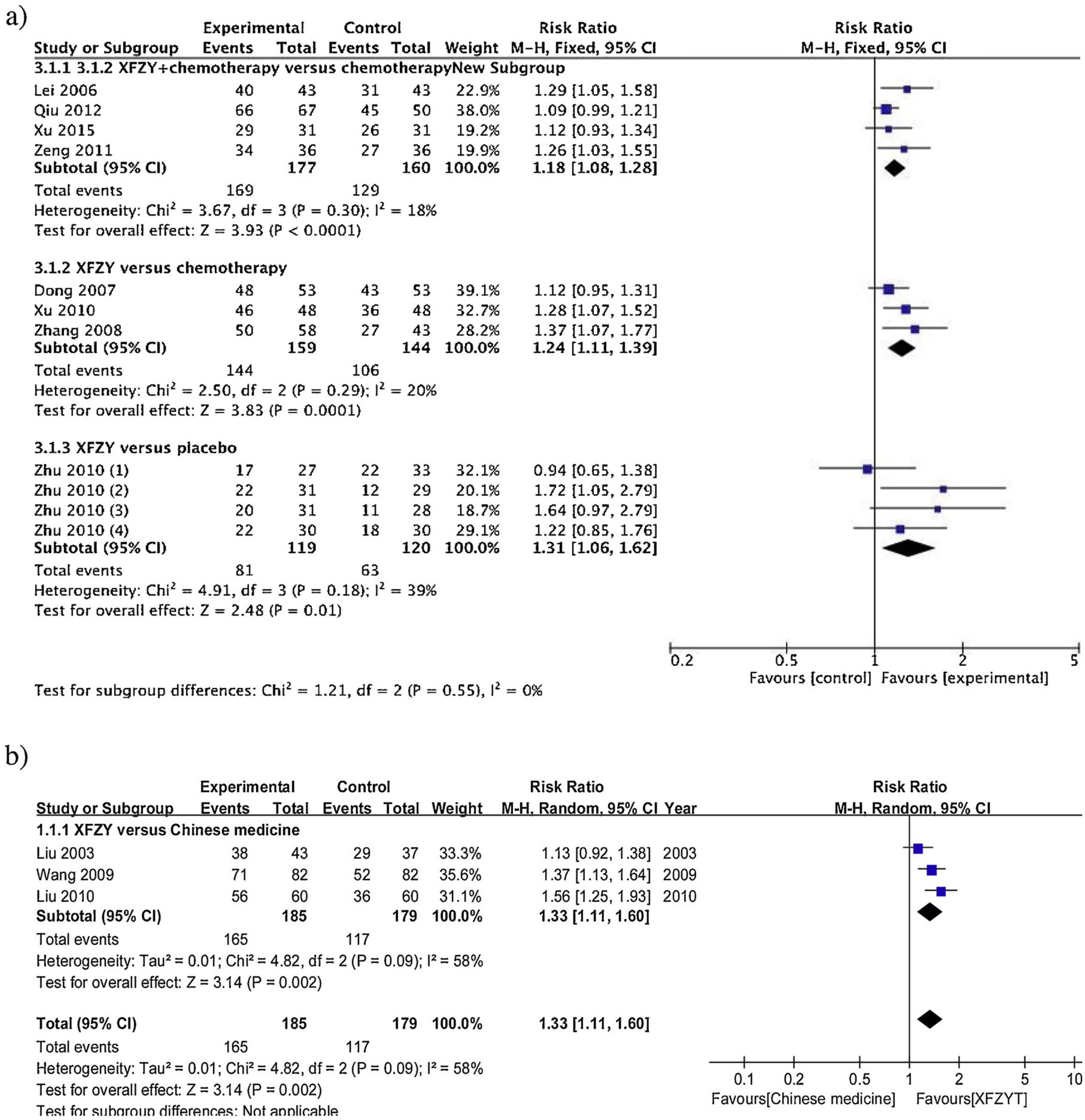

Fig. 2. (1) Comparison of the effective rate between treatment groups and control groups under fixed effects model. (2) Comparison of the effective rate between treatment groups and control groups under random effects model.

3.6. Publication bias

Funnel plots (Fig. 7) based on the effect rates exhibited asymmetrical distribution, indicating that parameters including random assignment of patients to treatment groups, concealment of randomization and blinding to investigators, patients, or outcome assessors may present publication bias. The Egger's test (P = 0.049) also indicated obvious publication bias, although there is no significant indication from Begg's test (p = 0.101).

4. Discussion

Our current meta-analysis examined the efficacy of XFZY prescription on patients with hyperlipidemia. Distinct from previous meta-analysis by Liao et al.[42] which was based on different dosage forms of XFZY prescription, such as decoction, capsule and oral liquid, we re-defined the inclusion criteria and exclusion criteria to recruit a greater diversity of patient groups such as Chinese medicines as control medicine. We further extended time period of publication for investigated literature to June 15, 2017, and performed a sensitivity analysis to explore the influence of trial quality on the effect size. Similarly, we assessed the outcomes including effective rates or lipid levels (TC, TG, LDL-C and HDL-C).

Our results indicated that XFZY prescription, serving as either monotherapy or concomitant therapy with lipid-lowering drugs, functioned with higher effective rates than that of the control groups (Fig. 2). In terms of regulating lipid levels, especially TC and LDL-C lowing, the efficacy of XFZY prescription was significantly more effective than the control medicine (Figs. 3 and 5). In regulating TG, it was consistent with finding of previous research[35,36] that the efficacy of XFZY prescription was no significantly different from that of lipid-lowering drugs, however, XFZY prescription combined with lipid-lowering drugs functioned with higher effective rates compared with lipid-lowering drugs alone (Fig. 4.1 and 4.2). Although effectiveness of the comparison of XFZY prescription with lipid-lowering drugs was higher than that of mono-lipid-lowering drugs at lowering TC, LDL-C and TG, in term of regulating HDL-C, there was no significantly difference between the two groups (Fig. 6), which was not conformed with the

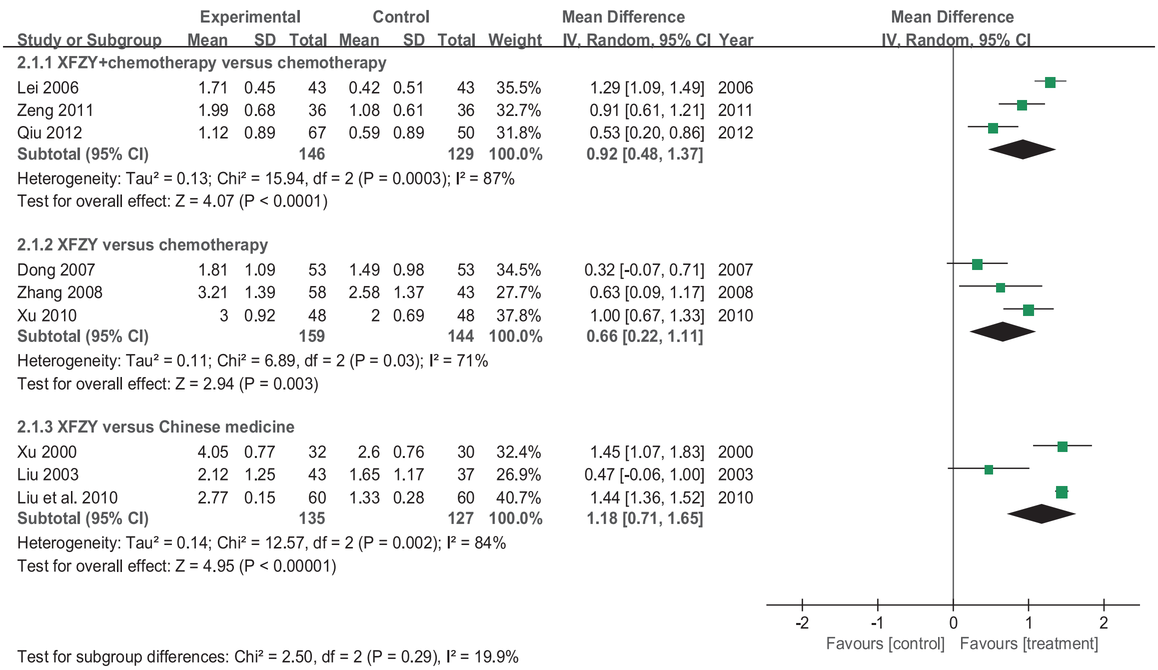

Fig. 3. Comparison of the efficacy of XFZY prescription on TC lowing between treatment groups and control groups under random effects model.

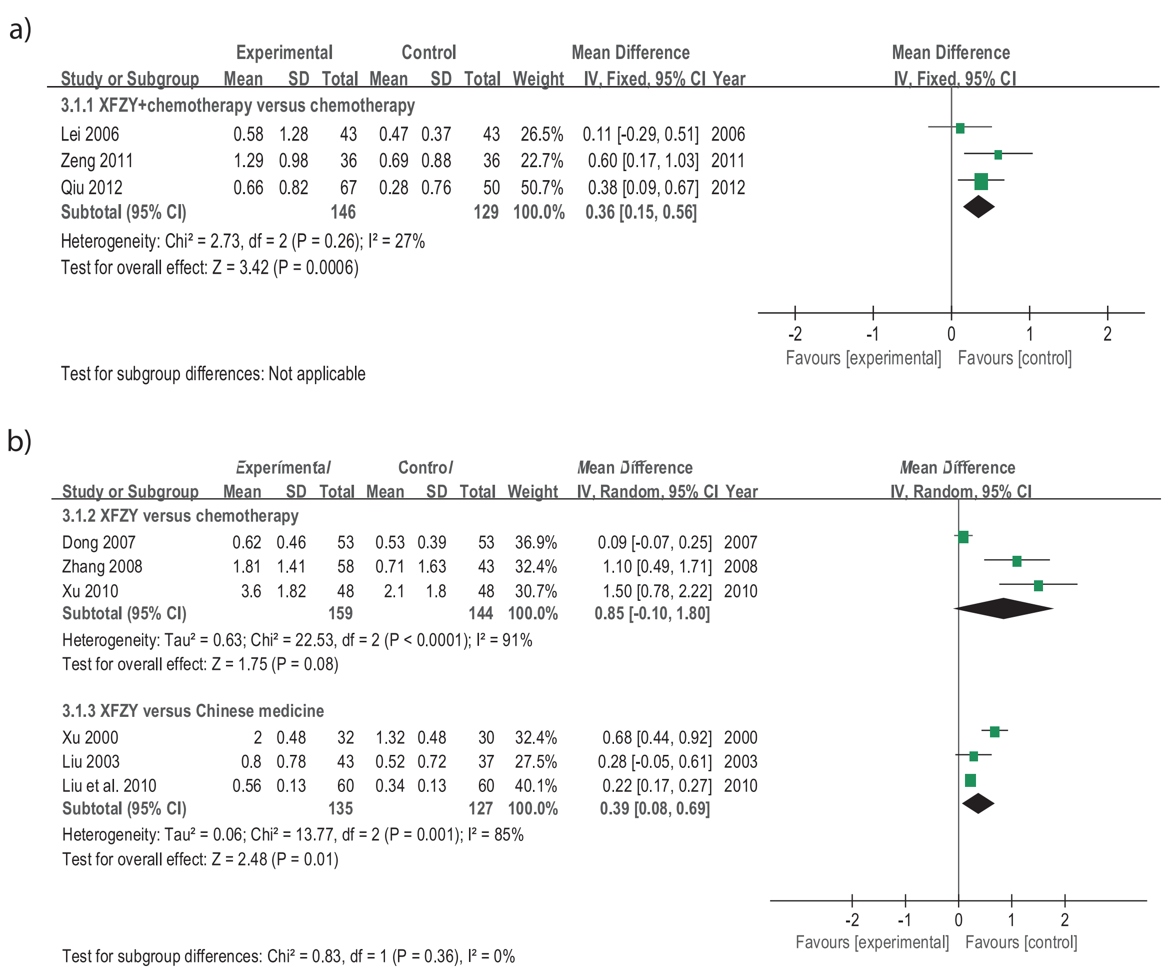

Fig. 4. (1) Comparison of the efficacy of XFZY prescription on TG lowing between treatment groups and control groups under fixed effects model. (2) Comparison of the efficacy of XFZY prescription on TG lowing between treatment groups and control groups under random effects model.

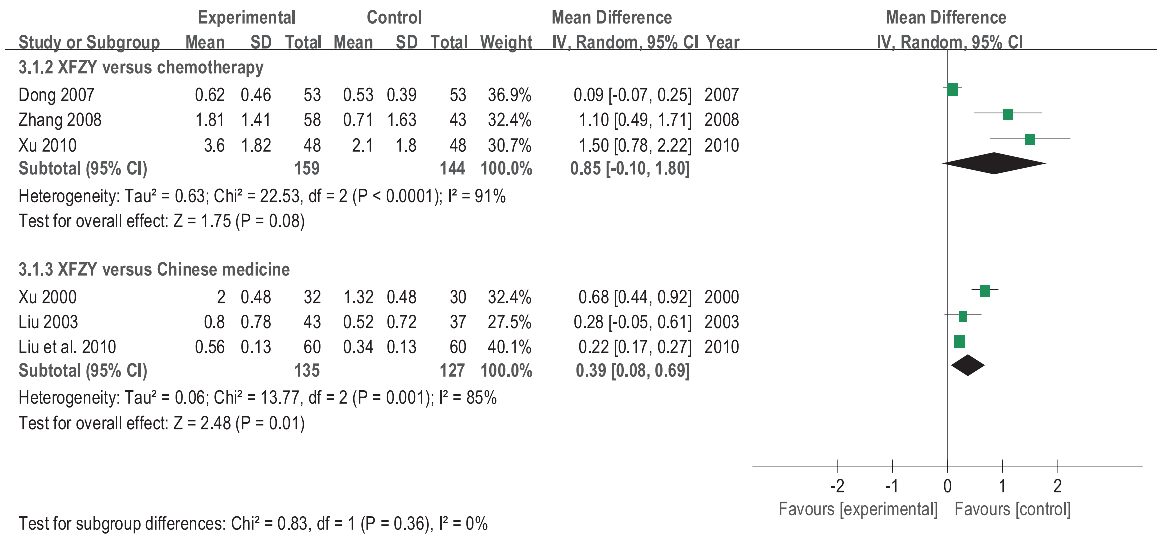

Fig. 5. Comparison of the efficacy of XFZY prescription on LDL-C lowing between treatment and control groups under random effects model.

results of other traits.[33],[37]

There was no overt side effect by XFZY prescription reported in the included trials, and one possible explanation is the coexistence of other phytochemicals in XFZY prescription may moderate the side effects. The heterogeneity was found in lowering lipid index evaluation (Figs. 3, 4.2 and 6), which is possibly attributed to the modification of the XFZY preparation, dosage, course of treatment and control medicines.

Meanwhile, limitations may exist in this meta-analysis. First, methodological quality of the included trials was not highly compelling, since randomization and blinding were not reported clearly, and the allocation concealment as well as the withdrawal/dropout were not mentioned for most of the included trails. Only one trial excluded placebo effect[35] so the selection bias might exist. Second, available number of trials was not statistically sufficient to engage in subgroup analysis by formulation, dosage, and control medicines. Third, three trials[30,37,41] specifically stated the subtypes of hyperlipidemia, but none reported the outcomes according to the subtypes of hyperlipidemia. Moreover, since the demographic details were not provided, we were not able to complete meta-analysis based on the subtypes of hyperlipidemia and demographic factors. Fourth, most of the studies published in Chinese were of low methodological quality and selective publication of positive results,[43,44] which may lead to bias. Finally, lack of long-term follow-up data, long-term efficacy and safety, and side effect in recruited studies may cause unreliable results and inability to truly reflect general trends.

5. Conclusion

This meta-analysis preliminarily indicated that the XFZY prescription, whether applied as monotherapy or adjunctive therapy, is an effective and safe traditional Chinese medicine for patients with hyperlipidemia. However, methodological quality of the most included studies was not high, hence the results should be interpreted with caution. Rigorously designed, large-scale and multicenter trials are needed to estimate the efficacy and safety of XFZY prescription on hyperlipidemia in the future.

Declaration of interest

All authors declare no conflicts of interest in this study.

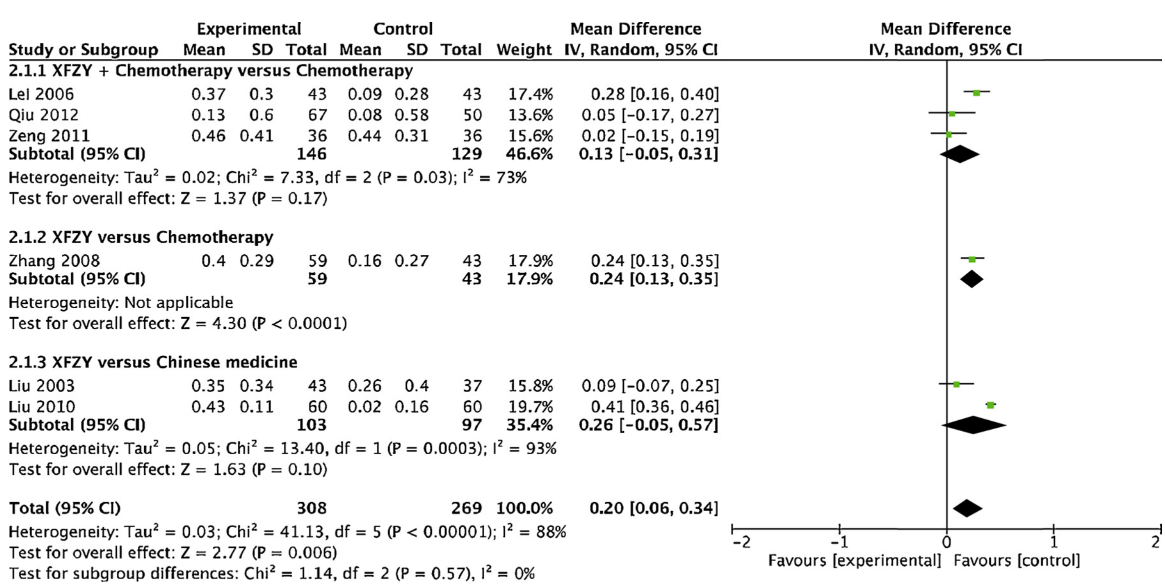

Fig. 6. Comparison of the efficacy of XFZY prescription on HDL-C regulating between treatment and control groups under random effects model.

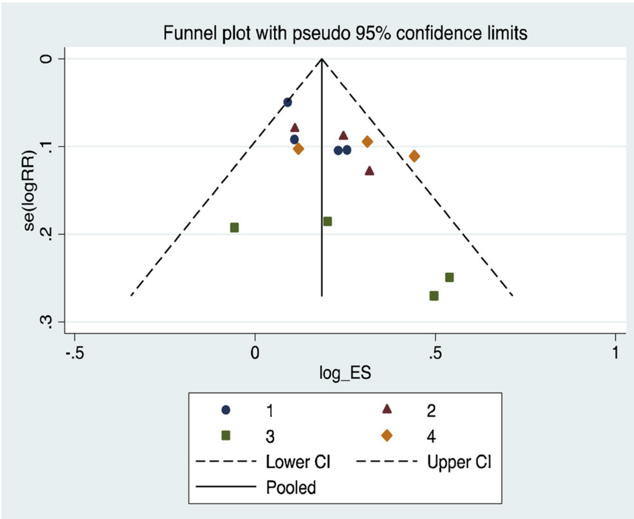

Fig. 7. Funnel plot of comparison of the effective rate between treatment group and control group. Group 1: XFZY prescription plus chemotherapy versus chemotherapy; group 2: XFZY prescription versus chemotherapy; group3: XFZY prescription versus placebo; group 4: XFZY prescription versus Chinese medicine.

Acknowledgments

The study was supported by the Youth Foundation of National Natural Science Foundation of China (No.81703936), Youth Foundation of National Natural Science Foundation of China (No.81202807), the Freedom Explore Program of Central South University (No.2012QNZT121), and scientific research projects of Education Department of Hunan Province (No.12C0525). Sui-yu Hu Inheritance Studio of National Prominent Chinese Medicine Doctor, State Administration of Traditional Chinese Medicine (N0.2014.20), China Postdoctoral Science Foundation (No.2015M572254).

References

1. Park A. Hyperlipidaemia. *Medicine*. 2009;9:497–499.
2. Packard CJ, Shepherd J. Lipoprotein metabolism in lipase deficient states: Studies in primary and secondary hyperlipidaemia. *Biochem Soc Trans*. 1993;21:503–506.
3. Hlaing TT. Hyperlipidaemia. *Medicine*. 2013;10:607–609.
4. Wierzbicki AS, Perera D, Ewang-Emukowhate M. Dyslipidaemia: What's around the corner? *Clin Med*. 2014;14(Suppl. 6):s41–44.
5. McLaughlin T, Reaven G, Abbasi F, et al. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? *Am J Cardiol*. 2005;96:399–404.
6. *Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease*. 2008; 2008 London.
7. Calabro P, Yeh ET. Multitasking of the 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor: Beyond cardiovascular diseases. *Curr Atheroscler Rep*. 2004;6:36–41.
8. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. *Nature*. 1990;343:425–430.
9. Rozman D, Monostory K. Perspectives of the non-statin hypolipidemic agents. *Pharmacol Ther*. 2010;127:19–40.
10. Elis A, Lishner M. Non-every day statin administration–a literature review. *Eur J Intern Med*. 2012;23:474–478.
11. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A, 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*. 2002;106:3143–3421.
12. Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Statin-fibrate combination for mixed dyslipidaemia: A limited option? *Curr Med Res Opin*. 2010;26:2137–2140.
13. Choi HD, Shin WG. Safety and efficacy of statin treatment alone and in combination with fibrates in patients with dyslipidemia: A meta-analysis. *Curr Med Res Opin*. 2014;30:1–10.
14. Langsjoen PH, Langsjoen JO, Langsjoen AM, Lucas LA. Treatment of statin adverse effects with supplemental coenzyme q10 and statin drug discontinuation. *BioFactors*. 2005;25:147–152.
15. Zhang HJ, Cheng YY. An hplc/ms method for identifying major constituents in the hypocholesterolemic extracts of chinese medicine formula' xue-fu-zhu-yu decoction'. *Biomed Chromatogr*. 2006;20:821–826.
16. Zhang L, Zhu L, Wang Y, et al. Characterization and quantification of major constituents of xue fu zhu yu by uplc-dad-ms/ms. *J Pharm Biomed Anal*. 2012;62:203–209.
17. Luan LJ, Mi SY, Hu L, Cheng YY. Simultaneous determination of five bioactive constituents in the traditional chinese medicinal preparation refined xue-fu-zhu-yu-tang by high-performance liquid chromatography with diode-array uv detection. *J Anal Chem*. 2006;61:139–146.
18. Shi WL, Zhang JS, Hu YQ. Prevention and treatment of blood vessels related diseases by xuefu zhuyu decoction (see text): Its clinical application and progress in researches of mechanisms. *Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi = Chin J Integr Tradit West Med*. 2013;33:712–716.
19. Song X, Wang J, Wang P, Tian N, Yang M, Kong L. ^{1}H NMR-based metabolomics approach to evaluate the effect of xue-fu-zhu-yu decoction on hyperlipidemia rats induced by high-fat diet. *J Pharm Biomed Anal*. 2013;78-79:202–210.
20. Liu L, Cheng Y, Zhang H. Phytochemical analysis of anti-atherogenic constituents of xue-fu-zhu-yu-tang using hplc-dad-esi-ms. *Chem Pharm Bull*. 2004;52:1295–1301.
21. Marimuthu S, Adluri RS, Rajagopalan R, Menon VP. Protective role of ferulic acid on carbon tetrachloride-induced hyperlipidemia and histological alterations in experimental rats. *J Basic Clin Physiol Pharmacol*. 2013;24:59–66.
22. Luo H, Li Q, Flower A, Lewith G, Liu JP. Comparison of effectiveness and safety between granules and decoction of chinese herbal medicine: A systematic review of randomized clinical trials. *J Ethnopharmacol*. 2012;140:555–556.
23. Izzo AA, Di Carlo G, Borrelli F, Ernst E. Cardiovascular pharmacotherapy and herbal medicines: The risk of drug interaction. *Int J Cardiol*. 2005;98:1–14.
24. *Guiding principle of clinical research on cardiovascular drugs (trial)*. Ministry of Health PRC; 1988:86–88.
25. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17:1–12.
26. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical-evidence of bias - dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Jama-J Am Med Assoc*. 1995;273:408–412.
27. O'Driscoll C, Laing J, Mason O. Cognitive emotion regulation strategies, alexithymia and dissociation in schizophrenia, a review and meta-analysis. *Clin Psychol Rev*. 2014;34:482–495.
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj*. 1997;315:629–634.
29. Begg CB. Publication bias. In: Cooper H, Hedges LV, eds. *The handbook of research synthesis*. New York: Russell Sage Foundation; 1994:399–409.
30. Xu JY. Clinical observation on 62 cases of hyperlipidemia treated with xuefuzhuyu capsule. *Beijing J Tradit Chin Med*. 2000;02:64.
31. Xu YZ. Curative analysis on 96 cases of hyperlipidemia treated with xuefuzhuyu capsule. *China Modern Doctor*. 2010;28:47–70.
32. Xu XJ, Lin KL, Wang ZP. Randomized parallel control study of xuefu zhuyu decoction combined with western medicine in treating phlegm and blood stasis type hyperlipidemia. *J Pract Tradit Chin Intern Med*. 2015;08:51–52.
33. Zeng XG. 36 cases of hyperlipidemia treated with xuefuzhuyu decoction combined with simvastatin. *Guiding J Tradit Chin Med Pharm*. 2011;03:40–41.
34. Wang XY. Clinical study of hyperlipidemia treated with xuefuzhuyu decoction. *China Foreign Med Treat*. 2009;08:87.
35. Zhang SG. 58 cases of hyperlipidemia treated with modified xuefuzhuyu decoction. *Hunan J Tradit Chin Med*. 2008;04:52–53.
36. Dong XM. The effect of xuefuzhuyu decoction on nailfold microcirculation of hyperlipidemia. *Zhejiang J Tradit Chin Med*. 2007;07:396–397.
37. Lei WN. Clinical observation of xuefuzhuyu decoction plus simvastatin in treating elderly patients with hyperlipidemia and hyperviscosity. *Guangxi J Tradit Chin Med*. 2006;05:12–14.
38. Liu J. Clinical observation on 67 cases of hyperlipidemia treated with xuefuzhuyu decoction. *Hebei J Tradit Chin Med*. 2012;10:1500–1501.
39. Liu W. Clinical observation on 43 cases of hyperlipidemia treated with xuefuzhuyu capsule. *Beijing J Tradit Chin Med*. 2003;05:63–64.
40. Zhu XJ, Li FG, Zhao L. Clinical study on qi-stagnancy and blood stasis in hyperlipidemia treated with xuefuzhuyu capsule. *Beijing J Tradit Chin Med*. 2010;09:685–687.
41. Liu L, Li C, Tang J. Curative effect observation of 60 cases of elderly primary hyperlipidemia treated with xuefuzhuyu decoction. *Chin J Nat Med*. 2010;05:330–332.
42. Liao JQ, Tian JX, Li TF, Song WJ, Zhao WH, Du JH. Xuefuzhuyu decoction for hyperlipidemia: A systematic review and meta-analysis of randomized clinical trails. *J Tradit Chin Med*. 2014;34:411–418.
43. Wu TX, Li YP, Bian ZX, Liu GJ, Moher D. Randomized trials published in some chinese journals: How many are randomized? *Trials*. 2009;10.
44. Jin ZC, Yu DH, Zhang LM, et al. A retrospective survey of research design and statistical analyses in selected chinese medical journals in 1998 and 2008. *PLoS One*. 2010;5:e10822.