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Red yeast rice preparations for dyslipidemia: An overview of systematic reviews and network *meta*-analysis

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ABSTRACT

This research was to summarize the comparative efficacy and safety of red yeast rice (RYR) preparations and analyze the treatment ranking of lipid-lowering agents including RYR. Thirty-one systematic reviews (SRs) involving 165 randomized trials with 14,987 dyslipidemia participants were included. All the SRs showed a high overall risk of bias. A Bayesian network *meta*-analysis was performed. Only five trials reported major adverse cardiovascular events (MACE) and three trials reported lipoprotein(a)[Lp(a)]. Compared to placebo or other lipid-lowering drugs, RYR preparations showed some regulating action on lipids and glucose metabolism, with fewer side effects ($P < 0.05$). Compared to placebo, RYR showed a tendency to reduce Lp(a) levels. Lipid-lowering agents ranked differently in each outcome. High-quality evidence showed RYR (Zhibituo) lowered total cholesterol and triglyceride levels more than placebo. This study reveals the efficacy and safety ranking of RYR preparations for dyslipidemia, and it's recommended that future trials should focus on MACE and Lp(a).

1. Introduction

Dyslipidemia, a common chronic disease, has become a public health issue and is highly prevalent among patients with diabetes, hypertension, and cardiac disease (Al Quran et al., 2022; Hu et al., 2022; Zhang et al., 2022). Globally, cardiovascular diseases caused 18.56 million deaths in 2019, of which 4.4 million were related to dyslipidemia (WHO, 2021), making it imperative to prevent and treat

Abbreviations: RYR, red yeast rice; Xuezhikang, XZK; Zhibituo, ZBT; CHD, coronary heart disease; MACE, major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; Lp(a), lipoprotein(a); FBG, fasting blood glucose; 2hPG, 2h postprandial blood glucose; HbA1c, glycosylated hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; SRs, systematic review; RCTs, randomized controlled trials; MeSH, Medical Subject Heading; PROSPERO, International prospective register of systematic reviews; INPLASY, International Platform of Registered Systematic Review and Meta-analysis Protocols; CNKI, China National Knowledge Infrastructure Database; CQVIP, Chongqing VIP; SinoMed, Chinese Biomedical Literature Database; AMSTAR 2, Assessment of Multiple Systematic Reviews-2; ROBIS, Risk of Bias In Systematic reviews; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; GRADE, the Grading of Recommendations, Assessment, Development, and Evaluation; FE, fixed effects; RE, random effects; OR, odds ratio; CI, confidence intervals; MD, mean difference; DIC, deviance information criteria; MCMC, Markov Chain Monte Carlo; Rhat, potential scale reduction factor.

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dyslipidemia.

Despite statins' effectiveness in reducing dyslipidemia and mortality from cardiovascular disease, adverse events caused by statins have limited their use (GBD Risk Factors Collaborators, 2018). Therefore, red yeast rice (RYR), the product of *Monascus purpureus* fermented on rice, has been used as an alternative medicine for patients with dyslipidemia, particularly those with statin intolerance (Wild et al., 2002).

RYR has been used and consumed medicinally for thousands of years. Since the discovery of the lipid-lowering ingredient Monacolin K by Dr. A. Endo (Endo, 1979) in 1979, RYR entered a modern era of research focused on functional relevance (Dai, 2020).

To date, 11 Monacolin species have been identified in RYR, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) and the synthesis of mevaleric acid, an intermediate for the synthesis of cholesterol (Fukami et al., 2021; Wang et al., 2014). Additionally, RYR contains ergosterols, amino acids, flavonoids, alkaloids, sterols, and isoflavones, which improve lipid metabolism (Cicero et al., 2021; Li et al., 2009). Furthermore, studies have shown that RYR benefits both primary and secondary prevention of cardiovascular disease (Becker et al., 2009; Karl et al., 2012; Ye et al., 2007).

A variety of systematic reviews (SRs) have assessed the effects of RYR on dyslipidemia in recent years, but the results are mixed and heterogeneous. Some SRs included not only single-herb preparation of RYR but also compounds containing RYR and coenzyme Q10 (Cicero et al., 2013, 2016), therefore cannot accurately show the curative effect and safety of RYR. Furthermore, Monacolin contents vary significantly in different RYR preparations. Currently, in China, preparations of RYR include Xuezhikang (XZK) (Zhao et al., 2004), Zhibituo(ZBT)(Liu et al., 2006), and RYR powder; outside of China, preparations of RYR include Cholestin(Heber et al., 1999) and Hypocol (Bogsrud et al., 2010). Given this, we plan to evaluate the methodological and reporting quality of existing SRs and take complete account of the heterogeneity of RYR preparations, to further analyze the efficacy and safety of different preparations of RYR using network *meta*-analysis.

2. Material and methods

The study was performed and reported following the PRISMA (Hutton et al., 2015), and the protocol was registered on INPLASY (INPLASY202230032).

2.1. Eligibility criteria

SRs of randomized controlled trials (RCTs) evaluating the efficacy and safety of RYR were included in this overview. All RCTs included in these SRs were screened for network *meta*-analysis. Dyslipidemia participants with or without comorbidities were eligible. Any single drug preparation of RYR used alone or combined with conventional lipid-lowering agents were included. The duration of intervention was limited to no less than three weeks. The comparator involved no intervention, placebo, and guideline-recommended lipid-lowering agents. The primary outcomes addressed at least one outcome: major adverse cardiovascular events (MACE) and lipid profiles including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and lipoprotein(a) [Lp(a)]. Additional outcomes addressed glucose metabolism indicators, including fasting blood glucose (FBG), 2 h postprandial blood glucose(2hPG), glycosylated hemoglobin A1c (HbA1c); blood pressure; adverse events including muscular adverse drug reactions, liver dysfunction, and gastrointestinal reactions.

2.2. Search strategy

Eight databases involved the PubMed, Embase, the Cochrane Library, Web of Science, China National Knowledge Infrastructure Database (CNKI), Wanfang Data, Chongqing VIP (CQVIP), and Chinese Biomedical Literature Database (SinoMed) were searched for SRs up to March 2022, without language restriction. The protocols for SRs were retrieved from the International Perspective Register of Systematic Reviews (PROSPERO) and the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY).

Supplementary Table S1 displays the detailed search strategy of PubMed.

2.3. Study selection

Two authors (FF Zhao and LY Chen) independently screened the eligible SRs for the overview, and then screened the RCTs from the SRs for inclusion in the network meta-analysis. Discrepancy was resolved through discussions with a third author (JPL).

2.4. Data collection

Two pairs of authors (FF Zhao, LY Chen, YX Guo, LJ Lu) extracted the data, and two pairs of authors (CL Lu, X Xue, XH Liu, XY Jin) checked the data and reached a consensus after discussion. The following items were collected via a standardized data collection form: review identification, author, publication year and languages, and country; review titles and objectives; registration of research protocol; eligibility criteria; the number of included trials and participants; intervention and comparator; outcome measures; the quality assessment; conclusions.

For network meta-analysis, the following items were collected from the RCTs: study identification; characteristics of participants (age, gender, country and locations, and comorbidities if available); comparator, RYR daily dosage, treatment duration; outcome data involved MACE, LDL-C, HDL-C, TC, TG, ApoA1, ApoB, Lp(a), FBG, 2hPG, HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), and adverse events including muscular adverse drug reactions, liver dysfunction, and gastrointestinal reactions.

2.5. Risk of bias assessment and quality assessment

Two authors (FF Zhao, LY Chen) independently assessed the methodological and reporting quality of included SRs, using the Risk of Bias In Systematic reviews (ROBIS) (Whiting et al., 2016), Multiple Systematic Reviews-2 (AMSTAR 2) (Shea et al., 2017), and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). In the network *meta*-analysis, two pairs of authors (FF Zhao, LY Chen, YX Guo, LJ Lu) assessed the quality of RCTs using the Cochrane's risk of bias tool (Cumpston et al., 2019). Discrepancy was resolved through discussion with a third author (JPL).

2.6. Data synthesis

The outcomes at the final time point were measured. Data were standardized to mean and standard deviation (SD). Units of LDL-C, HDL-C, and TC, TG were uniformly converted to mmol/L. Units of ApoA1 and ApoB were uniformly converted to g/L. Units of Lp(a) were uniformly converted to mg/L. Except for RYR preparations with the specified name, other RYR preparations were collectively referred to as RYR. The pooled results were presented as mean difference (MD) or log odds ratio (log OR) and 95% confidence intervals (CI). A *P*-value of<0.05 was considered statistically significant.

The Bayesian network *meta*-analysis was performed using Markov Chain Monte Carlo (MCMC) simulation through the Multinma Function (Dias et al., 2013; Phillippo et al., 2020; Zhang & Dong, 2021) based on RStudio software (2022.02.0). A potential scale reduction factor (Rhat) value close to 1 indicates good convergence of the MCMC algorithm (Zhang & Dong, 2021). An evidence network was performed, and the proportion of interventions was observed through asymmetry. Sub-nets were analyzed if the network was not fully connected. The data were

analyzed by adjusting the indirect comparison approach if closed loops were unavailable, while the mixed treatment comparison approach was performed when one or more closed loops were available.

For each network, both fixed effects (FE) and random effects (RE) models were fitted. The model with better fits was identified based on residual deviance, pD values, and deviance information criteria (DIC) values (Dias et al., 2013). The prior and posterior distributions were compared visually, and the residual deviance contributions of the involved RCTs were examined. The effects of direct and indirect comparisons were incorporated. Treatment rankings, rank probabilities, and cumulative rank probabilities were generated (Dias et al., 2013). The surface under cumulative ranking curve (SUCRA) values for each subnet were ranked.

2.7. Assessment of heterogeneity and inconsistency

The presence of network heterogeneity was assessed using calculating τ (tau) statistics (Brignardello-Petersen et al., 2019; Higgins & Thompson, 2002). Due to the diversity of complex baseline data, subgroup analyses were not conducted. Instead, we assessed inconsistency by fitting an inconsistency model and a node-splitting model. To evaluate the inconsistency of network, for the overall test, based on fitting the unrelated mean effect (UME) model, the potential inconsistency in the whole network evidence was evaluated by comparing the fit of the consistency model (FE or RE models) and the UME model (Tian & Li, 2020), and the forest plots were drawn to show the overall difference between the UME models and FE or RE models. In addition, for the local inconsistency estimate based on the existence of one or more closed loops, the consistency of direct and indirect comparisons was assessed by the node-split model. The consistency model was adopted if the P-value of more than 0.05; otherwise, the inconsistent model was used (Dias et al., 2010; van Valkenhoef et al., 2016). Further, a pairwise *meta*-analysis of RYR on LDL-C levels using a frequentist approach was performed to explore its differences from Bayesian approaches.

2.8. Assessment of reporting biases

A funnel plot was used to visually examine study effects in pairwise comparisons with at least ten trials.

2.9. Assessment of the certainty of evidence

Of the trials extracted from the included SRs, 247 trials were excluded due to being ineligible. Therefore, the certainty of the evidence was assessed via the entire network rather than by the quality of the evidence pooled within the included SRs. Two authors (FF Zhao, LY Chen) independently assessed direct evidence, indirect evidence, and combined evidence for outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (Brignardello-Petersen et al., 2020), if closed loops were available in the network; and adjusted indirect evidence as combined evidence for significant outcomes were assessed, when closed loops were unavailable (Salanti et al., 2014; Tian and Li, 2020).

3. Results

3.1. Description and methodological quality of included SRs

For this overview, 2,936 records were found, and 31 SRs(Casciola et al., 2013; Chen et al., 2011; Chen et al., 2018; Chen et al., 2004; Du et al., 2014; Du et al., 2015; Fogacci et al., 2019; Han et al., 2022; Li, Liu, et al., 2021; Li et al., 2013; Li et al., 2015; Li, Wang, et al., 2021; Li, Jiang, et al., 2014; Li, Jia, et al., 2014; Liu et al., 2006; Liu et al., 2020; Ong & Aziz, 2016; Pan et al., 2013; Peng et al., 2017; Qian et al., 2019; Shang et al., 2012; Sungthong et al., 2020; Tai, 2015; Wang & Chen, 2006; Xiong et al., 2021; Xu et al., 2017; Yang & Mousa, 2012; Yang et al., 2021; Zhan et al., 2010; Zhao et al., 2014; Zheng et al., 2019) were included (Fig. 1).

The included SRs were published between 2004 and 2022. Twenty SRs were published in Chinese and 11 in English. Twenty-four SRs were performed in China, three in the United States, one in Malaysia, one in Thailand, and one SR was of multinational cooperation (Italy, Poland, UK, France, USA, Australia, Croatia, Canada, Ukraine, Slovakia, Slovenia, Iran, and the Czech Republic) and one with two country cooperation (Norway and China). The number of RCTs in the included SRs ranged from six to 93, and the total sample size ranged from 361 to 10,699. The general characteristics of the included SRs are available in Table 1.

Based on the ROBIS, all the SRs showed a high overall risk of bias (Fig. 2). Following are the four domains.

(1) Study eligibility criteria: 15 SRs were assessed as low concern, while high concern for 16 SRs due to lack of protocol registration, restricted publication language or status.
(2) Study identification and selection: all SRs were assessed as high concern due to a lack of searches for unpublished literature, inadequate database selection, or lack of methods to minimize screening bias.
(3) Data collection and study appraisal: three SRs were assessed as low concern, while high concern for the remaining 28 SRs due to lack of methods to minimize data collection bias, or inadequate general characteristics of included studies, or lack of quality assessment, or non-reporting of methods to minimize errors in risk of bias evaluation.
(4) Synthesis and findings: three SRs were assessed as low concern, but unclear for two included SRs due to lack of synthesis, while high concern for the remaining 26 SRs due to insufficient robustness of results, or failure to address bias.

Based on AMSTAR 2, one SR had moderate confidence, and 30 had an overall low (7) or critically low (23) due to at least one vulnerability weakness (**Supplementary Fig. S1**). And based on PRISMA, most of the 31 studies reported incompletely on the risk of bias, exploration of heterogeneity, and sensitivity analysis (**Supplementary Fig. S2**).

3.2. Description and risk of bias of included RCTs

A total of 599 primary trials were included in the SRs. 165 studies met the eligibility criteria, involving 14,987 participants. The recruitment timeline ranged from late 1993 to early 2017. The general characteristics of the included primary studies are available in **Supplementary Table S2**, including the following items: study identification, participants, sample size, intervention, comparator, RYR daily dose, treatment duration, outcomes, country and locations, number of centers, publication languages, risk of bias, and citations.

All the included studies consisted of RCTs. One hundred fifty-five trials were designed as two-armed RCTs, while nine trials were designed as three-arm comparisons, and one trial as a four-arm comparison. A total of 20 trials were double-blinded, while five were single-blinded, the remaining 140 studies did not report any information regarding blinding. In addition, 159 trials were performed at a single center, while six trials were multicentric. The sample size of included trials ranged from 12 participants to 488 participants. The average number of included subjects in all trials was 90. All participants were diagnosed with dyslipidemia, including 23 trials with combined diabetes, 21 trials with combined coronary heart disease (CHD), and one trial with nephrotic syndrome, and non-alcoholic fatty liver, respectively. The mean age of the participants varied from 17.6 to 81 years old, while 36 trials did not report any age information. There were more males (6,561) than females (6,031), while 28 trials did not report gender distribution. RYR preparation involved XZK, ZBT, Hypocol, and Cholestin. A further six trials using RYR preparation did not specify its

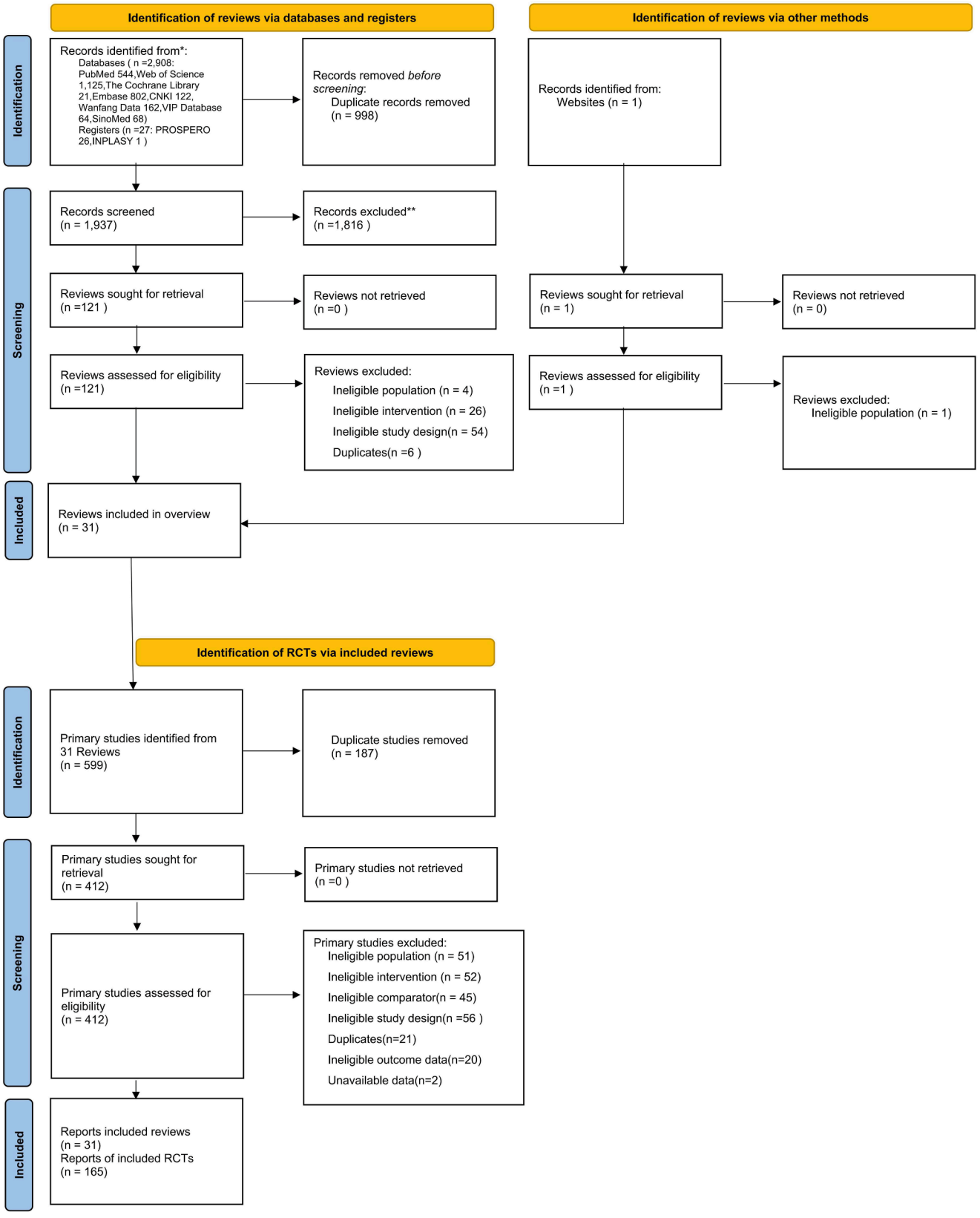

Fig. 1. The flow diagram. CNKI: China National Knowledge Infrastructure; SinoMed: China BioMedical Literature Service System; n: number; RCTs: randomized controlled trials.

Table 1
General characteristics of the included reviews.

Study ID	Country	Languages	No. of included trials	No. of participants (E/C)	participants	Intervention	Control	Primary Outcomes	Secondary Outcomes	Assessment
Zhao ZM 2014	China	Chinese	27	1400	dyslipidemia	XZK	lipid-lowering agents	TC, TG, LDL-C, HDL-C	/	/
Li GR 2021	China	Chinese	7	656 (324/ 332)	dyslipidemia	XZK	simvastatin	TC, TG, LDL-C, HDL-C, ADRs	/	Jadad
Li YH 2014	China	Chinese	19	6229 (3095/ 3134)	dyslipidemia + CHD	XZK + CHD ConT	CHD ConT + placebo / statins / none	TC, TG, LDL-C, HDL-C	/	ROB
Du JP 2014	China	Chinese	22	1031	dyslipidemia	XZK	lipid-lowering agents	TC, TG, LDL-C, HDL-C	/	/
Chen JS 2018	China	Chinese	9	1613	hypertension + CHD	XZK + atorvastatin	atorvastatin	TC, TG, HDL-C	/	/
Wang WX 2006	China	Chinese	11	1073 (536/ 532)	dyslipidemia	XZK	statins / fibrates / inositol nicotinate / probucol	TC, TG, LDL-C, HDL-C, ADRs	/	ROB
Li K 2013	China	Chinese	8	703 (356/ 347)	dyslipidemia + CHD		atorvastatin + CHD ConT / CHD ConT	TC, TG, LDL-C, HDL-C	/	ROB
Zheng SD 2019	China	Chinese	25	7875 (3985/ 3926)	dyslipidemia	XZK	statins / none	TC, LDL-C, HDL-C, ADRs, MACE	/	NR
Xu ZC 2017	China	Chinese	15	1450 (719/ 731)	dyslipidemia	XZK	statins	TC, TG, LDL, HDL, ADRs	/	ROB
Pan L 2013	China	Chinese	9	713 (360/ 353)	dyslipidemia + DM	XZK	simvastatin	TC, TG, LDL-C, HDL-C, FBG, 2hPG	/	Jadad
Zhan M 2010	China	Chinese	6	361 (185/ 176)	dyslipidemia + DM	antidiabetic drugs + XZK	antidiabetic drugs	TC, TG, LDL-C, HDL-C	FBG, 2hPG, HbA1c	ROB
Qian C 2019	China	Chinese	13	989 (504/ 485)	dyslipidemia + DM	antidiabetic drugs + XZK	antidiabetic drugs	TC, TG, LDL-C, HDL-C, FBG, 2hPG, HbAlc	/	Jadad
Liu YD 2020	China	Chinese	23	6542 (3260/ 3229)	dyslipidemia + CHD	XZK + CHD ConT	ConT + Statins / Placebo	TC, TG, LDL-C, HDL-C, ADRs	/	ROB, Jadad
Du JP 2015	China	Chinese	55	4812 (2406/ 2406)	dyslipidemia	XZK + health education	health education	TC, TG, LDL-C, HDL-C	/	/
Chen QY 2004	China	Chinese	17	/	dyslipidemia	ZBT	lovastatin	TC, TG, LDL-C, HDL-C, ADRs	/	/
Chen DS 2011	China	Chinese	16	1646 (809/ 837)	dyslipidemia	ZBT	simvastatin	TC, TG, LDL-C, HDL-C, ADRs	/	/
Tai HX 2015	China	Chinese	35	3229 (1735/ 1494)	dyslipidemia	ZBT	placebo/ statins / fibrates / inositol niacin / ethyl polyenoate/ polysaccharide sulfate / XZK	TC, TG, LDL-C, HDL-C	ADRs	ROB
Li Y 2014	China	English	13	804 (415/ 389)	dislipdemia	RYR (not including XZK and ZBT) / natural supplements with RYR	lipid-lowering agents	TC, TG, LDL-C, HDL-C	FBG	ROB
Shang Q 2012	China	English	22	6520 (3264/ 3256)	dyslipidemia + CHD	XZK	placebo / none / lipid-lowering agents	MACE	TC, TG, LDL-C, HDL-C	ROB
Liu J 2006	China, Norway	English	93	9625	dyslipidemia	RYR	placebo / none / lipid-lowering agents	TC, TG, LDL-C, HDL-C	/	generation of allocation sequence, allocation concealment, double blinding, drop outs

(*continued on next page*)

Table 1 (*continued*)

Study ID	Country	Languages	No. of included trials	No. of participants (E/C)	participants	Intervention	Control	Primary Outcomes	Secondary Outcomes	Assessment
Fogacci F 2019	Italy, Poland, UK, France, USA, Australia, Croatia, Canada, Ukraine, Slovakia, Slovenia, Iran, and the Czech Republic	English	53	8535 (4437/ 4303)	dyslipidemia	RYR supplementation alone / RYR supplementation in combination with other nutraceutical compounds	placebo /statin	musculoskeletal disorders	non-musculoskeletal ADRs	ROB
Ong YC 2016	Malaysia	English	10	905 (448/ 457)	dyslipidemia	RYR single preparation	simvastatin	TC, TG, LDL-C, HDL-C, ADRs	/	ROB
Yang CW 2012	USA	English	22	NR	dyslipidemia	RYR	placebo / statins	TG, LDL-C, HDL-C,	/	/
Min L 2015	China	English	21	1548 (794/ 764)	dyslipidemia + DM	XZK + antidiabetic drugs	placebo / statins / fenofibrates + antidiabetic drugs	TC, TG, LDL-C, HDL-C, ADRs	/	ROB
Yang P 2021	China	Chinese	11	1559 (782/ 777)	dyslipidemia	XZK + Statins	statins	TC, TG, LDL-C, HDL-C, ADRs	/	ROB, NOS
Xiong GH 2021	China	Chinese	7	578 (292/ 286)	dyslipidemia + DM	XZK	simvastatin	TC, TG, LDL-C, HDL-C, FBG, 2hPG, ADRs	/	ROB, PEDro Scale
Sungthong B 2020	Thailand	English	7	10699 (5374/ 5325)	dyslipidemia + CHD	RYR	lipid-lowering agents	MACE	TC, TG, LDL-C, HDL-C, ADRs	ROB, Jadad
Peng D 2017	USA	English	15	8713	dyslipidemia	RYR (not included RYR products with berberine or lovastatin)	lipid-lowering agents	serum lipid levels	/	GRADE
Li P 2021	China	English	15	1012 (481/ 531)	dyslipidemia	RYR alone / RYR combined therapies	lipid-lowering agents/ placebo	LDL-C	TC, TG, HDL-C, ApoA1, ApoB, ADRs	Jadad
Casciola AT 2013	USA	English	/	/	statin intolerance	RYR	lipid-lowering agents	ADRs	/	/
Han ZJ 2022	China	Chinese	15	1217 (612/ 605)	dyslipidemia + CHD	RYR / RYR + statins	statins / placebo	TC, TG, LDL-C, HDL-C	BP	Jadad

CHD: coronary heart disease, DM: diabetes, RYR:red yeast rice, XZK: Xuezhikang, ZBT: Zhibituo, ConT: conventional treatment, MACE: major adverse cardiovascular events, LDL-C:low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TC: total cholesterol, TG: triglyceride, FBG: fasting blood glucose, 2hPBG: 2 h postprandial blood glucose, HbA1c: glycosylated hemoglobin A1c, BP: blood pressure, ADRs: adverse drug reactions, involving muscular adverse drug reactions, liver dysfunction, and gastrointestinal reactions, ROB: risk of bias, GRADE: the Grading of Recommendations Assessment, Development, and Evaluation.

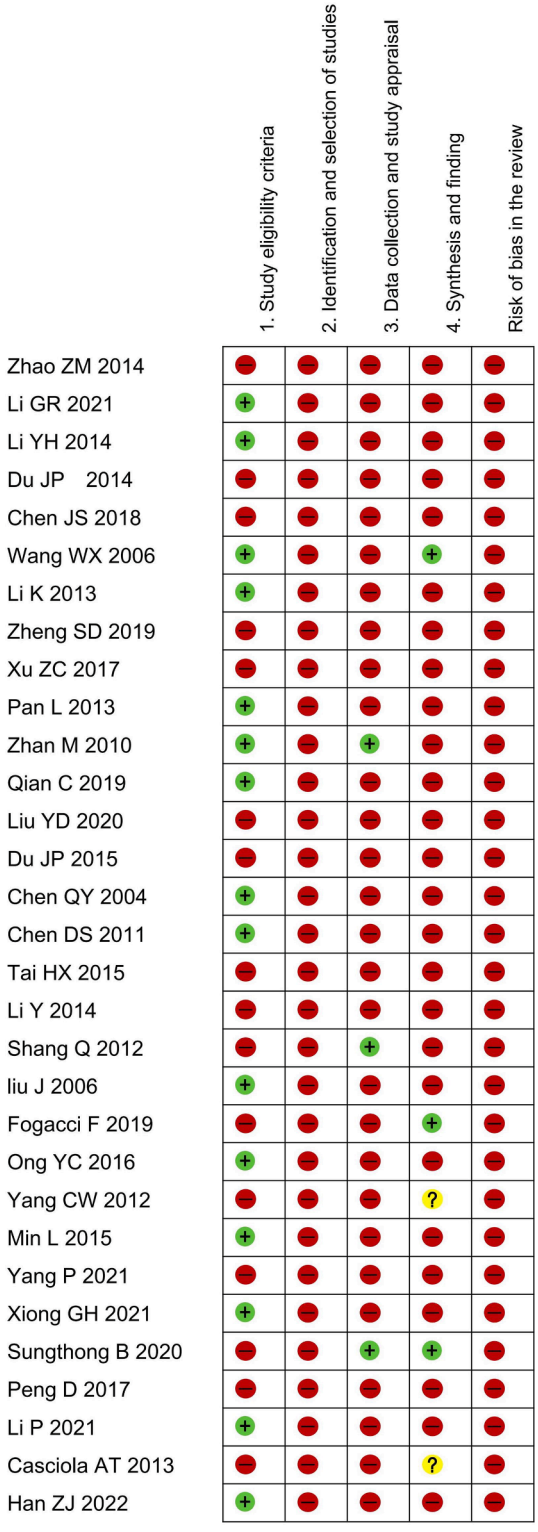

Fig. 2. Quality of the included SRs assessed by the ROBIS scale.

generic name and are therefore referred to as RYR. The daily dosages of XZK were arranged from 0.6 g to 3 g, with 1.2 g as common. The daily dosages of ZBT were arranged from 0.9 g to 3.15 g, with 3.15 g as common. The daily dosages of Cholestin and Hypocol were 2.4 g and four capsules, respectively. The daily dosages of RYR were arranged from 1.2 g to 4.8 g, with 1.2 g as common. The intervention duration was arranged from three weeks to 22 months, with eight weeks as common. Comparators involved placebo (13 trials), simvastatin (44 trials), atorvastatin (11 trials), inositol nicotinate (15 trials), ethyl polyoleate (10 trials), fluvastatin (7 trials), pravastatin (7 trials), fenofibrate (4 trials), lovastatin (6 trials), rosuvastatin (one trial), gemfibrozil (one trial), probucol (one trial). The remaining studies used conventional treatment for comorbidities, or another form or dose of RYR as a control.

The risk of bias in the included trials is summarized in Fig. 3.

3.3. *Effects of interventions*

Sub-networks are provided for some networks that are not fully connected. All Rhat values are close to 1, indicating good convergence of MCMC. Overall model fit seems adequate. Most posterior distributions are symmetric or approximately symmetric, and some prior and posterior distributions are similar (**Supplementary Figs. S3-S18**).

3.3.1. *Major adverse cardiovascular events*

Five RCTs (470 participants) addressed MACE. The network was not fully connected while made up of one sub-net, with four RCTs including four treatments (365 participants). The SUCRA values sequenced as simvastatin, fenofibrate, XZK, and XZK + fenofibrate (Fig. 4). Relative effects are shown in Table 2. **Supplementary Fig. S3** displays full results of the network *meta*-analysis.

3.3.2. *Lipid profiles*

3.3.2.1. Low-density lipoprotein cholesterol levels. A total of 103 RCTs including 9,871 participants reported on LDL-C. The network was not fully connected but consisted of four sub-nets. **Supplementary Fig. S4** displays results of the network *meta*-analysis. Sub-net 1 consisted of 78 RCTs including 24 treatments (7,868 participants), see Fig. 5**A**. Fig. 6 displays the forest plot for RE and UME models.

Node-splitting models fitted for 12 comparisons. Direct and indirect estimates did not differ significantly. The DIC of each inconsistency model remained, no node-splits resulted in reduced heterogeneity standard deviation compared to the consistency model, and the Bayesian *p*-values were all large (all P greater than 0.05).

Sub-net 2 consisted of 11 RCTs including six treatments (842 dyslipidemia participants with diabetes), see Fig. 5**B**. Compared to "XZK + antidiabetic drugs", the RE models showed a significant increase in LDL-C levels in the treatment of antidiabetic drugs (MD 0.68, 95% CI 0.14 to 1.26). The remaining comparisons showed insignificance.

Sub-net 3 consisted of 9 RCTs including six treatments (762 dyslipidemia participants with CHD), see Fig. 5**C**. Compared to "XZK + CHD conventional treatment", the RE models showed a significant increase in LDL-C levels in the treatment of placebo + CHD conventional treatment (MD1.81, 95%CI 1.01 to 2.6) and CHD conventional treatment (MD 0.78, 95%CI 0.43 to 1.13).

Sub-net 4 consisted of 2 RCTs including 3 treatments (112 dyslipidemia participants with diabetes), see Fig. 5**D**. Compared to "XZK + health education + antidiabetic drugs", the FE model showed a significant increase in LDL-C levels in the treatment of health education + antidiabetic drugs (MD 0.93, 95%CI 0.71 to 1.14).

According to the frequentist approach, XZK could result in higher LDL-C levels than atorvastatin (MD 0.56, 95%CI 0.09 to 1.03), and result in lower LDL-C levels than gemfibrozil (MD −0.36, 95%CI −0.70 to −0.02) and ethyl polyoleate (MD −0.62, 95%CI −1.09 to −0.14); and another RYR preparation ZBT could also decrease LDL-C levels compared to ethyl polyoleate (MD −0.52, 95%CI −0.69 to −0.36). XZK + CHD conventional treatment could decrease LDL-C levels compared to CHD conventional treatment (MD −0.96, 95%CI −1.29 to −0.64) while increasing LDL-C levels compared to atorvastatin + CHD conventional treatment (MD 0.29, 95%CI 0.03 to 0.56). And XZK + atorvastatin could lower LDL-C levels compared to atorvastatin (MD −0.42, 95%CI −0.60 to −0.24). XZK + antidiabetic drugs could lower LDL-C levels compared to antidiabetic drugs (MD −1.13, 95%CI −1.76 to −0.49). The

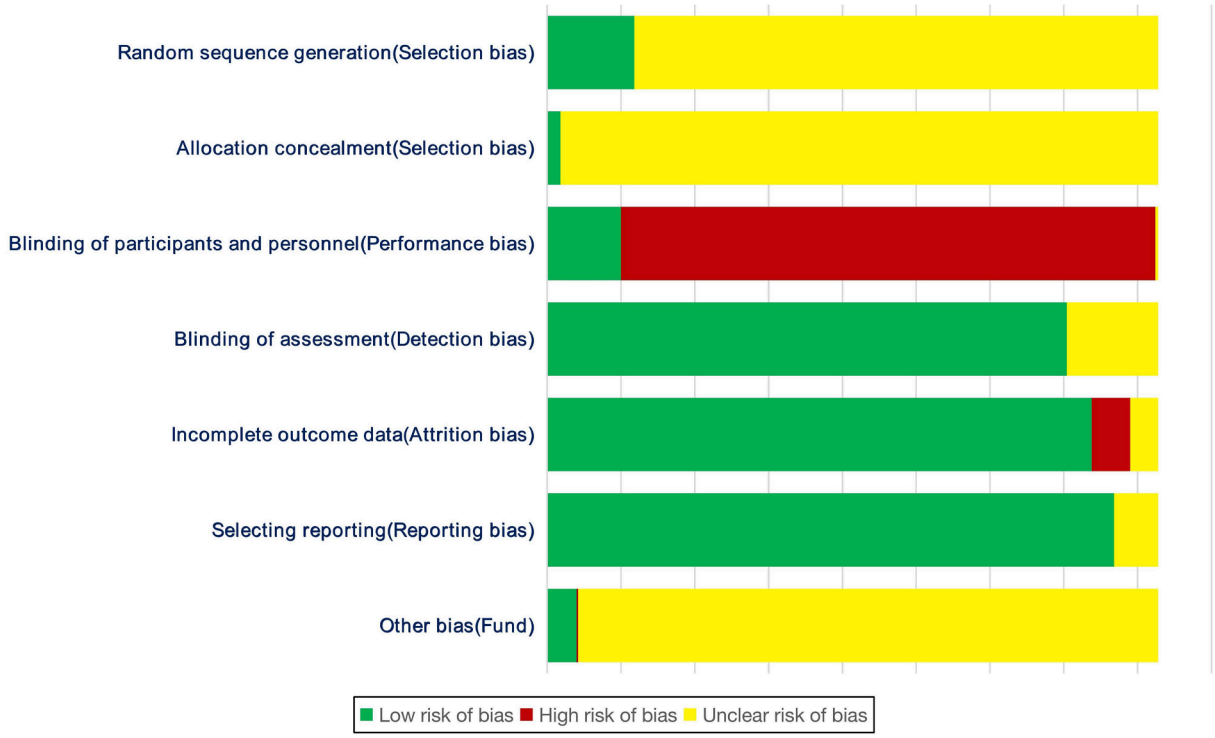

Fig. 3. Risk of bias of the included trials.

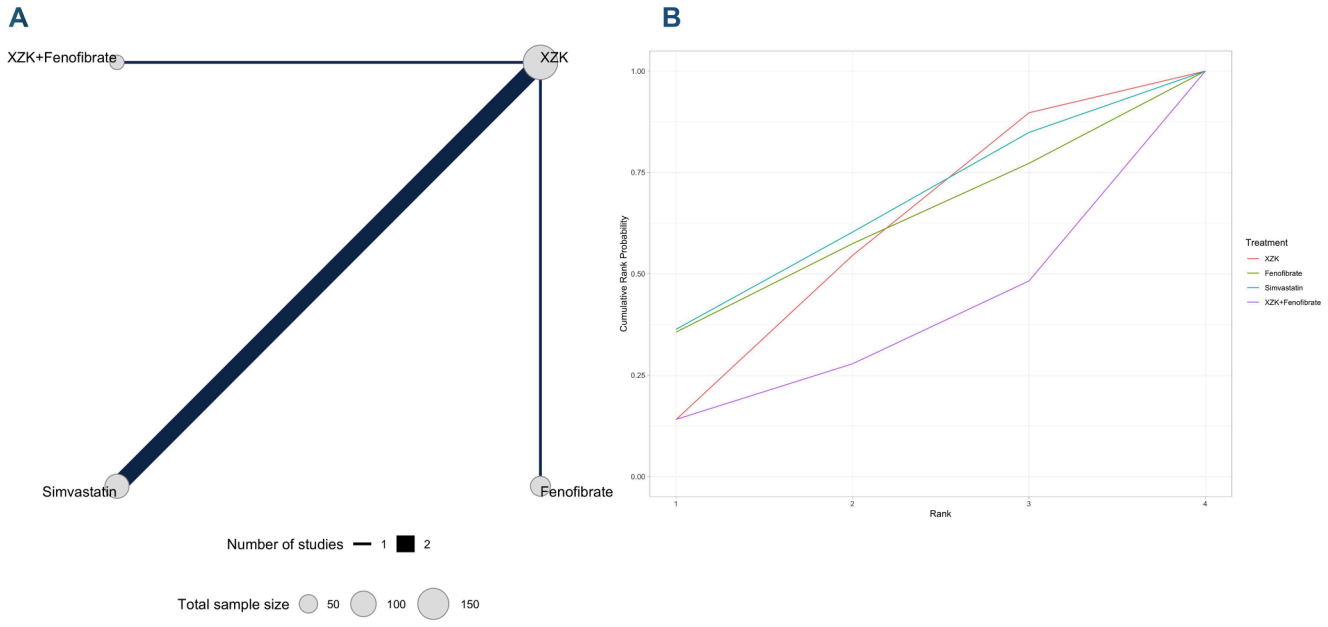

Fig. 4. Network evidence and SUCRA on outcome MACE. Fig. 4**A:** Network evidence, Fig. 4**B:** SUCRA, SUCRA: surface under cumulative ranking curve.

Table 2
League table for MACE.

XZK + Fenofibrate	—	—	—
2.94[-9.5,18.57]	**Simvastatin**	—	—
1.68[-15.73,18.2]	−1.27[-17.63,10.83]	**Fenofibrate**	—
1.43[-9.83,12.16]	−1.52[-13.35,6.09]	−0.25[-11.58,11.07]	**XZK**

MACE: major adverse cardiovascular events; XZK: Xuezhikang, preparation of red yeast rice.

remaining comparisons showed insignificance.

Another concern, the Bayesian approach showed different results for "gemfibrozil vs. XZK" (MD 0.37, 95%CI −0.25 to 0.99), "atorvastatin + CHD conventional treatment vs. XZK + CHD conventional treatment" (MD-0.09, 95%CI −0.92 to 0.72), and "XZK + atorvastatin vs. atorvastatin" (MD −0.17, 95%CI −0.66 to 0.31), which indicate no meaningful difference. The remaining comparison showed similar LDL-C effects between the Bayesian and the frequentist approaches, suggesting that the results of the Bayesian model may be more conservative or robust.

3.3.2.2. High-density lipoprotein cholesterol levels. Totally 123 RCTs

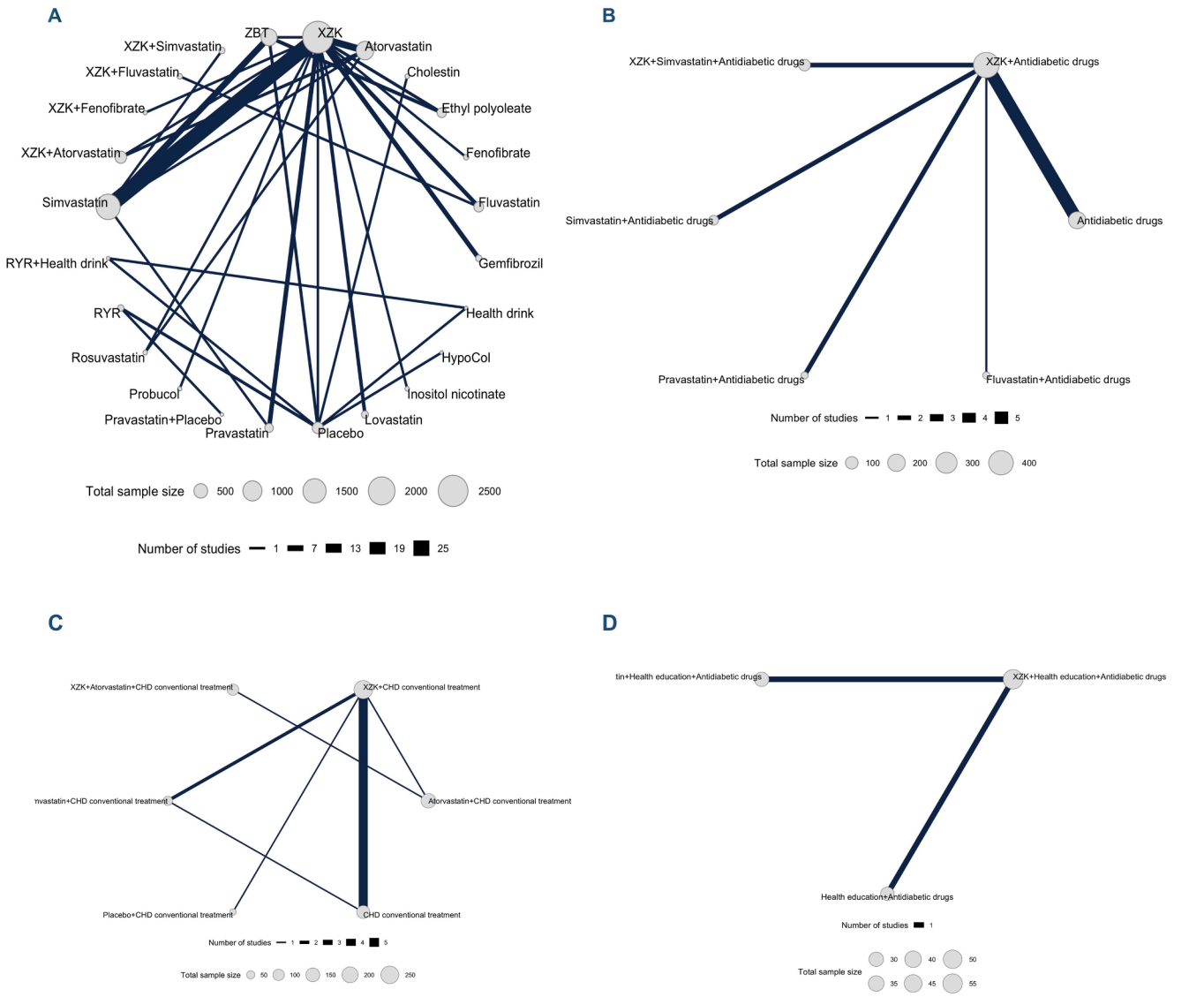

Fig. 5. Network evidence on outcome LDL-C levels. Fig. 5**A:** Sub-net 1 for dyslipidemia participants, Fig. 5**B:** Sub-net 2 for dyslipidemia participants with diabetes, Fig. 5**C:** Sub-net 3 for dyslipidemia participants with CHD, Fig. 5**D:** Sub-net 4 for dyslipidemia participants with diabetes.

including 11,694 participants reported on HDL-C. The network was not fully connected while made up of four sub-nets. **Supplementary Fig. S5** displays results of network *meta*-analysis. Sub-net 1 consisted of 97 RCTs including 24 treatments (9,525 participants). Compared to "XZK", the RE models showed a significant decrease in HDL-C levels in the treatment of placebo (MD −0.22,95%CI −0.37 to −0.07), inositol nicotinate (MD −0.21, 95%CI −0.34 to −0.09), and ethyl polyoleate(MD −0.15, 95%CI −0.26 to −0.03); and XZK + atorvastatin could result in higher HDL-C levels compared with XZK (MD 0.18, 95%CI 0.01 to 0.35) and atorvastatin (MD 0.17, 95%CI 0.02 to 0.34). Another RYR preparation ZBT showed a significant increasing effect on HDL-C compared to inositol nicotinate (MD 0.13, 95%CI 0.02 to 0.26). The remaining comparisons showed insignificance. Nevertheless, the UME models showed a different result for "XZK + atorvastatin vs. XZK" indicating no meaningful difference (MD −0.14, 95%CI −0.43 to 0.16). The SUCRA sequenced as XZK + atorvastatin, XZK + simvastatin, fluvastatin, rosuvastatin, XZK + fluvastatin, gemfibrozil, XZK, atorvastatin, Hypocol, pravastatin, simvastatin, fenofibrate, lovastatin, pravastatin + placebo, ZBT, Cholestin, RYR, ethyl polyoleate, probucol, inositol nicotinate, placebo, RYR + health drink, health drink, none. Node-splitting models fitted for 18 comparisons. Node-splitting the atorvastatin vs. XZK(P = 0.025), XZK + atorvastatin vs. XZK (P = 0.022), and XZK + atorvastatin vs. atorvastatin (P = 0.017) comparisons results in the lower DIC than the consistency model, meaning that there is substantial disagreement between the direct and indirect evidence on these comparisons. In the remaining 15 inconsistency models, there was no evidence of inconsistency.

Sub-net 2 consisted of 12 RCTs including six treatments (922 dyslipidemia participants with diabetes). Compared to "XZK + antidiabetic drugs", the RE models showed a decreasing trend in HDL-C levels in the treatment of antidiabetic drugs (MD −0.19, 95% CI −0.42 to 0.01). The remaining comparisons showed insignificance in XZK + antidiabetic drugs compared with statins + antidiabetic drugs. The SUCRA sequenced as fluvastatin + antidiabetic drugs, pravastatin + antidiabetic drugs, XZK + antidiabetic drugs, XZK + simvastatin + antidiabetic drugs, simvastatin + antidiabetic drugs, antidiabetic drugs.

Sub-net 3 consisted of 9 RCTs including six treatments (762 dyslipidemia participants with CHD). Compared to "XZK + CHD conventional treatment", the RE models showed a significant decrease in HDL-C levels in the treatment of placebo + CHD conventional treatment (MD −0.48, 95%CI −0.71 to −0.23) and CHD conventional treatment (MD −0.31, 95%CI −0.45 to −0.22). The SUCRA sequenced as XZK +

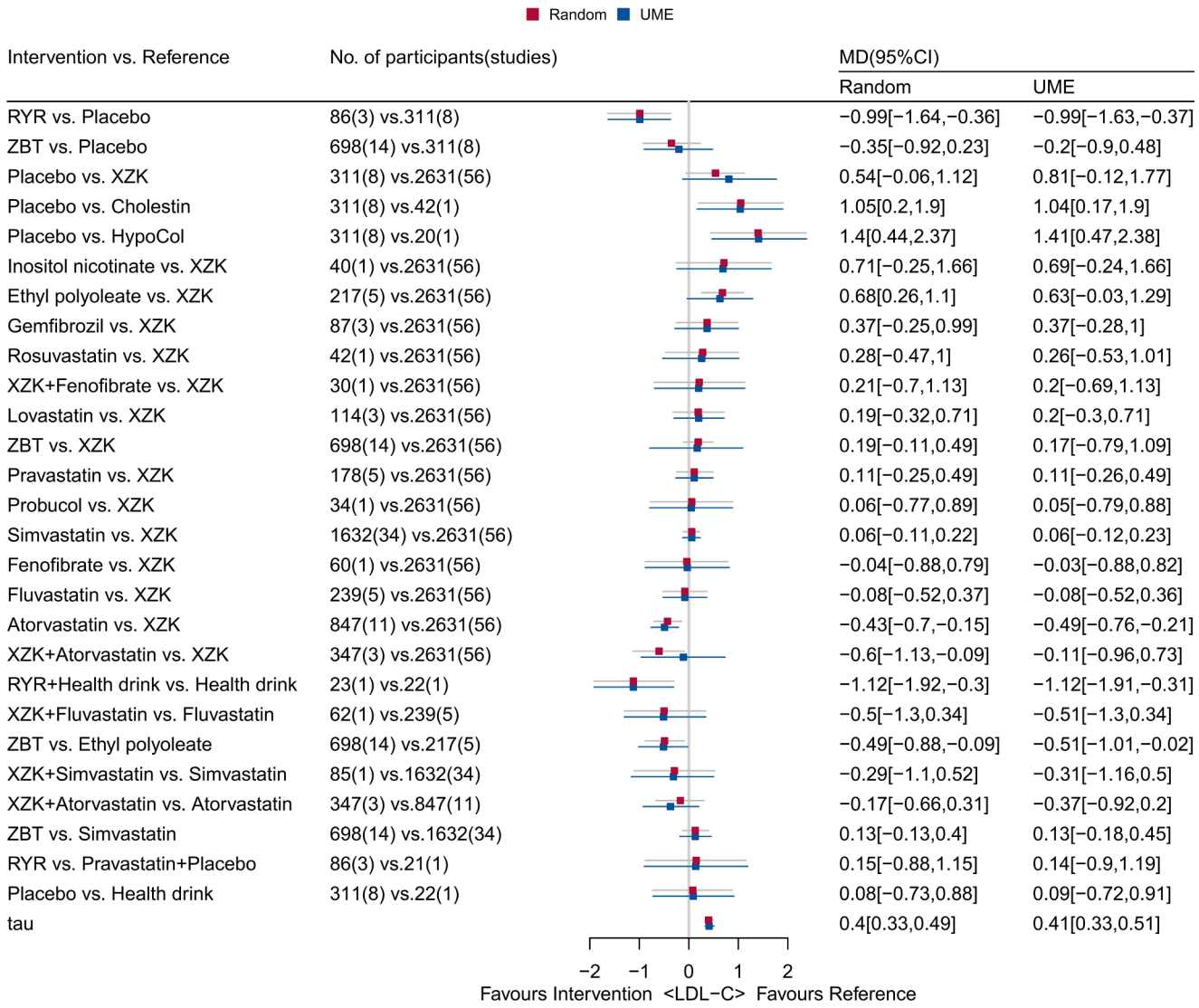

Fig. 6. Forest plot for RE and UME models for Sub-net 1 on LDL-C levels. RE: random effects, UME: unrelated mean effects, the estimations for each comparison shown in the graph represent overall estimation.

atorvastatin + CHD conventional treatment, simvastatin + CHD conventional treatment, XZK + CHD conventional treatment, atorvastatin + CHD conventional treatment, CHD conventional treatment, placebo + CHD conventional treatment. Node-splitting model fitted for 1 comparison: simvastatin + CHD conventional treatment vs. CHD conventional treatment. There was no evidence of inconsistency.

Sub-net 4 consisted of 2 RCTs including three treatments (112 dyslipidemia participants with diabetes). Compared to "XZK + health education + antidiabetic drugs", the FE model showed a significant decrease in HDL-C levels in the treatment of simvastatin + health education + antidiabetic drugs (MD −0.14, 95%CI −0.22 to −0.06). The SUCRA sequenced as XZK + health education + antidiabetic drugs, health education + antidiabetic drugs, simvastatin + health education + antidiabetic drugs.

3.3.2.3. Total cholesterol levels. Totally 135 RCTs including 12,734 participants reported on TC. The network was not fully connected but consisted of four sub-nets. **Supplementary Fig. S6** displays the network *meta*-analysis results.

Sub-net 1 consisted of 108 RCTs including 26 treatments (10,638 participants). Compared to "placebo", the RE models showed a significant decrease in TC levels in the treatment of RYR (MD −1.09, 95%CI −1.66 to −0.5) and ZBT (MD −0.78, 95%CI −1.12 to −0.45). While placebo could result in higher TC levels compared to another three RYR preparations Hypocol (MD 1.35, 95%CI 0.5 to 2.2), Cholestin (MD 1.04, 95%CI 0.21 to 1.86) and XZK (MD 0.97, 95%CI 0.62 to 1.34). Moreover, compared to "XZK", the RE models showed a significant increase in TC levels in the treatment of "None" (MD 2.57, 95%CI 1.79 to 3.53), ethyl polyoleate (MD 0.75, 95%CI 0.43 to 1.04), inositol nicotinate (MD 0.71, 95%CI 0.43 to 1.00). While administration of "XZK + health education" could result in lower TC levels than XZK (MD −2.07, 95%CI −2.81 to −1.32). "XZK + atorvastatin" could lower TC levels compared to XZK (MD −0.54, 95%CI −0.94 to −0.13) and atorvastatin (MD −0.45, 95%CI −0.82 to −0.08). ZBT could result in lower TC levels than ethyl polyoleate (MD −0.55, 95%CI −0.86 to −0.26) and inositol nicotinate (MD −0.52, 95%CI −0.79 to −0.26). Nevertheless, the UME model showed a different result for "XZK + atorvastatin vs. XZK" indicating no meaningful difference (MD 0.32, 95%CI −0.39 to 1.03). The remaining comparisons were not significant.

The SUCRA sequenced as XZK + health education, XZK + fluvastatin, XZK + atorvastatin, RYR + health drink, Hypocol, XZK + simvastatin, fluvastatin, pravastatin + placebo, atorvastatin, RYR, probucol, Cholestin, XZK, pravastatin, gemfibrozil, simvastatin, fenofibrate, rosuvastatin, ZBT, health drink, lovastatin, XZK + fenofibrate, inositol

nicotinate, ethyl polyoleate, placebo, none.

Node-splitting models fitted for 24 comparisons. Node-splitting the atorvastatin vs. XZK($P < 0.01$), XZK + atorvastatin vs. XZK(P < 0.01), and XZK + atorvastatin vs. atorvastatin ($P = 0.011$) comparisons showed substantial disagreement between the direct and indirect evidence. The remaining 21 comparisons showed no inconsistency.

Sub-net 2 consisted of 13 RCTs including 6 treatments (1,008 dyslipidemia participants with diabetes). Compared to "XZK + antidiabetic drugs", the RE models showed an increasing effect in TC levels in the treatment of antidiabetic drugs (MD 1.32, 95% CI 0.75 to 1.89). The SUCRA sequenced as XZK + antidiabetic drugs, fluvastatin + antidiabetic drugs, pravastatin + antidiabetic drugs, XZK + simvastatin + antidiabetic drugs, simvastatin + antidiabetic drugs, antidiabetic drugs.

Sub-net 3 consisted of 10 RCTs including six treatments (689 dyslipidemia participants with CHD). Compared to "XZK + CHD conventional treatment", the RE models showed a significant increase in TC levels in the treatment of placebo + CHD conventional treatment (MD 2.62, 95%CI 1.98 to 3.25) and CHD conventional treatment (MD 0.91, 95%CI 0.67 to 1.17). The SUCRA sequenced as XZK + atorvastatin + CHD conventional treatment, simvastatin + CHD conventional treatment, XZK + CHD conventional treatment, atorvastatin + CHD conventional treatment, CHD conventional treatment, placebo + CHD conventional treatment. Node-splitting model fitted for one comparison: simvastatin + CHD conventional treatment vs. CHD conventional treatment. There was no evidence of inconsistency.

Sub-net 4 consisted of 2 RCTs including three treatments (112 dyslipidemia participants with diabetes). Compared to "XZK + health education + antidiabetic drugs", the FE model showed a significant increase in TC levels in the treatment of health education + antidiabetic drugs (MD 1.02, 95%CI 0.8 to 1.24). The SUCRA sequenced as simvastatin + health education + antidiabetic drugs, XZK + health education + antidiabetic drugs, and health education + antidiabetic drugs.

3.3.2.4. Triglyceride levels. Totally 129 RCTs including 12,141 participants reported on TG. The network was not fully connected but consisted of four sub-nets. The network *meta*-analysis results are shown in **Supplementary Fig. S7**.

Sub-net 1 consisted of 102 RCTs including 26 treatments (9,915 participants). Compared to "placebo", the RE models showed a significant decrease in TC levels in the treatment of ZBT (MD −0.53, 95%CI −0.86 to −0.21). While placebo could result in higher TG levels than XZK (MD 0.67, 95%CI 0.33 to 1.02). Moreover, compared to "XZK", the RE models showed a significant increase in TG levels in the treatment of "ethyl polyoleate" (MD 0.41, 95%CI 0.13 to 0.7), "inositol nicotinate" (MD 0.35, 95%CI 0.09 to 0.61). While the UME model showed a different result for "inositol nicotinate vs. XZK" indicating no meaningful difference (MD 0.16, 95%CI −0.2 to 0.52). The remaining comparisons were not significant.

The SUCRA sequenced as gemfibrozil, XZK + health education, XZK + fluvastatin, XZK + atorvastatin, fenofibrate, atorvastatin, XZK + simvastatin, pravastatin, XZK, fluvastatin, Hypocol, simvastatin, lovastatin, rosuvastatin, ZBT, inositol nicotinate, Cholestin, probucol, ethyl polyoleate, pravastatin + placebo, RYR, None, XZK + fenofibrate, placebo, RYR + health drink, health drink. Node-splitting models fitted for 18 comparisons. There was no evidence of inconsistency.

Sub-net 2 consisted of 13 RCTs including 6 treatments (1,008 dyslipidemia participants with diabetes). Compared to "XZK + antidiabetic drugs", the RE models showed an increasing effect in HDL-C levels in the treatment of antidiabetic drugs (MD 0.78, 95% CI 0.29 to 1.23). The SUCRA sequenced as XZK + antidiabetic drugs, XZK + simvastatin + antidiabetic drugs, pravastatin, simvastatin + antidiabetic drugs, fluvastatin + antidiabetic drugs, antidiabetic drugs.

Sub-net 3 consisted of 10 RCTs including six treatments (819 dyslipidemia participants with CHD). Compared to "XZK + CHD conventional treatment", the FE models showed a significant increase in TC levels in the treatment of placebo + CHD conventional treatment (MD 1.29, 95%CI 0.96 to 1.61) and CHD conventional treatment (MD 0.48, 95%CI 0.39 to 0.59). Moreover, XZK + atorvastatin + CHD conventional treatment could lower TG level compared to atorvastatin + CHD conventional treatment (MD −0.73, 95%CI −0.99 to −0.45). The SUCRA sequenced as XZK + atorvastatin + CHD conventional treatment, atorvastatin + CHD conventional treatment, XZK + CHD conventional treatment, simvastatin + CHD conventional treatment, CHD conventional treatment, placebo + CHD conventional treatment. Node-splitting model fitted for one comparison: simvastatin + CHD conventional treatment vs. CHD conventional treatment. There was no evidence of inconsistency.

Sub-net 4 consisted of 2 RCTs including three treatments (112 dyslipidemia participants with diabetes). Compared to "XZK + health education + antidiabetic drugs", the FE model showed a significant increase in TC levels in the treatment of health education + antidiabetic drugs (MD 0.61, 95%CI 0.45 to 0.77) and simvastatin + health education + antidiabetic drugs (MD 0.26, 95%CI 0.04 to 0.48). The SUCRA sequenced as XZK + health education + antidiabetic drugs, simvastatin + health education + antidiabetic drugs, health education + antidiabetic drugs.

3.3.2.5. ApoA1 levels. Totally six RCTs including 530 participants reported on ApoA1. The network was not fully connected but involved two sub-nets. **Supplementary Fig. S8** shows the network *meta*-analysis results. Sub-net 1 consisted of 4 RCTs including four treatments (324 participants). The SUCRA sequenced as simvastatin, ZBT, Hypocol, and placebo. Sub-net 2 consisted of 2 RCTs including three treatments (206 participants). The SUCRA sequenced as XZK, fenofibrate, and gemfibrozil. For both sub-nets, the comparisons of the RE or FE models showed insignificance in ApoA1 levels.

3.3.2.6. ApoB levels. Totally nine RCTs including 784 participants reported on ApoB. The network was not fully connected while consisted of 1 sub-net, with 8 RCTs including eight treatments (724 participants). **Supplementary Fig. S9** shows the network *meta*-analysis results. Compared to "placebo", the FE models showed a significant decrease in ApoB levels in the treatment of RYR (MD −0.34, 95%CI −0.47 to −0.21) and ZBT (MD −0.1, 95%CI −0.19 to −0.02). While placebo could result in higher ApoB levels compared to Hypocol (MD 0.34, 95%CI 0.25 to 0.43) and XZK (MD 0.29, 95%CI 0.22 to 0.36). The SUCRA sequenced as fenofibrate, Hypocol, RYR, gemfibrozil, XZK, ZBT, placebo, and simvastatin.

3.3.2.7. Lp(a) levels. Totally three RCTs including 590 participants reported on Lp(a). The network was fully connected. **Supplementary Fig. S10** displays the network *meta*-analysis results. Compared to "placebo", the RE models showed a decreasing trend in Lp(a) levels in the treatment of ZBT(RYR). The SUCRA sequenced as simvastatin, ZBT, and placebo.

3.3.3. Glucose metabolism indicators, including FBG, 2hPG, and HbA1c

3.3.3.1. Fasting blood glucose. Totally 12 RCTs including 934 participants reported FBG. The network was not fully connected while made up of two sub-nets. The results of the network *meta*-analysis are available in **Supplementary Fig. S11**. Sub-net 1 consisted of 7 RCTs including four treatments (588 dyslipidemia participants with diabetes). The comparisons of the RE models showed insignificance in FBG levels. The SUCRA sequenced as XZK + antidiabetic drugs, XZK + simvastatin + antidiabetic drugs, simvastatin + antidiabetic drugs, and antidiabetic drugs.

Sub-net 2 consisted of 2 RCTs including three treatments (149 participants). Compared to "XZK", the FE models showed a significant increase in FBG levels in the treatment of "None" (MD 10.35, 95%CI 8.9 to 11.75). The remaining comparisons were not significant. The SUCRA

sequenced as XZK, ethyl polyoleate, and none.

3.3.3.2. Two hours postprandial blood glucose. A total of nine RCTs, including 583 participants, reported on 2hPG. The network was not fully connected, six RCTs involving 373 dyslipidemia participants with diabetes were included. **Supplementary Fig. S12** displays the network *meta*-analysis results. The comparisons of the RE models showed insignificance in 2hPG levels. The SUCRA sequenced as antidiabetic drugs, simvastatin + antidiabetic drugs, XZK + antidiabetic drugs, and XZK + simvastatin + antidiabetic drugs.

3.3.3.3. Hglycosylated hemoglobin A1c. Totally seven RCTs, including 584 participants, reported on HbA1c. The network was not fully connected, five RCTs involving 434 dyslipidemia participants with diabetes were included. **Supplementary Fig. S13** shows the network *meta*-analysis results. Compared to "XZK + antidiabetic drugs", the RE models showed a significant increase in HbA1c levels in the treatment of "XZK + simvastatin + antidiabetic drugs" (MD 1.74, 95%CI 0.03 to 2.39). The SUCRA sequenced as XZK + antidiabetic drugs, antidiabetic drugs, and XZK + simvastatin + antidiabetic drugs.

3.3.4. Blood pressure

Totally four RCTs, including four treatments (405 participants), reported on systolic blood pressure (SBP) and diastolic blood pressure (DBP). The network was fully connected. **Supplementary Figs. S14-S15** displays the network *meta*-analysis results. The comparisons of the FE models showed insignificance in SBP and DBP levels. For SBP, the SUCRA sequenced as ethyl polyoleate, XZK, ZBT, and placebo; and for DBP, the SUCRA sequenced as ethyl polyoleate, XZK, placebo, ZBT.

3.3.5. Adverse events including muscular adverse drug reactions, abnormal liver function, and gastrointestinal reactions

3.3.5.1. Muscular adverse drug reactions. Totally 12 RCTs including nine treatments (14,121 participants) addressed muscular adverse drug reactions. The network was fully connected. The network *meta*-analysis results are shown in **Supplementary Fig. S16**. Compared to "XZK", the FE models showed a significant decrease in muscular adverse drug reactions in the treatment of "placebo" (logOR −5.98, 95%CI −14.75 to −0.21), and atorvastatin could increase muscular adverse drug reactions compared to XZK (logOR 8.85, 95%CI 0.38 to 23.32). The remaining comparisons were not significant. The SUCRA sequenced as placebo, RYR, pravastatin + placebo, fenofibrate, ZBT, XZK, Cholestin, simvastatin, and atorvastatin.

3.3.5.2. Liver dysfunction. Totally 62 RCTs (5,789 participants) addressed liver dysfunction. The network was not fully connected but made up of three sub-nets. **Supplementary Fig. S17** shows the network *meta*-analysis results. For Sub-net 1, compared to "placebo", the RE models showed a significant decrease in liver dysfunction in the treatment of ZBT (logOR −104.93, 95%CI −257.8 to −17.8). While placebo could result in higher liver dysfunction than XZK (logOR 20.58, 95%CI 0.32 to 63.77). Moreover, compared to "XZK", the RE models showed a significant increase in liver dysfunction in the treatment of fluvastatin (logOR 36.8, 95%CI 3.25 to 100.49), atorvastatin (logOR 36.58, 95%CI 2.33 to 102.5), inositol nicotinate (logOR 24, 95%CI 2.23 to 71.39), and simvastatin (logOR 2.69, 95%CI 0.53 to 6.94). ZBT showed less liver dysfunction compared to XZK (logOR −84.35, 95%CI –233.23 to −6.53), inositol nicotinate (logOR −108.34, 95%CI −260.43 to −19.27), simvastatin (logOR −87.04, 95%CI −236.51 to −8.97), fenofibrate (logOR −86.49, 95%CI −234.95 to −7.92), and lovastatin (logOR −85.42, 95%CI −234.23 to −7.34). While the UME model showed different results for "ZBT vs. placebo" (logOR −60.05,95%CI −213.17 to 50.41) and "ZBT vs. XZK" (logOR −37.21,95%CI −206.73 to 106.96), indicating no meaningful difference. The SUCRA sequenced as ZBT, RYR, probucol, gemfibrozil, XZK + fenofibrate, ethyl polyoleate, XZK, Hypocol, rosuvastatin, lovastatin, fenofibrate, simvastatin, pravastatin, placebo, inositol nicotinate, atorvastatin, XZK + fluvastatin, and fluvastatin.

Node-splitting models fitted for 14 comparisons. Node-splitting the placebo vs. XZK(P = 0.029) and simvastatin vs. pravastatin (P = 0.036) comparisons showed substantial disagreement between the direct and indirect evidence on these comparisons. In the remaining 12 inconsistency models, there were no significant differences between the direct and indirect estimates. There was no evidence of inconsistency.

Sub-net 2 consisted of 2 RCTs, including three treatments (111 dyslipidemia participants with CHD). The comparisons of the FE models showed insignificance in liver dysfunctions. The SUCRA sequenced as CHD conventional treatment, simvastatin, and XZK + CHD conventional treatment.

Sub-net 3 consisted of 5 RCTs including 5 treatments (364 dyslipidemia participants with diabetes). Compared to "XZK + antidiabetic drugs", the FE models showed a significant increase in liver dysfunction in the treatment of fluvastatin + antidiabetic drugs (logOR 58.88, 95%CI 2.28 to 165.06). The SUCRA sequenced as antidiabetic drugs, pravastatin + antidiabetic drugs, RYR + antidiabetic drugs, XZK + antidiabetic drugs, and fluvastatin + antidiabetic drugs.

3.3.5.3. Gastrointestinal reactions. Totally 65 RCTs (6,074 participants) addressed gastrointestinal reactions. The network was not fully connected while made up of three sub-nets. **Supplementary Fig. S18** displays the network *meta*-analysis results. Sub-net 1 consisted of 55 RCTs including 20 treatments (5,338 participants), compared to "placebo", the RE models showed a significant increase in gastrointestinal reactions in the treatment of RYR (logOR 50.31, 95%CI 1.87 to 131.84). Moreover, compared to "XZK", the RE models showed a significant increase in gastrointestinal reactions in the treatment of probucol (logOR 56.12, 95%CI 2.72 to 165.09), ethyl polyoleate (logOR 1.94, 95%CI 0.75 to 3.02), fenofibrate (logOR 1.89, 95%CI 0.16 to 4.04), fluvastatin (logOR 1.77, 95%CI 0.44 to 3.25), and inositol nicotinate (logOR 1.03, 95%CI 0.12 to 1.93). While rosuvastatin could result in fewer gastrointestinal reactions than XZK (logOR −78.44, 95%CI −217.48 to −3.69). ZBT showed less gastrointestinal reactions compared to ethyl polyoleate (logOR −2.26, 95%CI −3.25 to −1.24), fenofibrate (logOR −2.21, 95% CI −4.55 to −0.43), and inositol nicotinate (logOR −1.35, 95%CI −2.38 to −0.41). Furthermore, RYR showed more gastrointestinal reactions than pravastatin + placebo (logOR 106.34, 95%CI 6.97 to 279).

While the UME model showed different results for "ethyl polyoleate vs. XZK" (logOR 0.91, 95%CI −1.22 to 2.7), "fenofibrate vs. XZK" (logOR 1.53, 95%CI −0.56 to 3.97), and "ZBT vs. inositol nicotinate" (logOR −0.83, 95%CI −2.43 to 0.72), indicating no meaningful difference. The SUCRA sequenced as rosuvastatin, gemfibrozil, lovastatin, ZBT, XZK + rosuvastatin, XZK, XZK + fenofibrate, simvastatin, placebo, XZK + fluvastatin, pravastatin, XZK + atorvastatin, atorvastatin, inositol nicotinate, Hypocol, fluvastatin, fenofibrate, ethyl polyoleate, probucol, RYR.Node-splitting models fitted for 12 comparisons. Node-splitting the fenofibrate vs. XZK (P = 0.017), lovastatin vs. XZK(P = 0.021), ZBT vs. fenofibrate(P = 0.013), and ZBT vs. lovastatin (P = 0.03) comparisons showed substantial disagreement between the direct and indirect evidence on these comparisons. In the remaining eight inconsistency models, there were no significant differences between the direct and indirect estimates. There was no evidence of inconsistency.

Sub-net 2 consisted of 2 RCTs including three treatments (191 dyslipidemia participants with CHD), and Sub-net 3 consisted of 6 RCTs, including six treatments (407 dyslipidemia participants with diabetes). The comparisons of the FE models showed insignificance in gastrointestinal reactions. The SUCRA of Sub-net 2 sequenced as atorvastatin + CHD conventional treatment, CHD conventional treatment, simvastatin + CHD conventional treatment, and XZK + CHD conventional treatment. For Sub-net 3, The SUCRA sequenced as antidiabetic drugs,

pravastatin + antidiabetic drugs, XZK + antidiabetic drugs, fluvastatin + antidiabetic drugs, simvastatin + antidiabetic drugs, XZK + simvastatin + antidiabetic drugs.

3.4. Reporting bias

The pairwise comparisons funnel plots generally appeared symmetrical, and the graphs for lipid profiles (LDL-C, HDL-C, TC, and TG) in XZK vs. atorvastatin comparisons presented some evidence of small-study effects which might be caused by selective outcome reporting (**Supplementary Fig. S19**).

3.5. Grading of the evidence certainty

Overall, the evidence for ten outcomes in 138 comparisons was assessed. Two outcomes (TC, TG) in "ZBT vs. placebo" showed high-quality evidence. Six outcomes (involving LDL-C, HDL-C, TC, TG, liver dysfunction, and gastrointestinal reactions) in 29 comparisons showed moderate evidence, which mostly downgraded one level for high risk of bias or imprecision. Eight outcomes (involving LDL-C, HDL-C, TC, TG, ApoB, muscular drug reactions, liver dysfunction, and gastrointestinal reactions) in 80 comparisons showed low evidence, mostly downgraded one level for high risk of bias and imprecision. Furthermore, ten outcomes in 27 comparisons showed very low evidence, which mostly downgraded one level for the high risk of bias, indirectness, and imprecision (**Supplementary Table S3**).

4. Discussion

Thirty-one SRs (165 trials) on RYR preparations for dyslipidemia were included, corresponding to 14,987 participants. Regarding the risk of bias assessments, all the SRs were assessed as having a high overall risk of bias by the ROBIS tool, and 23 SRs had very low overall confidence in AMSTAR 2, indicating that the quality of SRs for data screening, collection, and synthesis needs to be strengthened. For RCTs, blinding and completeness of reporting need to be focused on.

In patients with dyslipidemia, this *meta*-analysis suggests that RYR preparations such as XZK and ZBT may result in lower LDL-C, TC, and TG levels and higher HDL-C levels compared to other lipid-lowering agents such as ethyl polyoleate; while XZK alone may result in higher LDL-C levels than atorvastatin alone. In terms of adverse events, the RYR preparations showed fewer muscle adverse reactions, liver dysfunction and gastrointestinal reactions than other lipid-lowering agents such as inositol nicotinate and statins. Regarding the efficacy and safety, Hypocol, XZK combined atorvastatin, XZK combined health education, and gemfibrozil rank highest in regulating LDL-C, HDL-C, TC, and TG, respectively; Ethyl polyoleate ranks highest in regulating SBP and DBP; Placebo, ZBT, and rosuvastatin rank highest with the minimal muscular adverse reaction, liver dysfunction, and gastrointestinal reactions, respectively. It reveals that lipid-lowering agents, including RYR preparations, rank differently for each outcome. The efficacy and safety ranking of various RYR preparations may be due to the varying content of active lipid-lowering ingredients.

Regarding comorbidities, the management of dyslipidemia patients with diabetes or CHD is complex, because of numerous healthcare providers and poor compliance (Martone et al., 2022; Sabouret et al., 2022). In this network, for dyslipidemia patients with diabetes, the combination of XZK and antidiabetic drugs could result in lower levels of LDL-C, TC, and TG, and higher levels of HDL-C, compared to antidiabetic drugs alone. Also, the combination of XZK, antidiabetic drugs, and health education could decrease levels of LDL-C, TC, and TG, and increase levels of HDL-C, compared to antidiabetic drugs and health education. As for the SUCRA sequence, fluvastatin combined antidiabetic drugs rank highest in regulating LDL-C and HDL-C, and XZK combined antidiabetic drugs rank highest in regulating TC, TG, FBG, and HbA1c. For dyslipidemia patients with CHD, the combination of XZK and CHD conventional treatment could result in lower levels of LDL-C, TC, and TG, and higher levels of HDL-C, compared to CHD conventional treatment alone; while could increase LDL-C levels compared to the combination of atorvastatin and CHD conventional treatment. As for the SUCRA sequence, XZK combined atorvastatin and conventional treatment ranks highest in regulating LDL-C, HDL-C, TC, and TG; conventional treatment and atorvastatin combined conventional treatment rank highest with minimal liver dysfunction and gastrointestinal reactions, respectively. The discrepancy may be related to drug interaction, or to the pathophysiological mechanism of dyslipidemia complicated with diabetes (Vergès, 2015) or coronary heart disease (Mitu et al., 2020).

Although there is no statistical difference, RYR preparations show an antihypertensive trend, which still indicates that RYR preparations have multiple regulatory effects, and its mechanism of action still needs to be further explored.

Regarding quality evidence, high-quality evidence demonstrates the efficacy of ZBT in reducing TC and TG. Several RYR preparations showed moderate quality evidence of stronger modulation of lipid-regulating effects and fewer adverse effects, compared to placebo, inositol nicotinate, ethyl polyoleate, or simvastatin. In addition, XZK combined atorvastatin shows more beneficial effects on regulating HDL-C and TC levels than atorvastatin alone, with moderate evidence.

Furthermore, Lp(a) levels are of increasing concern due to their strong association with cardiovascular events (Zhu et al., 2022). In this study, Zhibituo (RYR) showed a trend towards lower Lp(a) levels compared to placebo.

The first *meta*-analysis of RYR for primary hyperlipidemia was published in English (Liu et al., 2006), which involved 93 trials, observing the major lipid profiles, including TC, TG, LDL-C, and HDL-C, indicating short-term beneficial effects of RYR preparations on lipid modification. However, our network *meta*-analysis explored more trials (165 RCTs) and more lipids profiles involving TC, TG, LDL-C, HDL-C, ApoA1, ApoB, and Lp(a), thus we found the beneficial effects of RYR preparations on lowering ApoB. Furthermore, we explored the glucose metabolism outcomes closely associated with lipids metabolism, and confirmed that XZK has a hypoglycaemic effect.

Compared to a *meta*-analysis of 15 high-quality RCTs of RYR for dyslipidemia (Li, Wang, et al., 2021), which was published in English recently and found the RYR's effect in reducing Apo B, our network *meta*-analysis provided grading evidence to confirm this. Furthermore, we explored the MACE, which was closely associated with dyslipidemia (Yannas et al., 2021). The ranking of the four interventions sequenced from high to low as simvastatin, fenofibrate, XZK, and XZK combined fenofibrate. Only five trials addressed MACE, due to the limited data, no meaningful conclusions can be drawn about the treatment's benefits and harms. The findings suggest that future trials on lipid-lowering of RYR consider MACE as an outcome.

5. Strengths and limitations

This is the first overview and network *meta*-analysis generating the efficacy and safety rankings of different RYR preparations for dyslipidemia, with a critical assessment of existing SRs.

Since the diversity of the comparisons and reported outcomes, grading evidence assessment for the insignificant effects on individual outcomes was not performed, and the pairwise not included in the network was not analyzed either. Trials of direct comparison of lipid-lowering agents were not included in this SR, which is the main reason for the low sample size of some direct comparisons in our network, and therefore may result in a degraded level of evidence. Based on this, we did not evaluate the evidence for effects ranking. To improve the robustness of the results of traditional medicine network *meta*-analysis, it is necessary to consider the inclusion of standard control drugs (recommended by evidence-based clinical guidelines) in direct comparison trials in the future. It should be noted that ZBT tablets and

ZBT capsules may differ in composition, with ZBT tablets being single drug preparations of RYR and one type of ZBT capsules being a compound formula containing RYR (Diao Group, 2003), and due to limited information on the drugs in the trials, ZBT capsules were excluded from this study.

Most RCTs and SRs did not report the content of monacolin K in the RYR preparations, thereby making the comparisons of dosage impossible. In addition, other components in RYR, such as RYR pigments, also have lipid-lowering potential (Zhou et al., 2019), unfortunately none of the included studies reported the content of other lipid-lowering components in RYR.

The RCTs included in this study were extracted from RCTs included in previously published systematic reviews, searched until March 2022, and included RCTs published from 1996 to 2018. Although RYR RCTs have been published in recent years, supplemental searches were not conducted for RCTs published in the last two years since the large number of included studies and the timing of implementation.

6. Conclusions

The findings of this study reveal all tested lipid-lowering agents compared with RYR preparations, ranked differently for efficacy and safety in regulating lipids and glucose metabolism in dyslipidemia patients, with or without diabetes or CHD. For dyslipidemia patients, RYR preparations may have stronger lipid-lowering effects and fewer adverse events than some lipid-lowering agents and certain statins, but this is not entirely absolute. For dyslipidemia with diabetes or CHD, RYR combined with antidiabetic drugs or CHD conventional treatment might help patients reach lipid goals earlier. The results inform clinicians with a reference for selecting the appropriate lipid-lowering agents based on the patient's condition and goals. The mechanism can be studied from the drug interaction, the pathophysiology of dyslipidemia comorbidities, and the varying content of active lipid-lowering ingredients of RYR. Future trials should focus on MACE as an important outcome in comparison with conventional lipid-lowering agents.

Ethics statement

The research did not include any human subjects and animal experiments hence ethical approval is not required.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2023.105508.

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