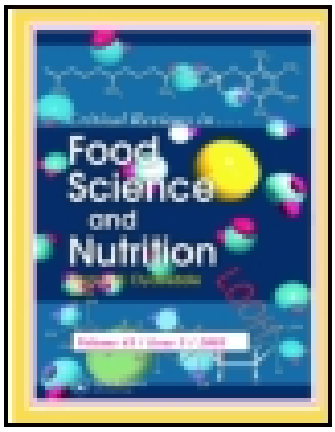

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The Effects of Red Yeast Rice Dietary Supplement on Blood Pressure, Lipid Profile and C-reactive Protein in Hypertension: A Systematic Review

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The effects of red yeast rice dietary supplement on blood pressure, lipid profile and C-reactive protein in hypertension: A systematic review

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Abstract

Interest is increasing regarding the potential health effects of red yeast rice (RYR) consumption, which is described as a "natural statin" in China. This review aims to evaluate the

efficacy of RYR on blood pressure (BP), lipid profile, and C-reactive protein (CRP) in treating hypertension. Seven electronic databases including the Cochrane Central Register of Controlled Trials, EMBASE, PubMed, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Scientific Journal Database (VIP), the Chinese Biomedical Literature Database (CBM), and the Wanfang database were searched. To investigate the role of RYR for hypertension, randomized controlled trials for the use of RYR either as monotherapy or in combination with conventional medicine versus placebo, no intervention, or conventional medicine for hypertension were identified. A total of 21 trials containing 4558 patients were analyzed, the majority of which had low methodological quality. "RYR plus conventional therapy" exhibited significant lowering effects on serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and CRP but exhibited no significant effect on systolic BP, diastolic BP, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) compared with "placebo plus conventional therapy". "RYR plus conventional therapy" showed significant lowering effects on systolic BP, TC, LDL-C, and CRP but no effect on diastolic BP, TG, and HDL-C compared with "placebo plus conventional therapy". No significant difference in BP and lipid profile between "RYR plus conventional therapy" and "statins plus conventional therapy" was observed. "RYR plus statins" appeared to be more effective in lowering BP, TC, TG, and LDL-C but without a significant difference in HDL-C compared to statins. No serious adverse events were reported. The results of this meta-analysis suggested some supportive but limited evidence regarding RYR for

hypertension. Further rigorously designed trials are warranted before RYR could be recommended to hypertensive patients.

Keywords

Monascus purpureus, hongqu, red Koji, natural statin, antihypertensive effect, lipid-lowering effect

Introduction

Hypertension has been a devastating medical, societal, and economic problem [1]. Data from a recent survey demonstrated that hypertension is associated with serious morbidity and increased mortality [2, 3]. Persistent elevation of blood pressure (BP), therefore, has been well recognized as the main attributable risk factor accounting for 30% of all deaths worldwide [4]. From a worldwide perspective, approximately 7 million deaths and 64 million disability-adjusted life years annually are related to poorly controlled BP [5]. Findings from prospective cohort studies have established a graded positive association between BP and risk of cardiovascular diseases (CVDs), beginning at 115 mmHg for systolic blood pressure (SBP) [6]. Because hypertension and hyperlipidemia often interrelate and share common pathophysiologic pathways, statin therapy is increasingly favored for the treatment of hypertension [7]. Statin therapy has exhibited a relatively small but significant antihypertensive effect beyond its lipid-lowering capacity [8-11]. Prospective clinical trials from the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) revealed that the administration of additional atorvastatin was associated with a 36% decrease in nonfatal myocardial infarction and fatal coronary heart disease (CHD) and a 27% decrease in the incidence of fatal and nonfatal stroke for hypertensive patients [12]. More recently, meta-analyses have demonstrated that statin therapy not only moderately reduced BP but also effectively decreased cardiovascular morbidity

and mortality to the same extent in both hypertensive and nonhypertensive individuals [13, 14]. Therefore, adequate control of these co-existing risk factors in hypertensive patients as early as possible is of great importance [15]. Although the benefits of current therapies have been well established, the increasing burden of hypertension and its complications highlights the need for innovative approaches for the prevention and management of the disease. Currently, there is an increasing scientific interest in complementary therapies such as nutrients and herbal medicine [16-18].

Red yeast rice (RYR) is a traditional Chinese product made by fermenting *Monascus purpureus*, a type of yeast, over rice. RYR, also known as "*hongqu*" or red *Koji*, consists mainly of nonglutinous rice, red yeast, and byproducts of the fermentation [19]. In East Asia, health-enhancing qualities of RYR have been recorded for more than 1200 years (first documented in the *Tang* Dynasty in 800 AD) as has its use for producing wines, red soybean cheese, and other fermented food products [20]. Moreover, its medicinal properties have also been observed by ancient physicians. In the *Ben Cao Gang Mu* written by *Shizhen Li* (1518-1593), one of the most prominent pharmacologists of the *Ming* Dynasty (1368-1644), RYR was characterized as "sweet in flavor and warm in property". Based on traditional Chinese medicine theory, it can promote blood circulation to remove blood stasis and strengthen spleen to promote digestion [21]. RYR has continued to be used as a dietary staple in many countries, including China, Japan, France, Italy, Norway, and the United States since World War II [22].

As a traditional Chinese herbal medicine with hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibiting activity, RYR contains a family of naturally occurring statins (monacolins), one of which is lovastatin [23]. It significantly reduced serum total cholesterol (TC, decreased by 0.97 mmol/L), triglycerides (TG, decreased by 0.23 mmol/L), and low-density lipoprotein cholesterol (LDL-C, decreased by 0.87 mmol/L), but did not notably improve high-density lipoprotein cholesterol (HDL-C, increased by 0.08 mmol/L) [24]. This finding was also supported by a large number of clinical studies over the past 20 years, with TC, TG, and LDL-C reduced by 19%-32%, 20%-48%, and 23%-43%, respectively, and HDL-C increased by 8%-20% [25-31]. Due to its marked lipid-lowering effect, RYR is recognized as a "natural statin" in China and as an effective and relatively safe alternative approach for hyperlipidemia [24].

More recently, a proprietary RYR named "*xuezhikang*" in Chinese has been authoritatively approved by the China Food and Drug Administration (CFDA, available at http://www.sda.gov.cn) as a dietary supplement [31]. Each capsule (300 mg) contains the combination of lovastatin, also termed monacolin K (2.5-3.2 mg), unsaturated fatty acids, essential amino acids, lovastatin hydroxyl acid, ergosterol and some other components, all of which are inherently contained in RYR without additional ingredients [32, 33]. It has been marketed in several European countries including Norway and Italy, bringing notable economic and clinical benefits [30]. There is mounting evidence from clinical trials suggesting that RYR plays an important role in the prevention and treatment of CVDs including CHD [34-44],

hyperlipidemia [31, 38-41, 44], cardiac syndrome X [45], and hypertension [42, 43, 46]. The cardiovascular pharmacological mechanisms involve regulating the lipid profile, reducing the degree of inflammatory reaction, improving endothelial function, reducing the formation of oxygen free radical, reducing lipid oxidation, and inhibiting the expression of tissue factor and nicotinamide adenine dinucleotide phosphate oxidase activation, all of which are highly relevant to BP reduction and the prevention of hypertension [38-41, 44, 47, 48]. Currently, interest regarding the potential health effects of RYR consumption for hypertension is increasing. However, no sound evidence such as meta-analyses and systematic reviews have been published to evaluate the effects of RYR for hypertensive patients. Thus, we aimed to systematically review the data from randomized controlled trials (RCTs) to ascertain its role for hypertension.

Methods

Eligibility criteria

Types of studies

Original RCTs that investigated the effects of RYR as monotherapy or adjunctive therapy in hypertensive patients were considered in this systematic review. We did not include quasi-randomized trials and animal experiments.

Types of participants

Patients with hypertension were included regardless of their age, sex, or nationality. The diagnostic criteria for hypertension should have met at least one of the international or domestic

guidelines and was defined as SBP ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg on at least two occasions [1]. If no detailed diagnostic criteria were reported but with the study included the declaration of definite hypertension, those trials were included as well. Participants were excluded if they had acute infection, acute myocardial infarction, severe arrhythmia, symptomatic heart failure, hepatic failure, or renal failure.

Types of interventions

Interventions in the treatment groups included RYR used alone or in combination with conventional medicine. Interventions in the control groups included placebo, no intervention or conventional medicine. No limitations on blinding, dosage or treatment duration were imposed. If an add-on study design was applied, patients in the treatment group should have been treated with the same type and dosage of conventional therapy under the same standard as was used in the control group. Trials were excluded for the following reasons: (a) randomization was not used; (b) other non-conventional therapies including herbal medicine, yoga, qigong, Tai Chi, acupuncture, moxibustion, and massage were applied in either the treatment or control groups; (c) no clinical data could be extracted; and (d) the trial was a duplicated study reporting the same data in more than one publication.

Types of outcome measures

The primary outcomes were defined as SBP and DBP. The secondary outcomes were defined as blood lipids (serum TC, TG, LDL-C, and HDL-C) and C-reactive protein (CRP). CRP

is highly related to vascular stiffness, atherosclerosis and the development of end-organ damage and cardiovascular events in hypertensive individuals [49-51]. Additionally, the combined action of elevated CRP and LDL-C further increased the risks of hypertension and prehypertension [52]. Therefore, increased blood lipids [53-55] and circulating levels of CRP [56-58] are closely associated with hypertension. In this review, blood lipids were measured in mmol/L. If cholesterol (TC, HDL, and LDL) or TG were published in mg/dL, they were multiplied by a respective factor of 0.02586 for cholesterol or 0.01129 for TG for conversion into mmol/L. At least one of the above outcomes should have been reported in the included trials.

Search strategy

We identified RCTs of RYR for hypertensive patients in the following seven electronic databases from their inception up to April 2014: the Cochrane Central Register of Controlled Trials (CENTRAL, 1996-2014, available at http://www.cochrane.org/editorial-and-publishing-policy-resource/cochrane-central-register-controlled-trials-central), EMBASE (1980-2014, available at http://www.elsevier.com/online-tools/embase), PubMed (1959-2014, available at http://www.ncbi.nlm.nih.gov/pubmed/), the Chinese National Knowledge Infrastructure (CNKI, 1979-2014, available at http://www.cnki.net/), the Chinese Scientific Journal Database (VIP, 1989-2014, available at http://www.cqvip.com/), the Chinese Biomedical Literature Database (CBM, 1978-2014, available at http://sinomed.imicams.ac.cn/), and the Wanfang Database

(1985-2014, available at http://www.wanfangdata.com.cn/). The references of the articles identified were also searched manually. To include further relevant studies, ongoing registered clinical trials were also searched through the websites of both international and China-based clinical trial registries (available at http://clinicaltrials.gov/ and http://www.chictr.org/). Our literature search had no language or publication status restriction. The following search terms were used as subject headings and keywords and were modified to suit different databases: ("hypertension" OR "primary hypertension" OR "essential hypertension" OR "high blood pressure" OR "blood pressure" OR "xue ya" OR "gao xue ya") AND ("red yeast rice" OR "*hongqu*" OR "red *Koji*" OR "red-yeast Chinese rice" OR "monascus purpureus" OR "cholestin" OR "*xuezhikang*" OR "*xue zhi kang*") AND ("clinical trial" OR "randomized controlled trial" OR "randomised controlled trial").

Study selection

To ensure accuracy, 2 reviewers independently screened the titles and abstracts of the potentially eligible articles based on the pre-determined search strategy. Then, the full-text articles were retrieved and examined according to the above inclusion criteria.

Data extraction

Data from each included clinical trial were independently extracted by 2 reviewers according to the pre-set data extraction form. The following details were extracted from each trial: (a) general information: primary author(s), title of the study, publication year, and name of

the journal; (b) characteristics of the included participants: age, sex distribution, sample size, diagnosis standard, and baseline data of BP, blood lipids and CRP; (c) characteristics of the included trials: study design, interventions in the treatment and control groups, intention to treat analysis, drop-out, dosage, and treatment duration; (d) outcome measures: SBP, DBP, TC, TG, LDL-C, HDL-C, and CRP; and (e) reporting of adverse events (AEs). In cases of missing information or any questions that arose regarding the outcomes, we contacted the corresponding authors or pharmaceutical company *via* email, telephone, or fax whenever possible. Discrepancies were resolved through discussion between the reviewers or consultation with a third party.

Quality assessment

The methodological quality of the included trials was independently evaluated by two reviewers using the Cochrane collaboration tool [59]. The "risk of bias" included the following seven aspects: (a) random sequence generation (selection bias); (b) allocation concealment (selection bias); (c) blinding of participants and personnel (performance bias); (d) blinding of outcome assessment (detection bias); (e) incomplete outcome data (attrition bias); (f) selective reporting (reporting bias); and (g) other sources of bias (from Chapter 8: Assessing risk of bias in included studies). Each aspect was assessed for low, high, or unclear risk of bias. According to how the above criteria were met, the methodological quality of the trial was categorized into three levels: (a) low risk of bias (all the items had low risk of bias); (b) high risk of bias (at least

one item had high risk of bias); or (c) unclear risk of bias (at least one item was unclear in risk of bias). Disagreements were resolved by discussion of the study details until consensus were reached.

Statistical analysis

The data of outcome measures after treatment were used to evaluate the differences between the treatment and control groups. We used the statistical package Revman 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) for data synthesis. Both dichotomous and continuous outcomes were extracted from the primary trials, without any conversion. Continuous outcomes were presented as weighted mean difference (WMD) and dichotomous outcomes as risk ratio (RR), both with a 95% confidence interval (CI). Meta-analysis was performed if outcomes were similar in clinical characteristics. Subgroup analysis was conducted according to the types of comparisons. I^2 statistics were used to assess the heterogeneity [59]. A fixed effects model was used if no significant heterogeneity of the data existed ($P > 0.10$, $I^2 \leq 50\%$), whereas a random effects model was used if significant heterogeneity presented ($P \leq 0.10$, $I^2 > 50\%$). Publication bias was assessed using a funnel plot analysis. $P < 0.05$ was considered to be statistically significant.

Results

Study identification

We identified 466 potentially relevant articles on RYR from electronic and manual searches.

By reviewing titles and abstracts, we excluded 320 duplicate records and 90 citations that were clearly review articles, experts' commentaries, case reports, case series, or non-clinical studies. A total of 56 full-text articles were retrieved for further assessment of which 35 were excluded for the following reasons: participants did not meet the inclusion criteria (n = 16), duplication (n = 10), no control group (n = 1), intervention included other medical therapies (n = 7), and no data for extraction (n = 1). Therefore, 21 RCTs involving 4558 participants met the eligibility criteria and were included in the final analysis [60-80]. The flow diagram of the process was summarized in Figure 1.

Study characteristics

Basic characteristics of the included trials and participants were summarized in Table 1 and Table 2. The average sample size of all included studies was 217, ranging from 40 to 2704 per trial. The included trials were published between 2005 and 2013, all of which were conducted in the People's Republic of China and were written in 2 languages (English, n = 4; Chinese, n = 17). All trials adopted RYR as adjunctive therapy in the treatment groups for hypertensive patients. Three trials used a three-group study design [62, 63, 68] of which 1 trial included conventional therapy, "valsartan plus conventional therapy", and "RYR plus valsartan and conventional therapy" [62], whereas the other 2 trials included conventional therapy, "pravastatin plus conventional therapy", and "RYR plus conventional therapy" [63, 68]. Notably, 1 trial conducted by Gong *et al* included 2 control groups, namely conventional therapy and "valsartan plus

conventional therapy"; however, only the "valsartan plus conventional therapy" group could be matched with the RYR group and thereby be included for statistical analysis [62]. Four trials compared "RYR plus conventional therapy" with "placebo plus conventional therapy" [60, 61, 67, 70]. One trial compared "RYR plus statins" with statins [77]. The remaining 13 trials compared "RYR plus conventional therapy" with conventional therapy [64-66, 69, 71-76, 78-80]. Patients in the treatment groups received the same type of RYR capsule under the same standard procedure, ingesting a daily dosage that ranged from 1200 mg to 1800 mg. The placebos used in the control groups matched RYR in aroma, color, and appearance. Conventional therapeutic interventions included aspirin, nitrates, and antihypertensive drugs, but without lipid-lowering drugs. All studies provided the baseline data for the comparability between the groups. The duration of treatment ranged from 1 month to 4.5 years.

Study quality

According to Cochrane's risks of bias tool previously referenced, the methodological quality of the included studies was variable. Among the 21 trials, only 1 was a multicenter, randomized, double-blind, placebo-controlled trial with low risk of bias [60]. Seven RCTs had an adequate method for random sequence generation [60, 61, 64, 68, 70, 73, 74], whereas the remaining 14 trials did not [62, 63, 65-67, 69, 71, 72, 75-80]. Allocation concealments were adequately performed in only 1 trial [60]. Blinding of participants and personnel was described in 4 trials [60, 61, 67, 70], whereas blinding of the assessor was only reported in 1 trial [60]. Four

trials used a placebo control [60, 61, 67, 70]. Dropouts and withdrawals were reported in 7 trials [60-63, 68, 70, 79]. The details of the included trials' risk of bias were listed in Table 3.

Efficacy assessment

All studies focused on the effect of RYR on hypertensive patients. Subgroup analysis was conducted among four different types of comparisons, including "RYR plus conventional therapy" *versus* "placebo plus conventional therapy" [60, 61, 67, 70], "RYR plus conventional therapy" *versus* conventional therapy [62-66, 68-69, 71-76, 78-80], "RYR plus statins" *versus* statins [77], and "RYR plus conventional therapy" *versus* "statins plus conventional therapy" [63, 68].

"RYR plus conventional therapy" *versus* "placebo plus conventional therapy"

Four trials evaluated the effect of RYR *versus* placebo as adjunctive therapy in treating hypertension [60, 61, 67, 70]. There were 1472 patients in the RYR group and 1447 in the placebo group.

Blood pressure. Meta-analysis did not reveal a significant lowering effect of RYR on SBP (WMD = -3.29 mmHg; 95% CI: -6.68 to 0.09; $P = 0.06$) and DBP (WMD = -1.31 mmHg; 95% CI: -3.54 to 0.93; $P = 0.25$) compared with the placebo group, with I^2 ranging from 63% to 67% (Figure 2).

Lipid profile. (a) Serum TC level: compared with placebo, a meta-analysis of 4 trials revealed a significant cholesterol-lowering effect of RYR (WMD: -0.50 mmol/L; 95% CI: -0.56

to -0.43; $P < 0.00001$) with no significant heterogeneity (chi-square = 5.62, $P = 0.13$; $I^2 = 47\%$) (Figure 3a). (b) Serum TG level: most of the trials reported serum TG levels before and after intervention except for 1 trial [61]. RYR had no significant effects on the level of TG (WMD: -0.38 mmol/L; 95% CI: -0.79 to 0.03; $P = 0.07$) with high heterogeneity (chi-square = 28.30, $P < 0.00001$; $I^2 = 93\%$) when compared with placebo (Figure 3b). (c) Serum HDL-C level: there was no significant difference of serum HDL-C level between the RYR group and the placebo group (WMD = 0.07 mmol/L; 95% CI: -0.02 to 0.16; $P = 0.14$) with high heterogeneity (chi-square = 8.07, $P = 0.04$; $I^2 = 63\%$) (Figure 3c). (d) Serum LDL-C level: RYR was found to significantly reduce the level of LDL-C (WMD: -0.63 mmol/L; 95% CI: -0.82 to -0.44; $P < 0.00001$) with high heterogeneity (chi-square = 9.20, $P = 0.03$; $I^2 = 67\%$) compared with placebo (Figure 3d).

C-reactive protein. One trial conducted by Ye *et al* evaluated the effect of RYR on serum CRP level [61]. As compared to the placebo group, the administration of RYR for 72 weeks significantly reduced the level of CRP (0.31 ± 0.13 mg/L *versus* 0.40 ± 0.17 mg/L, $P < 0.05$). The trial demonstrated that long-term therapy with RYR had better anti-inflammatory effects than placebo, as measured by CRP, which was also independent of the antihypertensive and lipid-lowering effects of RYR in hypertensive patients.

"RYR plus conventional therapy" *versus* conventional therapy

A total of 16 trials compared "RYR plus conventional therapy" with conventional therapy for the treatment of hypertension [62-66, 68-69, 71-76, 78-80]. There were 712 patients in the

"RYR plus conventional therapy" group and 695 in the conventional therapy group.

Blood pressure. All studies reported BP outcomes before and after treatment. Meta-analysis showed that compared with the conventional therapy group, SBP was significantly lower in the "RYR plus conventional therapy" group (WMD: -5.62 mmHg; 95% CI: -8.38 to -2.86; $P < 0.0001$); however, no significant effects on DBP were found in the "RYR plus conventional therapy" group (WMD: -2.20 mmHg; 95% CI: -5.66 to 1.26; $P = 0.21$), with I^2 ranging from 91% to 97% (Figure 4).

Lipid profile. (a) Serum TC level: eight studies evaluated the effect on serum TC level of the "RYR plus conventional therapy" group as compared to the conventional therapy group [62-65, 68, 71, 78, 79]. There were 346 patients in the "RYR plus conventional therapy" group and 341 in the conventional therapy group. A significant reduction of TC level was found in the "RYR plus conventional therapy" group (WMD: -0.91 mmol/L; 95% CI: -1.54 to -0.29; $P = 0.004$) with significant heterogeneity (chi-square = 339.93, $P < 0.00001$; $I^2 = 98\%$) as compared with the conventional therapy group (Figure 5a). (b) Serum TG level: meta-analysis of 7 trials [63-65, 68, 71, 78, 79] reporting TG level before and after treatment did not reveal a significant lowering effect on TG in the "RYR plus conventional therapy" group (WMD: -0.18 mmol/L; 95% CI: -0.42 to 0.06; $P = 0.13$) with significant heterogeneity (chi-square = 80.06, $P < 0.00001$; $I^2 = 93\%$) (Figure 5b). (c) Serum HDL-C level: six trials [63-65, 68, 71, 79] assessed the effect of the "RYR plus conventional therapy" on serum HDL-C level as compared to conventional therapy.

Meta-analysis did not detect any significant between-group difference (WMD: 0.10 mmol/L; 95% CI: -0.06 to 0.26; $P = 0.21$) with significant heterogeneity (chi-square = 22.86, $P = 0.0004$; $I^2 = 78\%$) (Figure 5c). (d) Serum LDL-C level: the pooled analysis of 5 trials [63, 64, 68, 71, 79] indicated that compared with the conventional therapy group, LDL-C level was significantly lower in the "RYR plus conventional therapy" group (WMD: -0.66 mmol/L; 95% CI: -1.18 to -0.14; $P = 0.01$) with significant heterogeneity (chi-square = 58.36, $P < 0.00001$; $I^2 = 93\%$) (Figure 5d).

C-reactive protein. The effect on CRP level was reported in 4 trials [66, 68, 69, 74]. There were 220 patients in the "RYR plus conventional therapy group" and 204 in the conventional therapy group. Meta-analysis revealed a significant lowering effect on CRP level in the "RYR plus conventional therapy" group (WMD: -0.77 mg/L; 95% CI: -1.20 to -0.34; $P = 0.0004$) with significant heterogeneity (chi-square = 13.22, $P = 0.004$; $I^2 = 77\%$) (Figure 6).

"RYR plus conventional therapy" *versus* "statins plus conventional therapy"

Two trials compared the BP and lipid profile of the "RYR plus conventional therapy" group with those of the "statins plus conventional therapy" group [63, 68]. There were 75 patients in the "RYR plus conventional therapy" group and 72 in the "statins plus conventional therapy" group.

***Blood pressure*.** The trials showed clinical homogeneity and were combined according to the fixed effects model (both with $I^2 = 0\%$). Pooled analysis did not reveal any significant

difference on SBP (WMD: -0.13 mmHg; 95% CI: -2.40 to 2.13; P = 0.91) or DBP (WMD: 0.23 mmHg; 95% CI: -1.63 to 2.09; P = 0.81) between the 2 groups (Figure 7).

Lipid profile. As no significant clinical heterogeneity was found regarding TC, TG, HDL-C, and LDL-C levels, the fixed effects model was chosen in the meta-analysis (I^2 = 0%, respectively). No significant difference was detected regarding the level of TC (WMD: -0.06 mmol/L; 95% CI: -0.24 to 0.13; P = 0.54), TG (WMD: -0.07 mmol/L; 95% CI: -0.18 to 0.05; P = 0.25), HDL-C (WMD: -0.03 mmol/L; 95% CI: -0.10 to 0.04; P = 0.39), and LDL-C (WMD: -0.03 mmol/L; 95% CI: -0.19 to 0.14; P = 0.77) between the 2 groups (Figure 8).

"RYR plus statins" *versus* statins

One trial conducted by Zhou and Lin in hypertensive patients complicated with CHD compared BP, TC, TG, HDL-C, and LDL-C levels in the "RYR plus atorvastatin calcium" group with the atorvastatin calcium group [77]. At the end of treatment, compared to the atorvastatin calcium group, the "RYR plus atorvastatin calcium" group showed a significant reduction in SBP (124.16 ± 1.16 mmHg *versus* 136.78 ± 10.25 mmHg, $P < 0.05$), DBP (81.35 ± 4.31 mmHg *versus* 87.19 ± 4.29 mmHg, $P < 0.05$), TC (4.16 ± 1.16 mmol/L *versus* 5.15 ± 1.41 mmol/L, $P < 0.05$), TG (1.35 ± 0.38 mmol/L *versus* 2.41 ± 0.27 mmol/L, $P < 0.05$), and LDL-C level (2.89 ± 0.45 mmol/L *versus* 4.03 ± 0.96 mmol/L, $P < 0.05$). However, there was no significant difference in HDL-C level (1.23 ± 0.42 mmol/L *versus* 1.25 ± 0.30 mmol/L, $P > 0.05$). The trial demonstrated that the "RYR plus atorvastatin calcium" therapy was more effective than

atorvastatin calcium alone in lowering BP and improving blood lipids for hypertension with CHD; that is, as a complementary therapy to statins, RYR could enhance the antihypertensive and lipid-lowing effects more significantly.

Adverse events

AEs was reported in 9 trials [60, 62, 64, 67, 72, 73, 77, 79, 80], and AEs were not mentioned in the remaining studies. AEs on symptoms and signs were reported in 8 (38.10%) of the 21 reviewed studies [60, 62, 64, 67, 73, 77, 79, 80]; however, no AEs were found in 3 trials [64, 73, 79]. Only 5 trials provided detailed information about AEs [60, 62, 67, 77, 80]. Among them, 1 trial compared the "RYR plus conventional therapy" with the "placebo plus conventional therapy" group [60], 3 compared the "RYR plus conventional therapy" with the conventional therapy group [62, 67, 80], and 1 compared the "RYR plus statins" *versus* statins group [77]. Eight frequently reported AEs, including gastrointestinal discomfort, allergic reactions, myalgias and psychoneurological symptoms, erectile dysfunction, edema, skin rash, dizziness, and cough, were summarized in Table 4. Meta-analysis of 5 trials revealed no significant difference regarding AEs between the RYR and the control groups (RR: 1.39; 95% CI: 0.81 to 2.38; P = 0.23) (Figure 9).

Additionally, AEs of RYR were also evaluated by biochemical indicators, including glutamate pyruvate transaminase (GPT or ALT) and glutamic oxaloacetic transaminase (GOT or AST) (hepatic function); blood urea nitrogen (BUN) and creatinine (Cr) (renal function); and

creatine kinase (CK) (muscle function). Biochemical indicators were reported in 6 trials [60, 62, 68, 72, 77, 79]; however, no changes were observed in 4 trials [62, 67, 77, 79]. The other 2 trials [60, 72] reported GPT, BUN, and Cr levels in detail but did not reveal significant differences between the RYR and the control groups.

Publication bias

Funnel plot analyses of the 16 trials comparing the "RYR plus conventional therapy" group *versus* the conventional therapy group regarding SBP and DBP were conducted, which showed that clinical heterogeneity might exist in this review (Figure 10).

Discussion

Summary of evidence

Two recently published systematic reviews revealed that statins could significantly reduce the risk of cardiovascular events and death in both primary and secondary prevention of CVDs [81, 82]. Numerous clinical studies have demonstrated that hypertension and hyperlipidemia are interrelated metabolically, epidemiologically, and clinically. The association of hypertension and hyperlipidemia powerfully contribute to a greater increase in cardiovascular risk. Beyond its cholesterol-lowering actions, additional health benefits of statin therapy are currently coming into focus. A small reduction of BP, albeit of clinical significance, along with significant reductions in cardiovascular morbidity and mortality have been observed in hypertensive patients [13, 14, 83, 84]. This robust evidence, along with the likely coexistence of hypertension and

hyperlipidemia, supports an integrated approach of combining antihypertensive agents with statins for the management of hypertension. This approach was also recommended in recent guidelines to minimize the potential for developing a cardiovascular event [1]. Therefore, the use of statins has become an adjunctive treatment for hypertension [85]. Due to the potential side effects of statins, dietary supplements and natural products are becoming increasingly popular worldwide. RYR, a dietary supplement and herbal medicine considered to be a safe treatment alternative to statins in China for centuries [24], has been gradually recognized as an emerging complementary therapy in the management of hypertension [86]. The question remains whether RYR could be used as adjunctive therapy for the management of hypertension as has occurred with statin therapy.

This study is the first systematic review of the English and Chinese literature to derive the efficacy and safety of RYR for hypertension. The overall results from 21 included randomized trials with a total of 4558 hypertensive patients suggested that “RYR plus conventional therapy” exhibited significant lowering effects on serum TC (decreased by 0.5 mmol/L), LDL-C (decreased by 0.63 mmol/L), and CRP (decreased by 0.09 mg/L) but exhibited no significant effect on SBP, DBP, TG, and HDL-C compared with “placebo plus conventional therapy”; “RYR plus conventional therapy” showed significant reduction of SBP (decreased by 5.62 mmHg), serum TC (decreased by 0.91 mmol/L), LDL-C (decreased by 0.66 mmol/L), and CRP (decreased by 0.77 mg/L) but no effect on DBP, TG, and HDL-C compared with “placebo plus

conventional therapy"; no significant difference was found with respect to BP and lipid profile between "RYR plus conventional therapy" and "statins plus conventional therapy"; "RYR plus statins" appeared to be more effective in lowering BP, TC, TG, and LDL-C levels but without a significant difference in HDL-C compared to statins. However, due to significant heterogeneity in the studies' subject characteristics and low quality as assessed by Cochrane's risk of bias criteria, the results should be treated with caution.

Currently, combination therapy to decrease multiple cardiovascular risks by treating BP, blood lipids, inflammatory markers and other cardiovascular risk factors together has been the focus of a comprehensive intervention [87]. Is "RYR plus conventional therapy" more effective than conventional therapy in hypertension?

In our review, the effect of combination therapy (RYR plus conventional therapy) *versus* combination therapy specifically in hypertensive patients was assessed in 2 subgroups; however, conflicting evidence regarding the efficacy of combination therapy in lowering BP was provided. Negative results was observed between "RYR plus conventional therapy" and "placebo plus conventional therapy" groups with a slight decrease in SBP (decreased by 3.29 mmHg) and DBP (decreased by 1.31 mmHg); however, positive results for SBP (decreased by 5.62 mmHg) and a slight but not significant lowering effect on DBP (decreased by 2.20 mmHg) were observed between the "RYR plus conventional therapy" and the conventional therapy groups. Those apparently contradictory conclusions were also confronted by 2 recently published large statin

therapy studies (the UCSD Statin Study and PHYLLIS trials) on additional antihypertensive effects [88, 89]. One explanation may lie with the several limitations that existed in the included trials such as the differences among the subjects investigated, inadequate study designs, different interventions, modifications of antihypertensive drugs, small sample sizes, short treatment courses, etc. Another interesting finding was that positive effects on SBP but negative effects on DBP were observed between the "RYR plus conventional therapy" and the conventional therapy groups, which was also in accord with a previously published meta-analysis concerning statins [13]. Several mechanisms exist whereby RYR may affect BP, such as by improving the level of NO, by reducing inflammation and lipid peroxidation and thus improving endothelial function, by reducing the adhesion of monocytes and endothelial cell, and by inhibiting left ventricular hypertrophy and myocardial interstitial fibrosis [90-92]. Moreover, a large number of clinical studies have revealed that RYR could reduce large artery stiffness and improve systemic arterial compliance, which are expected to affect SBP in particular [69, 70, 72, 75, 78, 93].

Another valuable finding was the estimation of the lipid-lowering effect of combination therapy. Analysis of the two subgroups mentioned above showed significant lowering effects on TC (decreased by 0.5-0.91 mmol/L) and LDL-C (decreased by 0.63-0.66 mmol/L) compared to conventional therapy alone. Although no significant triglyceride-lowering effect and an increasing effect on HDL-C were observed with combination therapy, moderate but clinical meaningful effects on TG (decreased by 0.18-0.38 mmol/L) and HDL-C (increased by 0.07-0.10

mmol/L) were demonstrated in our review. This phenomenon occurs similarly with statins, which could be explained by the major components of RYR. Notably, the lipid modification effects of RYR in our review were different from the results of the recently published meta-analyses [24, 30]. A possible explanation was the variation in the baseline data for blood lipids and among participants with underlying diseases.

Data have suggested that the administration of statins or certain antihypertensive drugs could decrease CRP levels in a manner independent of their BP-lowering effect. Despite the significant lipid regulating effect, some additional benefits of RYR have been demonstrated in this review. The third finding was the evaluation of CRP levels with combination therapy. The concentration of CRP was significantly reduced in the 2 subgroup analyses, indicating that RYR was beneficial for reducing the degree of inflammatory reaction in hypertensive patients. Because the incremental decrease was relatively small, more evidence is warranted to confirm these findings.

The fourth finding was the evidence for the efficacy of RYR in decreasing cardiovascular morbidity and mortality in hypertensive patients. Although evidence with respect to statins for endpoint reduction was contradictory based on two broad-based studies (ASCOT-LLA and ALLHAT-LLT trials) [12, 94], long-term clinical benefits of statins on cardiovascular morbidity and mortality have been verified by the meta-analysis conducted by Messerli *et al* involving another 12 trials comprising 69, 984 hypertensive patients. Could the additional of RYR to

antihypertensive therapy provide benefit similar to statins for hypertension? The most striking finding of this systematic review was the estimation of a long-term therapeutic effect of RYR therapy in the secondary prevention of CHD. The China Coronary Secondary Prevention Study (CCSPS), the largest study included in this review, was a randomized, double-blinded, placebo-controlled, parallel-group clinical trial. The study was the first large-scale clinical trial in an Eastern population regarding RYR. A total of 2704 hypertensive patients with previous myocardial infarction were assigned either to the RYR (600 mg twice daily, n = 1363) or to the placebo (n = 1341) group for an average of 4.5 years. Although no significant difference in BP reduction was found, it appeared that RYR therapy provided greater benefit in reducing cardiovascular events. That is, RYR significantly reduced the incidence of coronary events by 43.0% ($P = 0.02$), deaths from CHD by 30.0% ($P < 0.01$), and all-cause mortality by 35.8% ($P = 0.001$) in a safe manner [60]. As the effect of RYR is partially attributed to its naturally occurring statins, it has been hypothesized that relatively high concentrations of unsaturated fatty acids and other natural compounds contained in RYR may exert cardiovascular effects in concert with statins to provide additional health benefits [86, 95]. Therefore, more rigorously designed trials directly comparing the effectiveness and safety of the long-term use of RYR and statins are warranted.

Additionally, in the other two subgroups, one subgroup comparing “RYR plus conventional therapy” *versus* “statins plus conventional therapy” demonstrated no significant differences in

BP and lipid profile, indicating that RYR maybe a potential alternative to statins. Previous investigations have also demonstrated that the administration of RYR (1.2 g/d) had a triglyceride-lowering effect, which was similar to that of lovastatin (20 mg/d), simvastatin (10-20 mg/d), pravastatin (10 mg/d), fluvastatin (20 mg/d), and atorvastatin (10 mg/d), but with fewer AEs [96, 97]. However, because only 2 studies with small sample sizes and poor methodological quality were included, more well designed trials comparing RYR *versus* statins are needed to confirm the results in the future. The other subgroup showed that "RYR plus atorvastatin calcium" was more effective than atorvastatin calcium in lowering SBP, DBP, TC, TG, and LDL-C. However, the results should be considered in the context of their methodological limitations and thus should be interpreted conservatively.

Furthermore, most clinical studies have not demonstrated severe AEs such as statin-associated myalgias, or increases in ALT, AST, BUN, Cr, and CK occurring with RYR use to date, which was likely one of the main reasons for its popularity. There may be a common misconception among some patients and physicians that "natural" means safe [98, 99]. In this review, a lack of knowledge about detailed reporting of AEs was observed. Only 9 trials reported AEs, with no significant difference in either symptoms and signs or biochemical indicators, whereas AEs were not mentioned in the remaining studies. Although the reported AEs appeared to be safe and were well tolerated in hypertensive patients, definite conclusions about the safety of RYR cannot be drawn due to the limited, inadequate recording and reporting.

Limitations

Notably, methodological issues did limit the extent to which confirmative conclusions might be drawn. With methodologically poorly designed studies, greater differences would be generated than by those that were rigorously conducted [100] and as such the small improvements in outcomes should be regarded with caution. A number of methodological weaknesses were evident in the primary studies. First, all of the trials were described as randomized but only 7 provided details on the randomization process [60, 61, 64, 68, 70, 73, 74] and 1 provided allocation concealment information [60]. The generation methods of the allocation sequence and allocation concealment were not clear in most trials due to insufficient reporting. Because what is declared to be random may not be random in actuality, potential selection bias might exist. Second, only 1 trial was described as double-blinded [60], and the other 3 were described as single-blind with the patient/participant being blinded [61, 67, 70]. Thus, either performance bias or detection bias might exist. Third, knowledge was lacking for the placebo control in the included trials. Only 4 studies claimed to use a placebo control for RYR [60, 61, 67, 70]. As we know, without a rigorous control for the placebo effect, the results might exaggerate the effect of RYR, which might be likely to generate false-positive results and significant systemic errors in the assessment of outcome measures. Fourth, only 7 trials [60-63, 68, 70, 79] reported dropouts or withdrawal in detail, whereas such information was not provided in the other 14 studies. In the absence of withdrawal reporting, the information regarding the

significance of possible dropout data and the impact of dropouts on the trials' reliability is rendered suspect. Fifth, the presence of significant clinical heterogeneity in this review should be duly noted. Due to the variations in methodological quality, participants, interventions, and antihypertensive drugs, the heterogeneity might weaken the reliability of the conclusions. Finally, the absence of studies regarding RYR outside of China is another weakness that potentially limited the generalizability of the findings.

Conclusions

Taken altogether, some encouraging but limited evidence exists for the use of RYR for hypertension. Although meaningful reductions in BP, blood lipids, and CRP has been observed, evidence for RYR for hypertension remained weak based on the available data. More rigorous, high-quality trials are required to provide a high level of evidence.

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Table 1. Basic characteristics of the included studies.

References	Sample size (randomized /analyzed)	Diagnostic criteria	Intervention	Control	Treatment duration	Outcome measures	Adverse events reporting	Main findings from original studies
Li JJ, et al. 2010 [60]	2704/2704	NR	T: RYR (600 mg bid) + conventional therapy (aspirin, β-blocker, ACEI, CCB, nitrate, no details)	C: placebo + conventional therapy (aspirin, β-blocker, ACEI, CCB, nitrates, etc., no details)	4.5 years on average	(1) SBP and DBP: significantly decreased in each group, $p < 0.05$; comparison between them: $p > 0.5$; (2) TC, TG, HDL-C, and LDL-C: $p < 0.05$; (3) coronary events	Y	Long-term RYR therapy resulted in significant reduction in cardiovascular events and death in hypertensive Chinese patients with previous myocardial infarction and with an excellent safety profile.

						: p < 0.0001; (4) deaths from coronary heart disease: p = 0.0059; (5) all-cause mortality: p = 0.012;		
Ye P, et al. 2009 [61]	60/55	WHO-ISH GMH-1999; CGMH-2004	T: RYR (1200 mg/day) + extended-release nifedipine (20mg bid)	C: placebo + extended-release nifedipine (20 mg bid)	18 months	(1) SBP and DBP: p > 0.05; (2) TC and LDL-C: p < 0.01; HDL-C: p > 0.05; (3) CRP: p < 0.05;	N	Long-term therapy with RYR improved left ventricular diastolic function, probably mediated through antifibrotic and anti-inflammatory effects and independent of BP and lipid

								profiles in patients with EH.
Gong C, et al. 2010 [62]	90/90	WHO-ISH GMH-2003	T: RYR (600 mg bid) + C1	C1: valsartan (80 mg qd) + C2 C2: conventional therapy (aspirin, β-blocker, CCB, diuretics, etc., no details)	24 months	(1) SBP and DBP: $p > 0.05$ (T vs C1); $p < 0.05$ (T vs C2); (2) TC: $p > 0.05$ (T vs C1, T vs C2);	Y	Combined therapy with RYR and valsartan may lower BP and improve left ventricular hypertrophy in hypertension.
Lu L, et al. 2009 [63]	102/88	WHO-ISH GMH-1999	T: RYR (600 mg bid) + C2	C1: pravastatin (20 mg qd) + C2; C2: conventional therapy (β-blocker, CCB, diuretics, no details)	2 months	(1) SBP and DBP: $p > 0.05$ (T vs C1, T vs C2); (2) TG: significantly decreased in RYR	N	NSD of BP and lipids profiles between RYR and conventional therapy/pravastatin group was observed in patients with EH.

						group, $p < 0.01$; comparison between them: $p > 0.05$; TC, HDL-C, and LDL-C: $p > 0.05$;		
Xu GZ 2008 [64]	86/86	CGMH-2005	T: RYR (600 mg bid) + C	C: amlodipine (5 mg qd)	1 month	(1) SBP and DBP: $p < 0.05$; (2) TC and TG: $p < 0.01$; HDL-C, and LDL-C: $p < 0.05$;	Y	Significant difference in BP and lipids profiles between RYR and amlodipine group was observed in patients with EH.
Zhang JL 2005 [65]	55/55	WHO-ISH GMH-1999	T: RYR (600 mg bid) + C	C: nifedipine (20 mg bid)	2 months	(1) SBP and DBP: $p > 0.05$;	N	Combined therapy with RYR and nifedipine may lower

						(2) TC, TG and HDL-C: $p < 0.05$;		BP, and improve lipids and insulin sensitivity index in EH patients with insulin resistance.
Xiong LH, et al. 2012 [66]	120/120	NR	T: RYR (600 mg bid) + C	C: conventional therapy (ACEI, ARB, β-blocker, diuretics, etc., no details)	2 months	(1) SBP and DBP: $p < 0.05$; (2) CRP: $p < 0.05$;	N	Combined therapy with RYR and antihypertensive drugs could markedly decrease the level of CRP, interleukin-6, and BP in hypertensive patients.
Wang XJ and Zhang SY 2007 [67]	60/60	WHO-ISH GMH-1999	T: RYR (600 mg bid) + benazepril (5-10 mg qd)	C: placebo + benazepril (5-10 mg qd)	1 month	(1) SBP and DBP: $p < 0.05$; (2) TC, TG, HDL-C, and LDL-C: signifi	Y	RYR combined with benazepril is more effective in lowering BP and improving lipids in hypertensive patients with hypertrigly

						cantly improved with RYR group, $p < 0.05$; comparison between them: NR;		ceridemia.
Zhou FW 2009 [68]	150/130	CGMH-2005	T: RYR (600 mg bid) + C2	C1: pravastatin (20 mg qd) + C2; C2: conventional therapy (β-blocker, CCB, diuretics, ACEI, or ARB, no details)	2 months	(1) SBP and DBP: $p > 0.05$ (T vs C1, T vs C2); (2) TG: significantly decreased in RYR group, $p < 0.01$; comparison between them:	N	RYR or pravastatin combined with antihypertensive drugs improve endothelial function and inhibit the inflammatory response in EH patients.

						NR; TC, HDL-C, and LDL-C: comparison between them: NR; (3) CRP: $p <$ 0.01 (T vs C2, C1 vs C2), $p >$ 0.05 (T vs C1);		
Gu XL, et al. 2010 [69]	135/135	WHO-ISH GMH-1999; NCPTCDC-1979	T: RYR (600 mg bid) + C	C: conventional therapy (aspirin, nitrates, metoprolol, or captopril, no details)	3 months	(1) SBP and DBP: $p >$ 0.05; (2) CRP: $p <$ 0.05;	N	NSD in BP but significant difference in CRP between RYR and conventional therapy group observed in hypertensive patients complicated by

								coronary heart disease.
Ye P, et al. 2006 [70]	120/100	WHO-ISH GMH-1999; CGMH-2004	T: RYR (600 mg bid) + extended-release nifedipine (20 mg bid)	C: placebo + extended-release nifedipine (20 mg bid)	6 months	(1) SBP: $p < 0.01$; DBP: $p > 0.05$; (2) TC and LDL-C: $p < 0.01$; TG and HDL-C: $p > 0.05$;	N	Significant difference in SBP, TC and LDL-C between RYR and placebo group observed in hypertensive patients.
Wang WP, et al. 2012 [71]	60/60	WHO-ISH GMH-1999	T: RYR (600 mg bid) + C	C: valsartan (80 mg qd)	4 months	(1) SBP and DBP: $p < 0.05$; (2) TC, TG, HDL-C, and LDL-C: $p < 0.05$;	N	RYR could decrease BP and lipids, and inhibit myocardial hypertrophy in hypertensive patients with left ventricular remodeling.
Liu P and Zhang XL 2013	77/77	CGMH-2005	T: RYR (600 mg bid) + C	C: conventional therapy (1-3	6 months	(1) SBP and DBP: $p <$	Y	Combined RYR and antihypertensive drugs may

[72]				types of antihypertensive drugs including β-blockers, CCB, diuretics, ACEI, or ARB, no details)		0.05; (2) TC, TG, and LDL-C: $p < 0.05$; HDL-C: $p > 0.05$;		decrease BP and lipids in elderly patients with simple systolic hypertension.
Zhang ZH, et al. 2013 [73]	40/40	CGMH-2005	T: RYR (600 mg bid) + C	C: conventional therapy (antihypertensive drugs, no details)	3 months	SBP and DBP: $p > 0.05$	Y	RYR could decrease microalbuminuria and protect renal function.
Chen Y, et al. 2011 [74]	82/82	CGMH-2005	T: RYR (600 mg bid) + C	C: conventional therapy (antihypertensive drugs including β-blockers, CCB, diuretics, ACEI, or ARB, no details)	2 months	(1) SBP and DBP: $p > 0.05$; (2) CRP: $p < 0.05$;	N	RYR could decrease CRP in hypertensive patients with normal blood lipids and high CRP level.
Xu ZW and Lv FJ 2013 [75]	60/60	CGMH-2010	T: RYR (600 mg bid) + C	C: conventional therapy (antihypertensive	3 months	SBP and DBP: $p > 0.05$	N	RYR significantly improved arterial elasticity in hypertensiv

				drugs including nifedipine sustained release tablets 20 mg bid, enalapril maleate 10 mg, candesartan cilexetil 8 mg, or diuretics)				e patients with normal blood lipids.
Ke XA, et al. 2007 [76]	60/60	CGMH-2005	T: RYR (600 mg tid) + C	C: amlodipine (5 mg qd-bid)	6 months	SBP and DBP: $p < 0.01$	N	RYR combined with amlodipine for long-term treatment could significantly reduce BP in hypertensive patients.
Zhou H and Lin L 2012 [77]	132/132	CGMH-2010	T: RYR (600 mg bid) + C	C: atorvastatin calcium (20 mg qd)	1 month	(1) SBP and DBP: $p < 0.05$; (2) TC, TG,	Y	Significant difference in BP, TC, TG, and LDL-C between RYR and atorvastatin calcium

						and LDL-C: $p < 0.05$; HDL-C: $p > 0.05$;		group observed in hypertensive patients with coronary heart disease.
Zhu ZT et al. 2008 [78]	220/220	NR	T: RYR (600 mg bid) + C	C: conventional therapy (antihypertensive drugs including CCB or ACEI, no details)	6 months	(1) SBP and DBP: $p > 0.05$; (2) TC and TG: $p < 0.01$;	N	RYR combined with antihypertensive drugs is more effective in lowering TC and TG in hypertensive patients.
Zeng XQ et al. 2008 [79]	58/58	CGMH-2004	T: RYR (600 mg bid) + C	C: amlodipine (5 mg qd)	3 months	(1) SBP: $p < 0.05$; DBP: $p > 0.05$; (2) TC and LDL-C: $p < 0.05$; TG and HDL-C: $p > 0.05$;	Y	Antihypertensive medications at a routine dose combined with RYR demonstrate a better effect on BP, TC and LDL-C in elderly patients.

Li YS and Feng XH 2008 [80]	146/146	WHO-ISH GMH-1999	T: RYR (600 mg bid) + C	C: enalapril (10 mg bid)	6 months	SBP and DBP: $p < 0.05$	Y	Significant difference in BP between RYR and enalapril group observed in hypertensive patients.

Abbreviations: ACEI: angiotensin converting enzyme inhibitors; BP: blood pressure; C: control group; CCB: calcium channel blocker; CGMH: Chinese Guidelines for the Management of Hypertension; CRP: C-reactive protein; DBP: diastolic blood pressure; EH: essential hypertension; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; N: no; NCPTCDC: National Committee on Prevention and Treatment of Cardiovascular Disease in China; NR: not reported; NSD: no significant difference; RYR: red yeast rice; SBP: systolic blood pressure; T: treatment group; TC: total cholesterol; TG: triglycerides; WHO-ISH GMH: World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension; Y: yes.

Table 2. Basic characteristics of the included subjects.

References	Male/Female	Age (yrs)	Baseline SBP (mmHg)	Baseline DBP (mmHg)	Baseline TC (mmol/l)	Baseline TG (mmol/l)	Baseline LDL-C (mmol/l)	Baseline HDL-C (mmol/l)	Baseline CRP (mg/L)	Baseline difference
Li JJ, et al. 2010 [60]	T: 1093/270 C: 1054/287	T: M: 59.40 ± 9.20 F: 63.00 ± 6.60 C: M: 59.20 ± 9.50 F: 63.20 ± 7.10	T: 137.70±16.60 C:137.70 ±16.80	T: 84.70±10.30 C: 84.40±10.10	T: 5.38± 0.68 C: 5.39± 0.67	T: 1.86± 0.86 C: 1.88± 0.86	T: 3.35± 0.73 C: 3.35± 0.75	T: 1.19± 0.38 C: 1.19± 0.37	NR	NSD
Ye P, et al. 2009 [61]	T: 15/13 C: 13/14	T: 56.30 ± 8.1	T: 145.00±16.00 C: 144.00±1	T: 89.00±14.00 C: 90.00±1	T: 4.96± 0.58 C: 4.73±	NR	T: 2.93± 0.41 C: 2.77±	T: 1.40± 0.37 C: 1.37±	T: 0.38± 0.16 C: 0.30±	NSD

		1 C: 56.44 ± 9.33	7.00	4.00	0.71		0.59	0.38	0.11	
Gong C, et al. 2010 [62]	T: 19/13 C1: 18/12 C2: 15/13	T: 59.00 ± 8.20 C1: 56.30 ± 7.50 C2: 58.90 ± 8.10	T: 212.00±24.00 C1: 164.00±21.00 C2: 160.00±20.00	T: 112.00± 14.00 C1: 110.00± 15.00 C2: 106.00± 12.00	T: 6.00± 1.40 C1: 6.10± 1.50 C2: 6.00± 1.30	NR	NR	NR	NR	NSD
Lu L, et al. 2009 [63]	T: 10/20 C1: 16/13 C2: 13/16	T: 60.17 ± 7.26 C1: 61.66 ± 8.4	T: 123.73±7.18 C1: 122.62±6.71 C2: 122.97±5.88	T: 75.43±8.01 C1: 77.14±6.20 C2: 77.38±5.77	T: 4.46± 0.52 C1: 4.44± 0.69 C2: 4.39± 0.68	T: 1.32± 0.32 C1: 1.23± 0.33 C2: 1.19± 0.35	T: 2.55± 0.52 C1: 2.53± 0.59 C2: 2.47± 0.56	T: 1.21± 0.19 C1: 1.24± 0.23 C2: 1.26± 0.28	NR	NSD

		1 C2: 61.21 ± 6.95								
Xu GZ 2008 [64]	T: 43 C: 43 F/M: NR	T: 32-76 C: 30-77	T: 162.85±20.54 C: 162.23±24.23	T: 92.62±15.46 C: 90.31±15.15	T: 6.42± 1.43 C: 6.21± 1.12	T: 2.13± 0.56 C: 1.89± 0.42	T: 4.11± 0.86 C: 3.85± 0.74	T: 2.36± 0.60 C: 2.24± 0.51	NR	NSD
Zhang JL 2005 [65]	T: 16/10 C: 16/13	T: 55.00 ± 2.50 C: 55.32 ± 9.31	T: 146.91±6.30 C: 146.70±15.20	T: 98.10±15.20 C: 97.40±14.80	T: 6.00± 1.00 C: 6.20± 0.50	T: 3.20± 1.40 C: 2.10± 0.70	NR	T: 1.10± 0.20 C: 1.20± 0.30	NR	NSD
Xiong LH, et al. 2012 [66]	T: 28/32 C: 29/31	T: 70.60 ± 11.30 C: 68.50 ± 10.50	T: 181.30±9.30 C: 178.90±7.90	T: 111.70± 6.80 C: 111.30± 8.10	NR	NR	NR	NR	T: 4.83± 2.79 C: 4.64± 2.56	NSD
Wang	T:	T:	T:	T:	T:	T:	T:	T:	NR	NSD

XJ and Zhang SY 2007 [67]	20/10 C: 21/9	57.00 ± 7.00 C: 57.00 ± 8.00	158.40±16.30 C: 159.60±15.60	95.80±10.90 C: 95.50±10.30	5.42± 0.90 C: 5.45± 0.87	2.12± 0.78 C: 2.15± 0.71	2.83± 0.52 C: 2.82± 0.55	0.99± 0.34 C: 0.96± 0.33		
Zhou FW 2009 [68]	T: 17/28 C1: 24/19 C2: 17/25	T: 60.69 ± 7.22 C1: 61.05 ± 8.45 C2: 61.33 ± 7.70	T: 128.02±8.62 C1: 125.88±7.85 C2: 125.86±6.93	T: 76.44±7.22 C1: 78.19±6.08 C2: 76.29±5.80	T: 4.56± 0.53 C1: 4.38± 0.67 C2: 4.41± 0.69	T: 1.36± 0.32 C1: 1.27± 0.35 C2: 1.23± 0.34	T: 2.51± 0.53 C1: 2.41± 0.61 C2: 2.46± 0.57	T: 1.21± 0.19 C1: 1.22± 0.23 C2: 1.26± 0.30	T: 2.57± 0.58 C1: 2.55± 0.56 C2: 2.54± 0.67	NSD
Gu XL, et al. 2010 [69]	T: 36/37 C: 33/29	T: 63.10 ± 5.90 C: 62.	T: 146.70±15.60 C: 145.20±15.80	T: 76.80±7.10 C: 76.20±7.80	NR	NR	NR	NR	T: 16.90 ±6.60 C: 16.56 ±5.80	NSD

		30 ± 6.70								
Ye P, et al. 2006 [70]	T: 26/25 C: 23/26	T: 56.00 ± 8.60 C: 57.20 ± 10.10	T: 144.00±16.00 C: 144.00±17.00	T: 89.00±14.00 C: 90.00±14.00	T: 5.27± 0.88 C: 5.28± 0.81	T: 1.87± 0.61 C: 1.88± 0.59	T: 2.94± 0.80 C: 3.02± 0.77	T: 1.48± 0.38 C: 1.49± 0.37	NR	NSD
Wang WP, et al. 2012 [71]	T: 15/15 C: 16/14	NR	T: 160.00±12.00 C: 161.00±11.00	T: 101.00± 9.00 C: 103.00± 7.00	T: 4.90± 1.20 C: 4.90± 1.40	T: 1.64± 1.23 C: 1.70± 1.57	T: 2.14± 1.12 C: 2.19± 1.26	T: 1.09± 0.36 C: 1.06± 0.43	NR	NSD
Liu P and Zhang XL 2013 [72]	T: 23/15 C: 24/15	T: 67.10 ± 5.70 C: 68.70 ± 5.40	T: 164.44±4.87 C: 163.39±6.78	T: 84.18±5.04 C: 83.26±6.72	NR	NR	NR	NR	NR	NSD
Zhang ZH, et al. 2013 [73]	T: 20 C: 20 F/M: NR	56.00 ± 10.00	T: 152.00±18.00 C: 149.00±1	T: 86.00±12.00 C: 82.00±1	NR	NR	NR	NR	NR	NSD

		(T/C: NR);	5.00	6.00						
Chen Y, et al. 2011 [74]	T: 42 C: 40 F/M: NR	51.00 ± 5.00 (T/C: NR)	T: 171.30±7.60 C: 170.90±6.50	T: 90.10±4.90 C: 89.40±4.30	NR	NR	NR	NR	T: 5.21± 0.90 C: 5.08± 0.79	NSD
Xu ZW and Lv FJ 2013 [75]	T: 16/14 C: 14/16	T: 57.40 ± 5.70 C: 56.30 ± 4.60	T: 153.20±12.30 C: 151.40±14.20	T: 96.20±4.20 C: 95.20±5.40	NR	NR	NR	NR	NR	NSD
Ke XA, et al. 2007 [76]	T: 30 C: 30 F/M: NR	NR	T: 146.00±6.00 C: 145.00±6.00	T: 94.00±5.00 C: 95.00±4.00	NR	NR	NR	NR	NR	NSD
Zhou H and Lin L 2012 [77]	T: 35/31 C: 34/32	T: 61.40 ± 7.80 C: 60.	T: 154.73±1.23 C: 153.12±11.47	T: 99.67±5.26 C: 101.65± 5.38	T: 5.73± 1.23 C: 5.78± 1.27	T: 2.62± 0.27 C: 2.65± 0.30	T: 4.49± 1.38 C: 4.58± 1.27	T: 1.29± 0.38 C: 1.32± 0.45	NR	NSD

		40 ± 7.50								
Zhu ZT et al. 2008 [78]	T: 110 C: 110 F/M: NR	59.00 ± 9.40 (T/C: NR)	T: 151.00±10.00 C: 153.00±6.00	T: 90.00±6.00 C: 92.00±9.00	T: 5.79±0.53 C: 5.74±0.65	T: 1.81±0.27 C: 1.78±0.15	NR	NR	NR	NSD
Zeng XQ et al. 2008 [79]	T: 30 C: 28 F/M: NR	76.80 ± 8.20 (T/C: NR)	T: 149.00±9.00 C: 149.00±8.00	T: 79.00±12.00 C: 79.00±11.00	T: 5.80±0.90 C: 5.80±0.80	T: 1.80±0.70 C: 1.90±0.60	T: 3.80±0.70 C: 3.70±0.80	T: 1.20±0.40 C: 1.20±0.50	NR	NSD
Li YS and Feng XH 2008 [80]	T: 73 C: 73 F/M: NR	52.70 ± 6.80 (T/C: NR)	T: 166.50±10.40 C: 168.40±8.60	T: 99.70±4.70 C: 100.20±6.60	NR	NR	NR	NR	NR	NSD

Abbreviations: C: control group; CRP: C-reactive protein; DBP: diastolic blood pressure; F: female; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; M: male; NR: no reported; NSD: no significant difference; SBP: systolic blood pressure; T: treatment group; TC: total cholesterol; TG: triglycerides.

Table 3. Methodological quality of the included studies based on the Cochrane handbook.

References	A	B	C	D	E	F	G
Li JJ, et al. 2010 [60]	+	+	+	+	+	+	+
Ye P, et al. 2009 [61]	+	?	+	-	+	?	?
Gong C, et al. 2010 [62]	?	?	?	?	+	?	?
Lu L, et al. 2009 [63]	?	?	?	?	-	?	?
Xu GZ 2008 [64]	+	?	?	?	+	?	?
Zhang JL 2005 [65]	?	?	?	?	+	?	?
Xiong LH, et al. 2012 [66]	?	?	?	?	+	?	?
Wang XJ and Zhang SY 2007 [67]	?	?	+	-	+	?	?
Zhou FW 2009 [68]	+	?	?	?	-	?	?
Gu XL, et al. 2010 [69]	?	?	?	?	+	?	?
Ye P, et al. 2006 [70]	+	?	+	-	-	?	?
Wang WP, et al. 2012 [71]	?	?	?	?	+	?	?
Liu P and Zhang XL 2013 [72]	?	?	?	?	+	?	?
Zhang ZH, et al. 2013 [73]	+	?	?	?	+	?	?
Chen Y, et al. 2011 [74]	+	?	?	?	+	?	?
Xu ZW and Lv FJ 2013 [75]	?	?	?	?	+	?	?
Ke XA, et al. 2007 [76]	?	?	?	?	+	?	?
Zhou H and Lin L 2012 [77]	?	?	?	?	+	?	?
Zhu ZT et al. 2008 [78]	?	?	?	?	+	?	?
Zeng XQ et al. 2008 [79]	?	?	?	?	+	?	?
Li YS and Feng XH 2008 [80]	?	?	?	?	+	?	?

Abbreviations: A: Adequate sequence generation; B: Concealment of allocation; C: Blinding (participants and personnel); D: Blinding (assessor); E: Incomplete outcome data addressed (ITT analysis); F: Free of selective reporting; G: other potential threat to validity; +: low risk of bias; -: high risk of bias; ?: unclear risk of bias.

Table 4. Risk ratio of the reported adverse events.

AEs	Total events/Group total		RR (95% CI)	No. of studies	Heterogeneity (I^2), %	*P*
	T	C				
Symptoms and signs						
Gastrointestinal discomfort	10/1363	3/1341	3.28 [0.90, 11.89]	60	NA	0.07
	3/32	1/30	2.81 [0.31, 25.58]	62	NA	0.36
	2/30	0/30	7.00 [0.38, 129.93]	67	NA	0.19
	0/66	1/66	0.33 [0.01, 8.04]	77	NA	0.50
Allergic reactions	3/1363	2/1341	1.48 [0.25, 8.82]	60	NA	0.67
Myalgias and psychoneurological symptoms	5/1363	2/1341	2.46 [0.48, 12.66]	60	NA	0.28
Erectile dysfunction	0/1363	3/1341	0.14 [0.01, 2.72]	60	NA	0.19
Edema	2/1363	0/1341	4.92 [0.24, 102.37]	60	NA	0.30
Skin rash	0/32	1/30	0.31 [0.01, 7.40]	62	NA	0.47
Dizziness	4/66	3/66	1.33 [0.31, 5.73]	77	NA	0.70
Cough	2/73	2/73	1.00 [0.14, 6.91]	80	NA	1.00
Others	2/1363	3/1341	0.66 [0.11, 3.92]	60	NA	0.64
Biochemical indicators						
GPT ↑	2/1363	3/1341	0.66 [0.11, 3.92]	60	NA	0.64
	7/38	4/39	1.80 [0.57, 5.64]	72	NA	0.32
BUN ↑	74/1363	80/1341	0.91 [0.67, 1.24]	60	NA	0.55
Cr ↑	60/1363	57/1341	1.04 [0.73, 1.48]	60	NA	0.85

Abbreviations: AEs: Adverse events; BUN: blood urea nitrogen; C: control; CI: confidence interval; Cr: creatinine; GPT: Glutamate pyruvate transaminase; NA: not applicable; RR: risk ratio; T: treatment; ↑: increase.

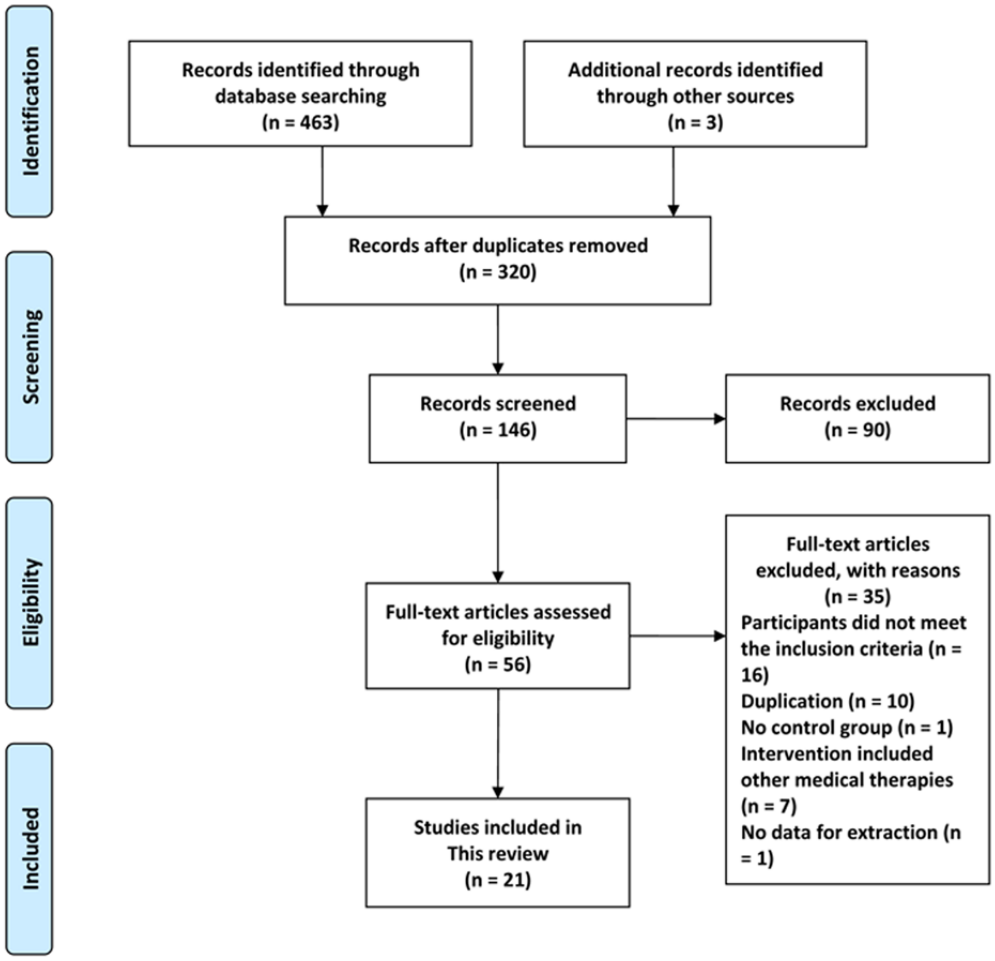
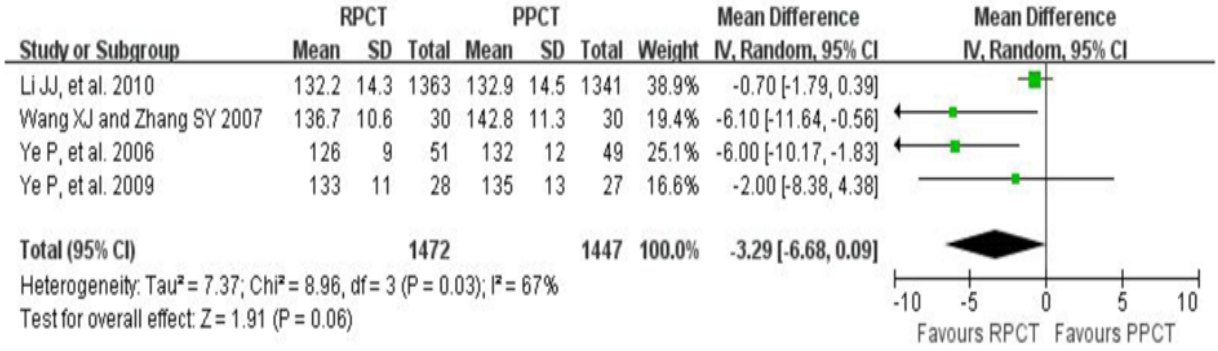
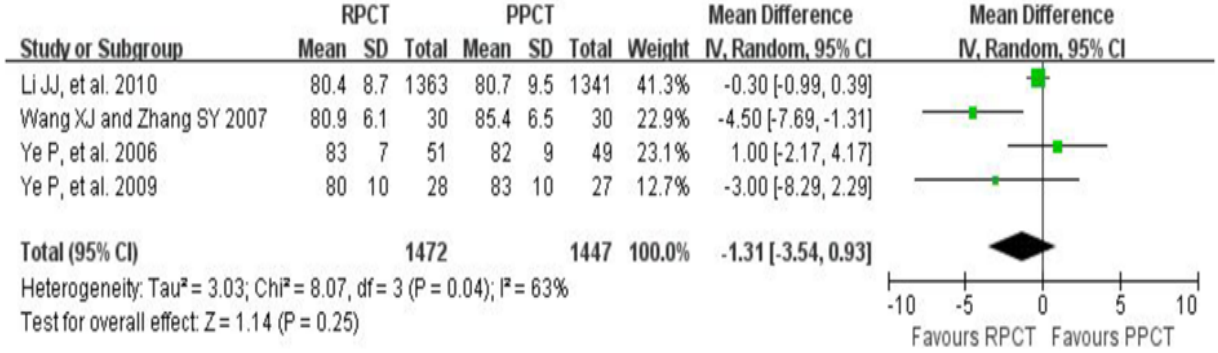


Figure 1. PRISMA 2009 Flow Diagram.



(a) SBP



(b) DBP

Figure 2. Forest plot of comparison of "RYR plus conventional therapy" *versus* "placebo plus conventional therapy" for the outcome of BP: (a) SBP and (b) DBP. BP: blood pressure; DBP: diastolic blood pressure; PPCT: placebo plus conventional therapy; RPCT: red yeast rice plus conventional therapy; RYR: red yeast rice; SBP: systolic blood pressure.

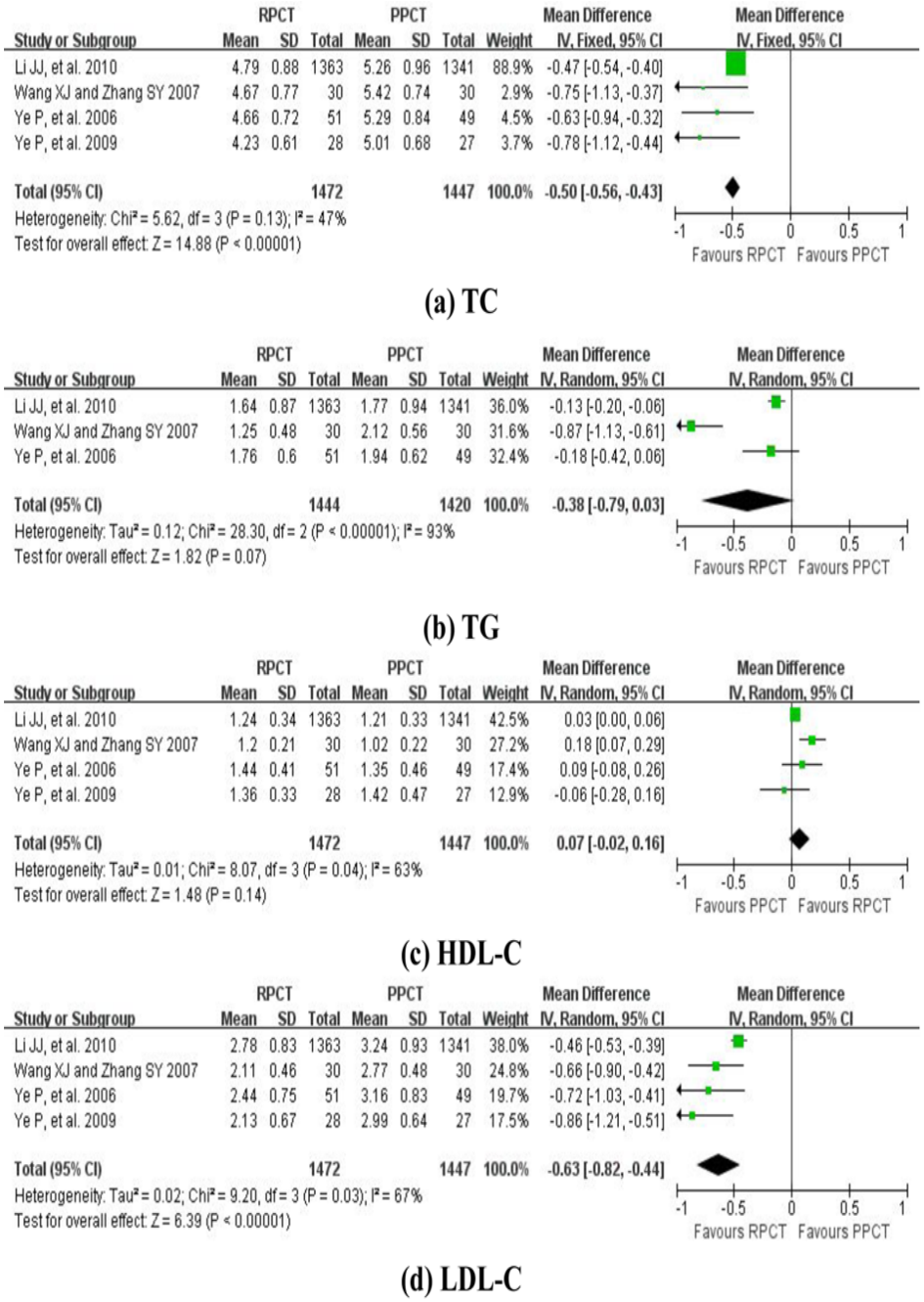
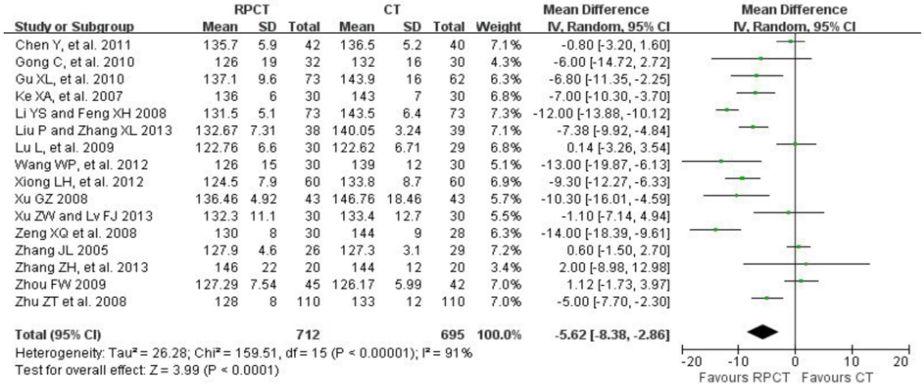
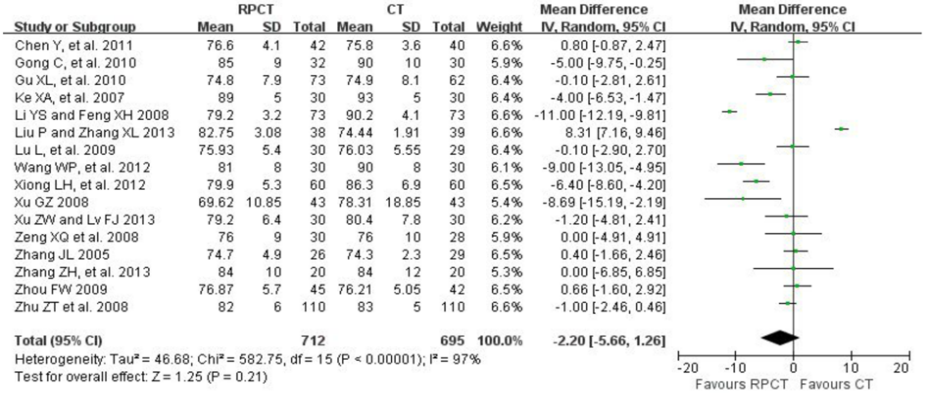


Figure 3. Forest plot of comparison of "RYR plus conventional therapy" *versus* "placebo plus conventional therapy" for the outcome of lipid profile: (a) TC, (b) TG, (c) HDL-C, and (d) LDL-C. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein

cholesterol; PPCT: placebo plus conventional therapy; RPCT: red yeast rice plus conventional therapy; RYR: red yeast rice; TC: total cholesterol; TG: triglycerides.



(a) SBP



(b) DBP

Figure 4. Forest plot of comparison of "RYR plus conventional therapy" *versus* conventional therapy for the outcome of BP: (a) SBP and (b) DBP. BP: blood pressure; CT: conventional therapy; DBP: diastolic blood pressure; RPCT: red yeast rice plus conventional therapy; RYR: red yeast rice; SBP: systolic blood pressure.

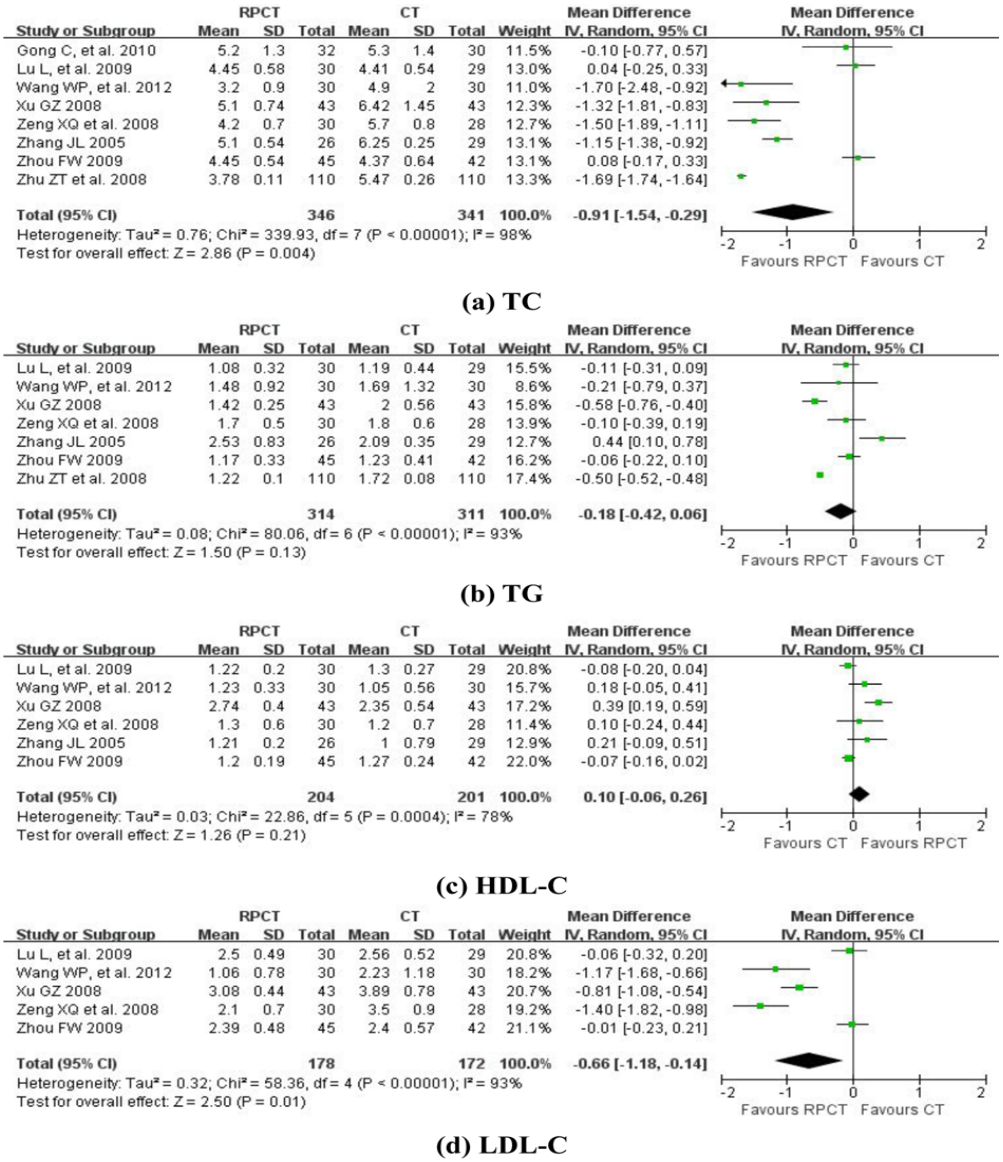


Figure 5. Forest plot of comparison of "RYR plus conventional therapy" *versus* conventional therapy for the outcome of lipid profile: (a) TC, (b) TG, (c) HDL-C, and (d) LDL-C. CT: conventional therapy; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; RPCT: red yeast rice plus conventional therapy; RYR: red yeast rice; TC: total cholesterol; TG: triglycerides.

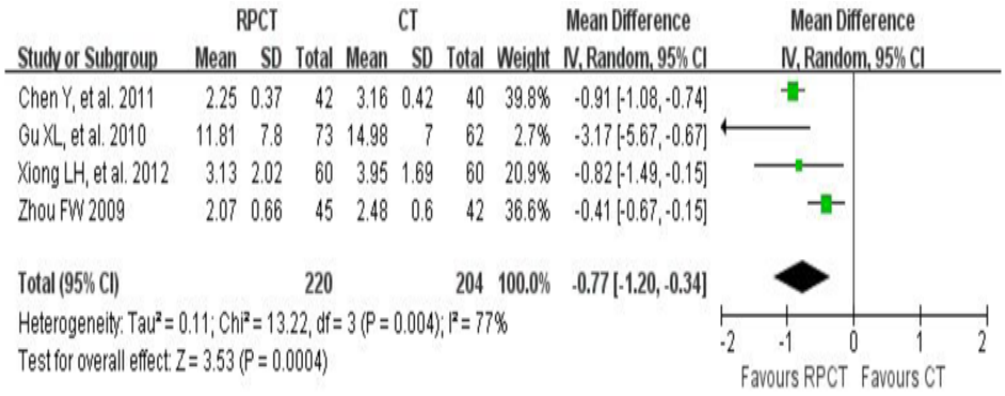
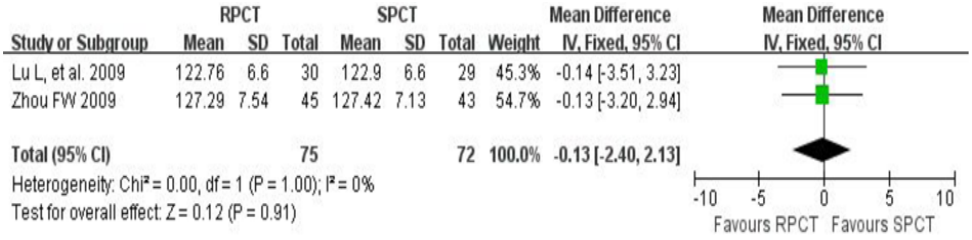
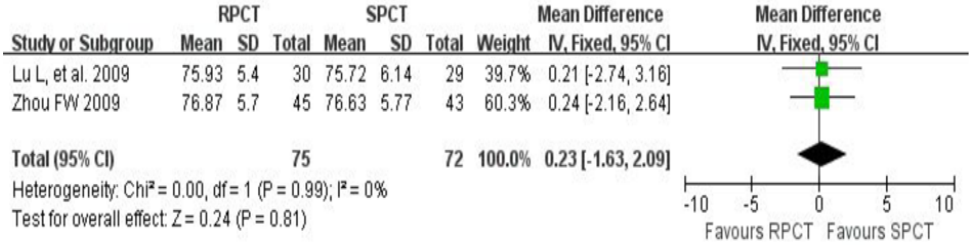


Figure 6. Forest plot of comparison of "RYR plus conventional therapy" *versus* conventional therapy for the outcome of CRP. CRP: C-reactive protein; CT: conventional therapy; RPCT: red yeast rice plus conventional therapy; RYR: red yeast rice.

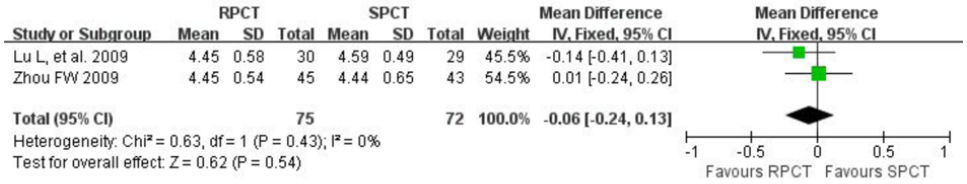


(a) SBP

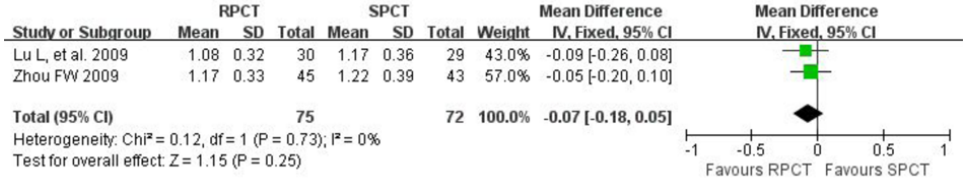


(b) DBP

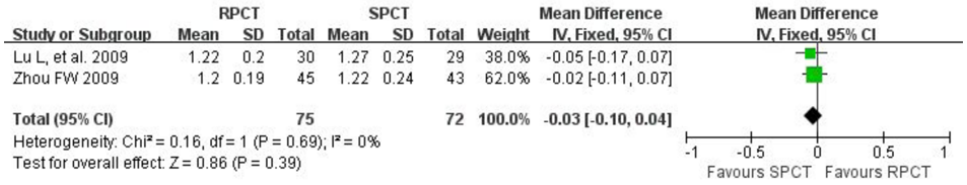
Figure 7. Forest plot of comparison of "RYR plus conventional therapy" *versus* "statins plus conventional therapy" for the outcome of BP: (a) SBP and (b) DBP. BP: blood pressure; DBP: diastolic blood pressure; RPCT: red yeast rice plus conventional therapy; RYR: red yeast rice; SBP: systolic blood pressure; SPCT: statins plus conventional therapy.



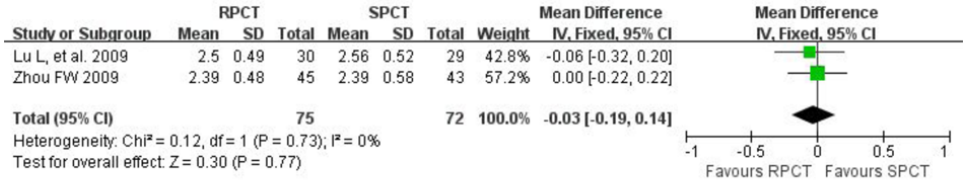
(a) TC



(b) TG



(c) HDL-C



(d) LDL-C

Figure 8. Forest plot of comparison of "RYR plus conventional therapy" *versus* "statins plus conventional therapy" for the outcome of lipid profile: (a) TC, (b) TG, (c) HDL-C, and (d) LDL-C. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; RPCT: red yeast rice plus conventional therapy; RYR: red yeast rice; SPCT: statins plus conventional therapy; TC: total cholesterol; TG: triglycerides.

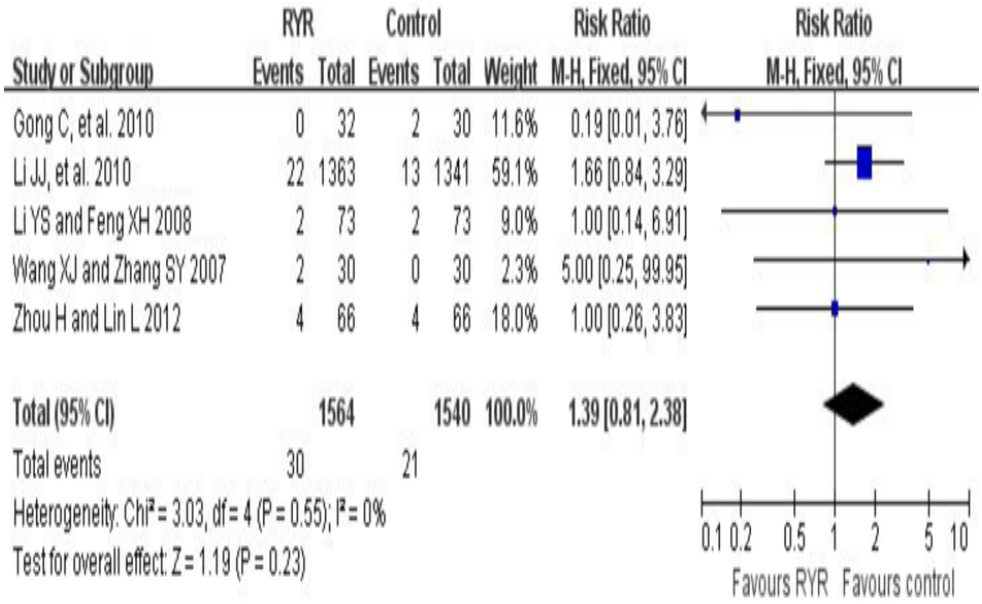


Figure 9. Forest plot of the reported adverse events. RYR: red yeast rice.

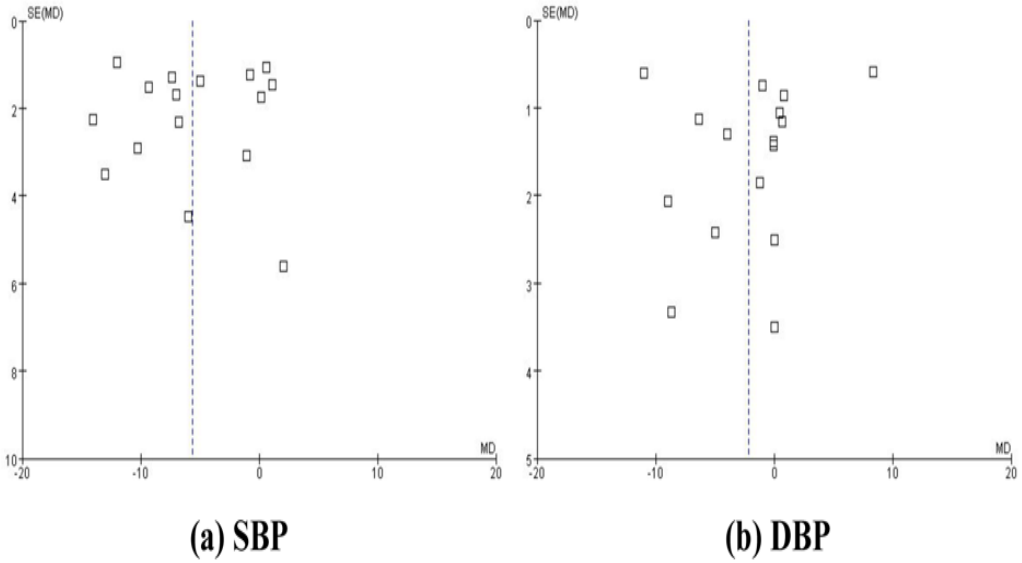


Figure 10. Funnel plot for assessing reporting bias for BP between "RYR plus conventional therapy" and conventional therapy: (a) SBP and (b) DBP. BP: blood pressure; DBP: diastolic blood pressure; RPCT: red yeast rice plus conventional therapy; RYR: red yeast rice; SBP: systolic blood pressure.