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REVIEW

A systematic, updated review of Xuezhikang, a domestically developed lipid-lowering drug, in the application of cardiovascular diseases

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Abstract Cardiovascular diseases (CVDs) are a major threat to public health globally. A large proportion of people with dyslipidaemia have poorly controlled lipid levels, emphasizing the need for alternative lipid-lowering treatments that are both effective and safe. Xuezhikang, a red yeast rice (RYR) extract, containing 13 kinds of monacolins and other bioactive components, emerges as one such promising option. Its discovery was built on a long history of RYR use as a functional food supplement and traditional Chinese medicine. Several randomized, controlled clinical trials have substantiated its lipid-lowering effects and its potential to protect against CVDs. Safety concerns with statins did not arise during decades of experience with Xuezhikang treatment in clinical practice. The approval of Xuezhikang in multiple regions of Asia marked a conceptual shift in CVD management, moving from single agents to polypills and from synthetic medicines to natural extracts. This review comprehensively addresses important topics related to this medicinal natural extract, including the ancient utilization of RYR, the development of Xuezhikang, its mechanisms of action, pleiotropic effects, clinical studies, challenges, and future perspectives to enhance our understanding regarding the role of Xuezhikang, a representative, domestic lipid-lowering drug of RYR, in prevention and treatment of CVD.

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1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality around the world, characterized by the predominance of atherosclerotic cardiovascular disease (ASCVD), in both developed and developing countries. The past few decades have seen a marked increase in CVD cases and deaths. The prevalence of CVD has risen from 271 million to 523 million and CVD deaths increased from 12.1 million to 18.6 million from 1990 to 2019[1]. The striking increase in CVD burden occurred despite the recommendation and implementation of CVD risk factor management, largely due to unstrict control of dyslipidaemia in clinical practice. Adequate control of blood cholesterol plays a pivotal role in the primary and secondary prevention of CVDs, particularly for ASCVD. However, most people with dyslipidaemia have poorly controlled lipid levels, which may have contributed at least in part to the persistent increase in CVD burden. According to a previous multi-centre study, dyslipidaemia was less common in China, but lipid levels were not significantly different in the United States. This is due to the fact that awareness and control rates of dyslipidaemia in China were 3- and 7-fold lower than that in the United States, respectively[2]. Statins have been considered cornerstone drugs and are the mainstay of lipid-lowering treatment. Nevertheless, their widespread use and adherence to treatment are restricted by fears and adverse reactions associated with statin intolerance, among other reasons, leading to an increased risk for CVD events[3,4]. Hence, alternative treatments for lipid-lowering would help to overcome the barriers to both CVD prevention and treatment[4].

Xuezhikang, an extract of cholestin, is available from Chinese red yeast rice (RYR). Although monacolin K and lovastatin and its derivatives constitute the main active components, the clinical benefits of Xuezhikang go beyond lipid lowering and include manifold, synergistic effects to modulate overall lipid profiles[5,6]. Xuezhikang holds particular significance as the domestic sole natural lipid-modifying medication studied for the secondary prevention of CVD, backed by evidence-based medicine. However, a noticeable gap exists in the literature, with a lack of systematic reviews covering the origin and evolution of Xuezhikang. Here, we systemically review the long history of RYR utilization as a functional food supplement and traditional Chinese medicine (TCM), the background of the discovery of Xuezhikang, its mechanisms of action, clinical benefits and supporting evidence, and its safety profile. We also highlight outstanding questions regarding this natural extract and propose future research. We hope to provide comprehensive information and improve knowledge of Xuezhikang as an important lipid-lowering and anti-CVD intervention.

2. Discovery of red yeast rice and clinical evidence

RYR is an ancient Chinese food supplement that has been described in books since before the first century (Fig. 1A)[7]. RYR is produced by incubating cooked rice with *Monascus* fungi, most frequently with *Monascus purpureus*, where the red pigments are produced by the fungi during the fermentation process[7]. As part of the Asian diet, RYR is commonly used as a food additive for preserving, colouring, and flavouring food (*e.g.*, fish, meat, and soybean products) and in brewing. The first record of RYR was found in Local Chronicles of Gutian, which was written during the Tang Dynasty (618−907), and since then RYR has been documented in many ancient books and medical compendiums, such as Qing Yi Lu (907−1127), Materia Medica in Daily (1271−1368), Compendium of Herbology (1578; Fig. 1B), and *Tian Gong Kai Wu* (1637; Fig. 1C)[8]. The production methods of RYR have been passed down from one generation to another, and the clinical activities of RYR, in particular its regulation of digestion and blood circulation, were well recognized in these ancient books. For instance, according to the Compendium of Herbology, the most complete and renowned compendium of Chinese medicine in ancient times[9], RYR improves spleen function to promote digestion, activates blood circulation to dissipate blood stasis, and can be used to treat haematochezia, abdominal distention, abdominal pain, sprain, fracture, and abnormal lochia[8]. In Chinese Materia Medica (1999), which is the largest compendium of TCM to date and was compiled by the China National Administration of Traditional Chinese Medicine, RYR is listed as an important medicine and the clinical benefits of RYR, including those for gastrointestinal and cardiovascular systems, are outlined[10]. Apart from using as a food additive, RYR is recognized as a medicinal ingredient commonly included in traditional Chinese folk medicine prescriptions for rejuvenating the body, promoting blood circulation, and restoring stomach balance[7].

The decades-long knowledge and application of RYR as both a functional food supplement and medicine sparked significant interest in molecules that can lower blood cholesterol. In 1979, the main bioactive component in RYR responsible for cholesterol reduction was identified to be monacolin K by Akira Endo[11]. A contemporary breakthrough occurred in 1978 when a study led by Alberts and Chen revealed that a fermentation product of *Aspergillus terreus* could inhibit 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, and the compound was later marketed as lovastatin[12]. However, back then production of monacolins at an industrial scale using RYR was impractical due to the low concentration of monacolins in the fermentation broth and instability of these compounds.

RYR is regulated as a drug in the United States and as a food supplement in Europe[13]. The lipid-lowering effects of RYR are supported by results from a myriad of clinical trials. A meta-analysis that included 20 randomized controlled trials showed that RYR at a dose of 1200−4800 mg per day, containing 4.8−24 mg monacolin K, was associated with an estimated change of low-density lipoprotein cholesterol (LDL-C) by −1.02 mmol/L (range, −1.20 to −0.83), triglycerides by −0.26 mmol/L (−0.35 to −0.17), total cholesterol (TC) by −1.0 mmol/L (−1.23 to −0.77), and high-density lipoprotein cholesterol (HDL-C) by 0.07 mmol/L (0.03−0.11) after 6−168 weeks of follow-up[14,15]. The extent of LDL-C reduction by RYR is presumed to be comparable to that achieved with low-intensity, low-dosed statins (pravastatin 40 mg, simvastatin 10 mg, lovastatin 20 mg)[16]. Consistent with this notion, a meta-analysis that included 15 high-quality randomized controlled trials showed that the reduction in LDL-C by RYR was significantly greater than that by placebo and similar to that by low-intensity, low-dosed statin controls whereas RYR was more effective in lowering triglycerides than statin controls[17−19]. Nevertheless, conflicting data also exist, as one recent study indicated that RYR (2400 mg daily) did not result in significant reductions in LDL-C compared to placebo and proved less effective than a low-dose statin (rosuvastatin 5 mg daily)[20]. Interestingly, clinical evidence also suggested that RYR could improve vascular parameters including carotid intima-media thickness, carotid elasticity, endothelial reactivity, arterial stiffness, and reduced inflammatory biomarkers including high-sensitivity C-reactive protein (hs-CRP),

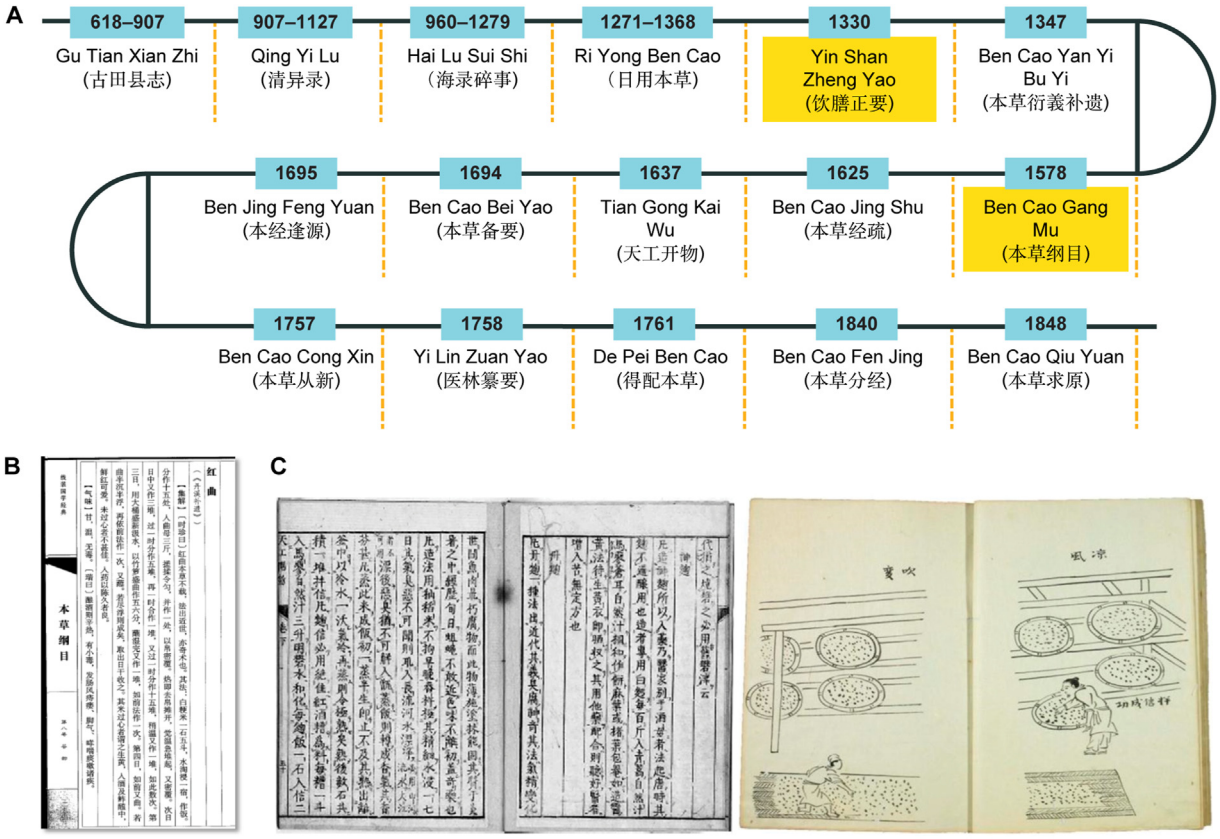

Figure 1 Historical documentation of red yeast rice in ancient books and medical compendium. (A) Red yeast rice references in various ancient books and medical compendiums since the 600s. (B) Production methods and clinical use of red yeast rice described in the *Compendium of Herbology* (1578). (C) Production methods of red yeast rice as described in *Tian Gong Kai Wu* (1637).

osteoprotegerin, matrix metalloproteinase-2 (MMP-2), and MMP-9[21–24]. Plaque indicators for carotid atherosclerosis (carotid plaque area, carotid plaque score, intima-media thickness) were improved by RYR according to a meta-analysis where most studies included were for Xuezhikang[17]. In addition, an area of intensive research is combining RYR with other nutraceuticals, for instance, berberine, based on the hypothesis that different bioactive nutraceuticals may have complementary and additive lipid-lowering and anti-CVD effects. Several nutraceutical combinations of berberine and RYR as well as other components were reported to improve the lipid profile, reduce blood glucose, lower blood pressure, decrease inflammatory biomarkers, and improve arterial stiffness and endothelial function[25–31]. Moreover, with regard to its safety, no issues have been identified with RYR. A meta-analysis of 53 randomized controlled trials demonstrated that RYR was not associated with increased risk of musculoskeletal disorders and was associated with reduced risk of non-musculoskeletal adverse events and serious adverse events[32]. Although several treatment guidelines consider RYR as an option for cholesterol reduction and CVD prevention, attitudes toward the efficacy of RYR are mixed, primarily due to large variability in the quantity of monacolin K (ranging from 0.09 to 5.48 mg per 1200 mg in one study) in these products[13,16,33–35]. Furthermore, the presence of citrinin, which is a nephrotoxic substrate generated as a by-product of the fermentation process, arouses safety concerns for RYR[36]. RYR extracts that have precise, specified compositions of active components without citrinin would address these concerns.

3. Discovery of Xuezhikang

In the 1990s, a *M. purpureus* strain that could produce a high level of monacolin K was isolated by Chinese scientists. Making use of this strain, Xuezhikang was developed and later the production process was established[6]. RYR is produced following standardized manufacturing procedures composed of fermentation, alcohol extraction, and other steps under fixed conditions. The composition of Xuezhikang is rigorously controlled and validated by high-performance liquid chromatography and ultraviolet spectroscopy: each pill of Xuezhikang contains 6 mg monacolins, 25.7 mg amino acids, 24 mg unsaturated fatty acids, 0.9 mg ergosterol, and 0.14 mg flavonoids[6]. There are 13 types of monacolins in Xuezhikang, including monacolin K lactone (lovastatin lactone), K hydroxy acid (lovastatin hydroxy acid), L, J, M, and X[37]. The quantity of lovastatin in Xuezhikang is 2.5 mg per pill, translating to 10 mg lovastatin per day at a daily dose of 1200 mg Xuezhikang[5,38].

4. Pharmacokinetic variations of Xuezhikang *versus* pure lovastatin

Notably, Xuezhikang exhibits a different pharmacokinetic profile of lovastatin compared with pure lovastatin, and the important distinction underlies more potent inhibitory activity against HMG-CoA, greater efficacy, and better safety of the former[37]. Administration of Xuezhikang (1200 mg) led to quicker absorption, a

greater C_{max}, and higher bioavailability of lovastatin (109% with Xuezhikang *versus* pure lovastatin) and lovastatin hydroxy acid (169% with Xuezhikang *versus* pure lovastatin) compared with an equivalent dose of pure lovastatin (20 mg)[37]. Lovastatin (lactone) is a prodrug, which is hydrolyzed by carboxylesterase to the active form of lovastatin acid in the intestine and liver[39]. The lactone form of lovastatin in the muscle may account for the muscle toxicity effects that are observed with lovastatin[40]. A study conducted on mice fed with a high-fat diet revealed that oral administration of Xuezhikang led to increased exposure to both lovastatin lactone and lovastatin acid in the plasma, intestine, and liver compared with oral pure lovastatin. However, in the muscle, Xuezhikang was associated with higher exposure to lovastatin acid but lower exposure to lovastatin lactone compared with pure lovastatin (Fig. 2). The differences in exposure in various tissues may be at least in part attributed to the effect of isoflavone and possibly other components in Xuezhikang, which increased the expression and activity of carboxylesterase in the intestine and liver[39].

The favourable pharmacokinetic properties of Xuezhikang are consistent with findings for RYR. It was demonstrated that the oral bioavailability of lovastatin was significantly increased when a RYR product was administered, compared to lovastatin tablets. The oral bioavailability of 22.8 mg lovastatin in RYR products was significantly higher than that of 20 mg lovastatin in lovastatin tablets [181 ± 46% *vs*. 100%][41]. It was also shown that the systemic exposure to lovastatin and its active metabolite, lovastatin acid, was much higher when it was given as a RYR product than as a lovastatin drug, which may then contribute to the greater potency of RYR products in lowering cholesterol[41]. In addition, the variation in the absorption rate, reflected by the time to reach the peak concentration (T_{max}), was reduced by giving RYR products[41]. Moreover, the dissolution of lovastatin from RYR products was higher. The reasons for this may be related to the content of fatty acids and sterols in RYR products and the decreased crystallinity of lovastatin in RYR products[42–44].

5. Mechanisms of action and multi-effects of Xuezhikang

5.1. *Lipid modification*

The primary mechanism by which Xuezhikang reduces blood cholesterol can be attributed to the inhibition of HMG-CoA reductase by monacolins (Table 1). It has been demonstrated that HMG-CoA reductase is the rate-limiting enzyme in the pathway for cholesterol biosynthesis, which mediates the conversion of HMG-CoA to mevalonate, a precursor of cholesterol[45]. Studies *in vivo* and in humans showed that the inhibitory activity of Xuezhikang against HMG-CoA reductase was more potent than pure lovastatin, along with a faster onset of action[37].

Lovastatin, as the major active component of Xuezhikang, has been studied in several clinical trials. These trials have shown that 5–6 mg/day of lovastatin given as a natural product has comparable efficacy to 20–40 mg/day of lovastatin tablet in lowering blood cholesterol[42,46,47]. These findings may be due to additive and/or synergistic pharmacological effects of RYR components and higher exposure to lovastatin.

Besides blocking cholesterol synthesis, Xuezhikang, similar to other kind of statins, upregulates hepatic expression of LDL-receptors and sterol regulatory element binding protein-2 (SREBP-2) and increases proprotein convertase subtilisin/kexin type 9 (PCSK9) in the blood, which in turn leads to enhanced cholesterol uptake and degradation in the liver and decreased circulating cholesterol levels[45,48].

Apart from lowering LDL-C, Xuezhikang has been found to have a modulatory effect on multiple elements of the lipid profile. One notable function of Xuezhikang is its ability to

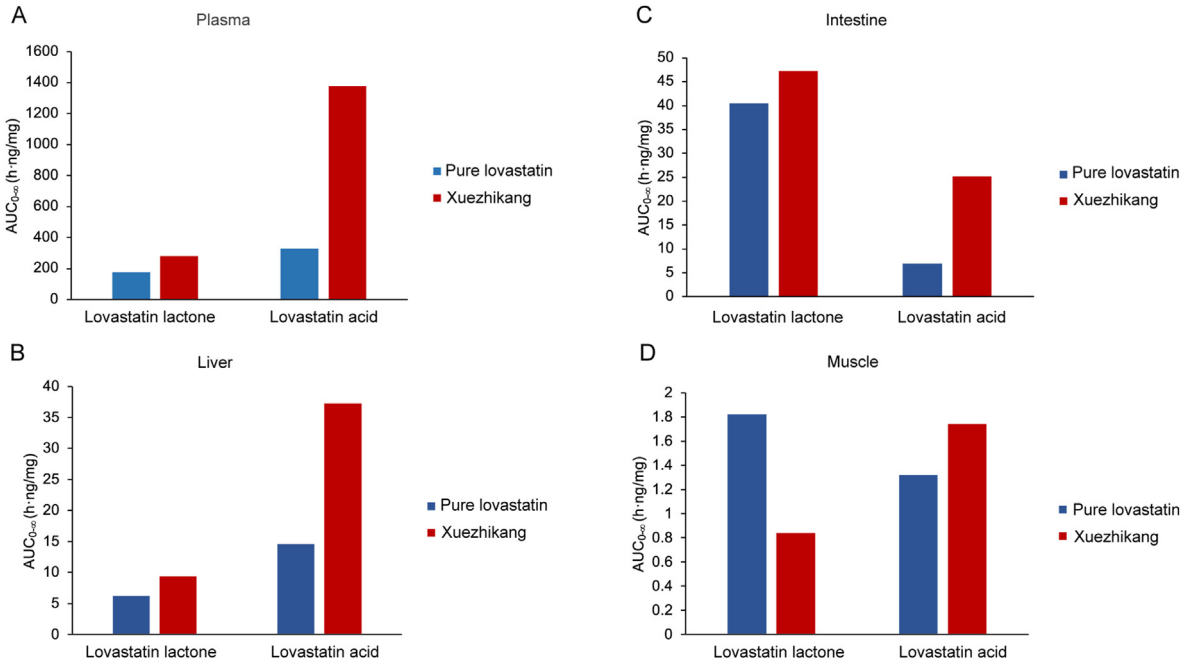

Figure 2 Pharmacokinetic Profile of Lovastatin Lactone and Lovastatin Acid in Various Tissues. Mean Area Under the Curve ($AUC_{0-\infty}$) of lovastatin lactone and lovastatin acid across different tissues in high-fat diet-fed mice after oral administration of Xuezhikang (1200 mg/kg) and pure lovastatin (10 mg/kg). (A) Plasma. (B) Intestine. (C) Liver. (D) Muscle.

Table 1 Pleiotropic effects of Xuezhikang and underlying mechanisms on the protein or pathway level.

Effect	Possible protein or pathway target	Main ingredient of Xuezhikang that may account for the effect	Ref.
Lipid modification	HMG-CoA reductase activity↓ → Cholesterol synthesis↓	Lovastatin and ergosterol	45
	Hepatic SREBP expression↑ → PCSK9↑ → LDL-receptor expression↑ → LDL-C degradation↑	Lovastatin	45,48
	Hepatic PPARα expression↑ → Apolipoprotein A5↑ → Triglyceride degradation↑	Lovastatin and unsaturated fatty acids	51
	Diacylglycerol acyltransferase 1/2 activity↓ → Triglyceride synthesis↓	Unsaturated fatty acids	6,52
	SREBP-1c↓ → Fatty acid and triglyceride synthesis↓	Unsaturated fatty acids	6,52
	Entry of cholesterol into micelles↓ → Intestine cholesterol absorption↓ Fecal excretion of cholesterol↑	Ergosterol	6,53
	SR-BI↑ Bile salt export pump ↑ CYP7A1↑ NTCP↓ → Hepatic elimination of bile acids and fecal excretion of lipids↑	Isoflavones	54
	CYP7A1↑ NTCP↓ → Hepatic elimination of bile acids and fecal excretion of lipids↑	Ergosterol	54
	NPC1L1↓ → Intestinal absorption of cholesterol↓	Ergosterol	54
	PCSK9↑ SR-BI↑ → Apolipoprotein B ↓ Oxidized LDL↓ Small LDL-C↓	Unsaturated fatty acids	6,55
Anti-inflammation	TNF-α↓ IL-6↓ hs-CRP↓ → Inflammation↓	Lovastatin, unsaturated fatty acids, and isoflavones	49,57,58,60
Anti-oxidative activity	Nrf-2 nuclear translocation↑ → HO-1 expression↑ → ROS↓	Lovastatin, unsaturated fatty acids, and isoflavones	62
	GPx1↑ → ROS↓	Selenium	63
	ERK1/2 activity↓ → p47 membrane translocation↓ → NADPH oxidase activity↓ → ROS↓	Lovastatin, unsaturated fatty acids, and isoflavones	61
	GSH/GSSG balance↑ → ROS↓	Lovastatin, unsaturated fatty acids, and isoflavones	61
Endothelial function protection and anti-atherosclerosis	Number and adhesion activity of CEPCs↑ → Endothelial function↑	Lovastatin	69,70
	TNF-α↓ IL-6↓ hs-CRP↓ MMP-9↓ → Inflammation↓ → Anti-atherosclerosis	Lovastatin, unsaturated fatty acids, and isoflavones	49,57,71–75
	Caveolin-1↓ → eNOS↑ → Nitrite and nitrate↑ → cGMP↑ → Erythrocyte deformation index↑ Blood viscosity and plasma viscosity↓	Lovastatin, unsaturated fatty acids, and ergosterol	76
	Endoplasmic reticulum stress↓ → Apoptosis↓ NF-κB pro-inflammatory pathway↓ → Atherosclerotic plague stability↑	Lovastatin, unsaturated fatty acids, and isoflavones	78
	GSH/GSSG balance↑ → ROS↓ → Endothelial cell injury↓	Lovastatin, unsaturated fatty acids, isoflavones, and selenium	61,63
	ERK1/2 activity↓ → p47 membrane translocation↓ → NADPH oxidase activity↓ → Tissue factor expression↓ → Blood coagulation ↓	Lovastatin, unsaturated fatty acids, and isoflavones	61
	Fibrinogen level↓ Plasminogen activator inhibitor-1 activity↓ glycoprotein-140 activity↓ → Platelet activity↓ Coagulation-fibrinolysis balance↑	Lovastatin, unsaturated fatty acids, and isoflavones	79
Cardio-protection under hypertension	PI3K-Akt signaling↑ → CEPCs proliferation, adhesion, and migration↑ → Endothelial regeneration↑	Lovastatin, unsaturated fatty acids, and isoflavones	70
	Fibulin-3↓ → MMP-2↓ MMP-9↓ → Left ventricular mass index↓ Wall-to-lumen area ratio of thoracic aorta↓ → Vascular remodeling↓	Lovastatin, unsaturated fatty acids, and isoflavones	81
Anti-NAFLD	TNF-α↓ → Liver inflammation↓ Steatosis ↓ Oxidative stress↓ Insulin resistance↓	Lovastatin, isoflavones, and selenium	87,88,90

Table 1 (*continued*)

Effect	Possible protein or pathway target	Main ingredient of Xuezhikang that may account for the effect	Ref.
Anti-diabetes	Expression of genes in glucose sensing↑ Insulin signaling↑ Expression of genes in oxidative stress↓ → Insulin secretion by pancreatic islets↑ Hyperglycemic injury↓ Insulin sensitivity↑	Unsaturated fatty acids and isoflavones	90,92,98
	Retinoid X receptor binding → SREBP-1↓ → Insulin resistance↓	Unsaturated fatty acids	94,96
Renal protection	TNF-α↓ IL-6↓ hs-CRP↓ → Renal protection↓	Lovastatin, unsaturated fatty acids, and isoflavones	58
	Bcl-2 associated X-protein expression↓ Bcl-2 expression↑ → Cytochrome *c* release and caspase-9 activity↓ → Renal cell apoptosis in diabetic kidney↓	Lovastatin	101
	RhoA and Rac1 activity↓ → Epithelial-to-mesenchymal transition ↓ → Renal interstitial fibrosis↓	Lovastatin	102
Anti-cancer	Inflammation↓ Angiogenesis↓ Cell proliferation↓ Susceptibility to apoptosis↑ → Anti-cancer effects	Unsaturated fatty acids	112
	DNA damage↓ Oxidative stress↓ Cell proliferation↓ Susceptibility to apoptosis↑ Immune function↑ → Anti-cancer effects	Selenium	113,114
Promotion of bone health	RANKL expression and secretion↓ → Osteoclastogenesis and bone loss↓ Osteoprotegerin expression↑ → Bone formation↑	Isoflavones	115,116
	Bone morphogenetic protein 2 expression↑→ Osteoblast differentiation↑	Lovastatin	117

Akt, protein kinase B; Bcl-2, B-cell lymphoma 2; CEPCs, circulating endothelial progenitor cells; cGMP, cyclic guanosine monophosphate; CRP, C-reactive protein; CYP7A1, cytochrome P450 family 7 subfamily A member 1; ERK 1/2,extracellular signal-regulated kinase 1/2; eNOS, endothelial nitric oxide synthase; GPx1, glutathione peroxidase 1; GSH, glutathione; GSSG, glutathione disulfide; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; HO-1, heme oxygenase-1; IL-6, interleukin 6; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MMP, matrix metalloproteinase; NADPH, nicotinamide adenine dinucleotide phosphate; NAFLD, non-alcoholic fatty liver disease; NF-κB, nuclear factor B; NPC1L1, Niemann-Pick C1 Like 1; NTCP, Na^+-taurocholate cotransporting polypeptide; Nrf-2, Nuclear erythroid factor2-related factor 2; NTCP, Na^+-taurocholate cotransporting polypeptide; OPG, osteoprotegerin; PAI-1, plasminogen activator inhibitor-1; PCSK9, proprotein convertase subtilisin/kexin type 9; PI3K, phosphatidylinositol-3-kinase; PPARα, peroxisome proliferator-activated receptor α; Rac1, Ras-related C3 botulinum toxin substrate 1; RANKL, receptor activator of nuclear factor kappa-B ligand; RhoA, Ras homolog family member A; ROS, reactive oxygen species; SR-BI, scavenger receptor class B type I; SREBP, sterol regulatory element binding protein; TNF-α, tumor necrosis factor-α.

effectively lower triglycerides[49,50]. In studies conducted on rats, Xuezhikang reduced triglycerides by a greater degree than simvastatin when the doses of two treatments were titrated based on similar LDL-C reductions[51]. This was attributed to a greater upregulation of hepatic peroxisome proliferators-activated receptors alpha (PPARα) expression by Xuezhikang, consequently leading to a higher level of apolipoprotein A5 in hepatocytes and plasma and a greater reduction of triglycerides in the plasma[51]. In addition, the unsaturated fatty acids in Xuezhikang can reduce triglycerides *via* a variety of mechanisms, including suppression of triglyceride synthesis and promotion of lipolysis and fatty acid transport[6,52]. The ergosterol component in Xuezhikang regulates blood LDL-C and triglyceride levels by inhibiting cholesterol synthesis, suppressing intestine cholesterol absorption (acting as a cholesterol absorption inhibitor), and elevating faecal cholesterol excretion[37,53]. Isoflavones and phytosterols that are part of Xuezhikang are also able to decrease triglycerides, LDL-C, and TC by suppressing intestinal cholesterol absorption and promoting faecal excretion of bile acids[54]. In addition, Xuezhikang can modify lipoprotein subfractions presented as a decrease in small LDL particles and an increase in large LDL particles in addition to the reduction in apolipoprotein B, oxidized LDL, and small LDL-C levels as well as an increase in HDL-C, which may be mediated by polyunsaturated fatty acids (PUFAs)[6,55,56].

5.2. *Anti-inflammation and anti-oxidative actions*

Anti-inflammation and anti-oxidative actions are crucial features of Xuezhikang for the prevention and treatment of CVD (Table 1). In models of hyperlipidaemic rats, several studies have reported that Xuezhikang showed a decrease in tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and hs-CRP levels, all of which are involved in the inflammatory response process, indicating its effects on inhibiting inflammation[57,58]. Moreover, Xuezhikang suppresses the activation of nuclear factor kappa B (NF-κB), a nuclear transcription factor regulating the expression of inflammatory key genes, and inhibits the release of inflammatory cytokines such as TNF-α and IL-6, as well as disrupting the adhesion of monocytes to endothelial cells, thereby alleviating inflammation both directly and indirectly[59]. The anti-inflammatory activity of Xuezhikang may also confer protective effects against brain

injury following cardiac arrest and cardiopulmonary resuscitation, as observed in rats[60].

Besides, Xuezhikang is capable of attenuating oxidative stress by balancing Glutathione (GSH), oxidized glutathione (GSSG) and reactive oxygen species (ROS), inhibiting the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in macrophages and reduced the production of ROS[61]. In atherosclerotic rats induced by a high-cholesterol diet, Xuezhikang has been shown to reduce NADPH oxidase activity, a major component of NADPH oxidase and oxidative stress, by decreasing membrane translocation of $p47^{phox}$ through inhibition of extracellular signal-regulated kinase 1/2 activation[61]. *In vitro* experiments showed that Xuezhikang upregulated the expression of heme oxygenase-1 (HO-1) to improve its antioxidant effect, which is a key molecule in the oxidation resistance. Furthermore, the selenium present in Xuezhikang has been reported to help with the activity of glutathione peroxidase 1 (GPx1) in endothelial cells, which may also have antioxidative effects[62,63].

5.3. *Endothelial function protection*

Vascular endothelial cells are an important functional "organ" that exert protective effects during CVD development. In the rat models fed with high-fat diets, Xuezhikang has been demonstrated to have the function of endothelial protection by increasing the expression of caveolin-1 expression in the walls of the aorta and upregulating the expression of endothelial nitric oxide synthase (eNOS) in endothelia[64] (Table 1). In addition, the study by Schunck et al. showed that rats treated with Xuezhikang had higher levels of eNOS than those treated with lovastatin, indicating that it is more effective than HMG-CoA reductase inhibitors in terms of eNOS upregulation and endothelial improvement, and the components of Xuezhikang, unsaturated fatty acids, and ergosterol, may synergistically enhance eNOS[64].

More importantly, a study has demonstrated that Xuezhikang attenuated oxidative stress by regulating the balance of GSH and GSSG, an important redox buffering pair, effectively enhancing endothelial function. Furthermore, RYR elevated levels of GSH eliminate reactive oxygen *in vivo* and reduce cellular injury by inhibiting HMG-CoA reductase[65]. It also has been reported that selenium, an extract from RYR, could help with the activity of GPx1 after a drop in GSSG occurs[65–67]. Moreover, as previously mentioned, Xuezhikang was found to effectively enhance both the quantity and function of circulating endothelial progenitor cells (CEPCs), which are pivotal in the process of endothelial repair and replacement, as they are essential for endothelial homeostasis and neovascularization under different detrimental factors[68–70].

5.4. *Anti-atherosclerosis*

As well known, LDL-C plays a primary role in the pathogenesis of atherosclerosis and therefore the aforementioned LDL-C lowering activity of Xuezhikang may account for its anti-atherosclerosis effects (Table 1). However, this is not the only way by which Xuezhikang protects against atherosclerosis and the underlying mechanisms are multifactorial and pleiotropic. As inflammation is a driver in the pathogenesis of atherosclerosis, one notable effect of Xuezhikang is the suppression of plasma inflammatory factors, such as CRP, TNF-α, IL-6, MMP-9, and fibrinogen, as observed in patients with different clinical conditions[49,57,71–75]. Moreover, a study *in vivo* showed that Xuezhikang upregulated endothelial nitric-oxide synthase expression in vascular endothelial and erythrocytes and nitric oxide (NO) production in the plasma, which decreased blood viscosity and improved hemorheology[76]. The elevation of NO production by Xuezhikang is consistent with the NO-elevating effects of statins[77]. In addition, Xuezhikang has been shown to inhibit vulnerable plaque progression and rupture in $ApoE^{-/-}$ mice, which might be mediated by its inhibition of inflammation associated with NF-κB pro-inflammatory pathway, endoplasmic reticulum stress, and apoptosis in macrophages in mouse carotid arteries[78]. Similarly, the unsaturated fatty acids in Xuezhikang have anti-inflammatory activities showing a decrease in plasma TNF-α, IL-6, CRP, oxidized LDL, and MMP-9 levels and they can prevent plaque formation and progression[6]. Both *in vitro* and *in vivo* studies demonstrated that Xuezhikang downregulated tissue factor expression and decreased NADPH oxidase activity, which might in turn inhibit blood clot formation and atherosclerosis[61]. In patients with dyslipidaemia, Xuezhikang treatment led to a decrease in the level of fibrinogen and the activities of plasminogen activator inhibitor-1 and glycoprotein-140, indicating that it inhibited platelet activity and regulated the coagulation-fibrinolysis balance[79]. Isoflavones, another kind of active component in Xuezhikang, have long been recognized to have anti-atherosclerosis benefits, likely achieved by lipid-lowering, antioxidant activities, inhibition of smooth muscle cell proliferation and migration within the arterial wall, prevention of plaque formation, and vascular dilation[37,80]. In summary, the Anti-atherosclerosis effects of Xuezhikang might be exerted by multiple actions.

5.5. *Cardio-protection under hypertension*

Under hypertension, Xuezhikang has been shown to suppress vascular remodelling, a process that results in structural changes and the narrowing of blood vessels. This effect has been demonstrated through a reduction in the left ventricular mass index and wall-to-lumen area ratio of the thoracic aorta in hypertensive rats treated with Xuezhikang, which was associated with decreased expression of Fibulin-3, MMP-2, and MMP-9[81]. Likewise, consistent findings were observed in patients with hypertension, where Xuezhikang induced a reduction in arterial stiffness and improvements in other arterial parameters, such as pressure-strain elasticity modulus, and pulse wave velocity[82]. Moreover, Xuezhikang improved left ventricular diastolic function, left ventricular hypertrophy, and heart rate turbulence in patients with hypertension[83,84]. When used in combination with antihypertensive drugs Xuezhikang increased the level, proliferation capability, and adhesion function of the vascular-repairing endothelial progenitor cells in the blood in patients with hypertension[69,70]. Notably, in a randomized controlled study, Xuezhikang combined with antihypertensive treatment could result in benefits independent of blood pressure-lowering effects in patients with essential hypertension controlled by anti-hypertensive medications by increasing the number of CEPCs and improving CEPCs mobilization and differentiation from bone marrow, promoting their migration and differentiation by phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) signal conduction pathway, preventing CEPCs senescence by modulating cellular cycling related proteins, and up-regulating the expression of the integrin in CEPCs to enhance their adherent and migratory capacities[70].

5.6. *Protection against liver disorders*

It has been suggested that non-alcoholic fatty liver disease (NAFLD) is a precursor for both the development of CVD and

cardiovascular events, which is also considered a common public health problem[85,86]. In rats on a high-fat diet, Xuezhikang reduced fat accumulation, inflammation, and steatosis, suggesting that it can protect against NAFLD[87]. Among other factors, flavonoids may account for the protective effects as they have been shown favourable biochemical profile on the regulation of lipid metabolism, improvement of insulin resistance, amelioration of inflammation and oxidative stress, and exerting a beneficial therapeutic effect on steatosis and liver inflammation, which are important for the prevention of NAFLD[88,89]. Meanwhile, Xuezhikang has been shown to reverse abnormal transaminase, and its common mechanism in the treatment of NAFLD is likely to be related to the inhibition of the expression of TNF-α in the liver[87]. Therefore, Xuezhikang has been recommended to try in patients with hyperlipidaemia who cannot tolerate other statins or who have elevated liver enzymes/muscle enzymes caused by other statins[37]. Besides, selenium has some protective effects in liver diseases by balancing a systematic redox and anti-inflammation in the blood[90]. A recent meta-analysis involving 50 studies with 9875 cases and 12,975 population controls, suggested that both body selenium status and selenium intake were negatively associated with advanced chronic liver diseases such as hepatitis, cirrhosis, and liver cancer[91].

5.7. *Improvement of insulin sensitivity*

Diabetes is a crucial risk factor for CVD, especially for ASCVD and it has been reported that more than 80% of patients with diabetes have cardiovascular complications. In diabetic mouse models, Xuezhikang has demonstrated the ability to attenuate oxidative stress, upregulate expression of genes in glucose sensing, protect pancreatic islets from damage, and increase insulin secretion, all of which contributed to improved glucose tolerance[92]. As an important component of Xuezhikang, *n*-3 PUFAs exhibit the potential to improve defects in insulin signalling and prevent alterations in glucose homeostasis and further long-term complications in patients with type 2 diabetes by regulating the activity of key transcription factors relating to genes expression in lipid oxidation and synthesis[93]. This regulation of gene expression proceeds through the inhibition of SREBP-1 and the regulation of nuclear receptors, such as PPARs, retinoid X receptor, and liver X receptor[94–96]. Likewise, Xuezhikang improved insulin resistance in rats fed a high-fat diet by downregulating TNF-α mRNA expression in the liver, which is a common mechanism for their hepatoprotective effects. In addition, Xuezhikang reversed aminotransferase abnormalities with reduced serum aspartate aminotransferase level[87]. Flavonoids and *n*-3 PUFAs may play a role in the regulation of insulin signalling pathways and glucose metabolism[97,98]. In rats, the *n*-3 PUFAs reduce the skeletal muscle triglyceride content, enhance the effectiveness of insulin for utilizing glucose and defend against the development of systemic insulin resistance[98,99]. In a randomized control trial, 324 participants were assigned to four energy-restricted diets of identical macronutrient composition but different long-chain *n*-3 PUFA content. Following an 8-week dietary intervention, the fish oil diet reduced fasting insulin and improved homeostasis model assessment of insulin resistance to a significantly greater extent than the control diet. It demonstrated that long-chain *n*-3 PUFAs consumption during energy reduction could exert positive effects on insulin resistance in young overweight or obsess individuals and, possibly, for the prevention of type 2 diabetes[100].

5.8. *Renal protection*

Interestingly, previous experimental or human studies have also shown renal protection of Xuezhikang. In the rat model of hyperlipidaemia or diabetes, Xuezhikang was shown to ameliorate kidney damage, which might be associated with its lipid-lowering, anti-inflammatory, and antioxidant activities presented by increased expression levels of macrophage scavenger receptors and improve uptake of ox-LDL[58,101].

Lovastatin, the major component of Xuezhikang, was proven to have the effect of renal fibrosis prevention through the inhibition of renal tubular cells' epithelial-to-mesenchymal transition in tubular epithelial cells and the activation of RhoGTPases, resulting in a reduction of Ras homolog family member A (RhoA) and Ras-related C3 botulinum toxin substrate 1 (Rac1) activation in both the cytoplasmic and membrane-bound forms[102]. Several studies have also reported that *n*-3 PUFAs can slow down the progression of kidney disease through their effects on lipid modulation, anti-inflammation, anti-hypertension, anti-thrombosis, inhibition of oxidative stress, improvement of hemodynamics, interference with cell proliferation, signal transduction and other relevant pathways[103,104]. A recent pool analysis, including 19 studies from 12 countries, showed that *n*-3 PUFAs played a favourable role for *n*-3 PUFAs in preventing chronic kidney disease[105].

5.9. *Other beneficial effects*

The China Coronary Secondary Prevention Study (CCSPS) study found that Xuezhikang could reduce the risk of death from cancer[106]. The antitumor effect of Xuezhikang is the result of the synergistic action of lovastatin with other beneficial components[107]. In addition, several studies have discovered that supplementing *n*-3 PUFAs to the diet of tumour-bearing mice or rats could inhibit the development of several malignancies, including lung, colon, mammary, and prostate cancers[108–111]. Some of the potential mechanisms underlying the antitumor activity of *n*-3 PUFAs include modulation of eicosanoid synthesis and inflammation, angiogenesis, proliferation, susceptibility to apoptosis, and estrogen signaling[112]. Moreover, selenium has been found to exert anticancer effects through a variety of mechanisms, including anti-oxidative damage, regulation of gene expression and cell cycle, promotion of cancer cell apoptosis, protection from DNA damage, and enhancement of immune function[113,114].

Besides, Xuezhikang stimulated the formation of new bone in bone defects *in vivo* and promoted bone cell production *in vitro*[115–117]. It has been demonstrated that flavonoids might have the ability to assist in the stimulation of bone formation and statins could slightly increase bone mineral density and thus reduce the risk of osteoporosis in later life[118,119]. Additionally, the Invecchiare in Chianti (InCHIANTI) study revealed that low plasma selenium is independently associated with poor skeletal muscle strength in community-dwelling older adults[120].

In addition, Xuezhikang has been found to reduce fat accumulation, remodel adipose tissue, and weight gain in rats on a high-fat diet, accompanied by regulation of gene expression in brown adipose tissue and improvements of glucose and lipid metabolism by a reduction in serum triglyceride, LDL-C, and fasting blood glucose levels as well as increasing in serum HDL-C levels[121]. Another study has demonstrated that *n*-3 PUFAs were protective in the secondary prevention of sudden cardiac death and recurrent fatal myocardial infractions due to fatal arrhythmias[122].

Magnesium, an essential component of Xuezhikang, acts as a neural-protective agent by participating in the regulation of metabolism and in the maintenance of the homeostasis of all the tissues, including the brain, where it harmonizes nerve signal transmission and preserves the integrity of the blood−brain barrier[123].

6. Pivotal clinical trials

The efficacy and safety of Xuezhikang are supported by two pivotal phase 2 clinical trials and the CCSPS, as well as mounting evidence from other studies. Based on positive results, Xuezhikang was approved for the prevention and treatment of adults with dyslipidaemia in China mainland in the 1990s, followed by its approval in other Asian areas. In the first registrational phase 2 trial of Xuezhikang that was conducted in China, patients with hyperlipidaemia received Xuezhikang (n = 324) or comparator treatment (n = 122). The results showed that Xuezhikang reduced LDL-C, TC, and triglycerides by 28.5%, 23.0%, and 36.5%, respectively, and increased HDL-C by 19.6% at week 8, these changes were superior to those in the comparator arm[124]. In the subsequent registrational, randomized, placebo-controlled, phase 2 trial that was conducted in the United States and China and included patients with dyslipidaemia (Xuezhikang, n = 78; placebo, n = 42), Xuezhikang treatment for 4−12 weeks resulted in significant reductions in LDL-C (by 27%) and non-HDL-C (by 24%) compared with placebo[125].

The CCSPS is the largest randomized controlled trial that evaluated secondary prevention of coronary events with a long-term follow-up and the only one that showed CVD benefits for a pharmacological intervention in China[106]. This study enrolled 4870 patients who had a documented previous myocardial infarction to randomly receive Xuezhikang (n = 2441) or placebo (n = 2429)[106]. After an average of 4.5 years of treatment, Xuezhikang reduced the risk of major coronary events by 45%, CVD mortality by 30%, and total mortality by 33% compared with placebo (Fig. 3). Furthermore, Xuezhikang exhibited superior effects in reducing cholesterol levels compared to placebo, with reductions of 10.9% in TC, 17.6% in LDL-C, 14.6% in triglycerides, and 16.6% in non-HDL-C[106]. The efficacy of Xuezhikang for CVD protection is noteworthy as the degree of reduction in the risk of major coronary events appears to be greater than those observed with statins of similar intensity, although comparison between trials should be made with caution because of differences in patient population, follow-up durations, clinical practice, and other factors[126−129].

Consistently, the clinical benefits of CVD prevention with Xuezhikang were shown in important high-risk subgroups (Fig. 3). The reduction in the risk for major coronary events with Xuezhikang was pronounced in patients with type 2 diabetes (n = 591), at 50.8% reduction, along with 44.1% reduction in the risk for coronary heart disease (CHD) and 44.1% reduction in all-cause mortality[130]. In elderly patients (aged 65−75 years; n = 1445), the reduction in risk with Xuezhikang *vs.* placebo was 36.9% for coronary events, 31.0% for CVD mortality, and 31.9% for total mortality[131]. In particular, the efficacy of Xuezhikang in preventing CVD was encouraging in patients with hypertension (n = 2704): the risks of coronary events, CHD deaths, and total deaths were reduced by 43.0%, 30.0%, and 35.8%, respectively[132]. The benefits were similar in elderly patients (aged ≥65 years) who had hypertension (n = 1530), with a 37.0% reduction in coronary events, 28.0% reduction in CHD deaths, and 35% reduction in all-cause deaths[133]. More interestingly, protection against CVDs with Xuezhikang remained in patients with abnormal liver tests (n = 820), whereas the use of statins may pose safety concerns. The risk of coronary events was substantially decreased by 76.3% and no safety signals of liver toxicity were observed[134]. This study may extend the known benefits of lipid-lowering by Xuezhikang in high-risk patients with nonspecific, preexisting abnormal liver tests to an under-studied ethnic group. The pleiotropic effects of Xuezhikang and possibly the synergistic actions of its components may contribute to effective cardio-protection and marked reductions in the risks for CVD events and mortality across all at-risk patient subgroups[130−134].

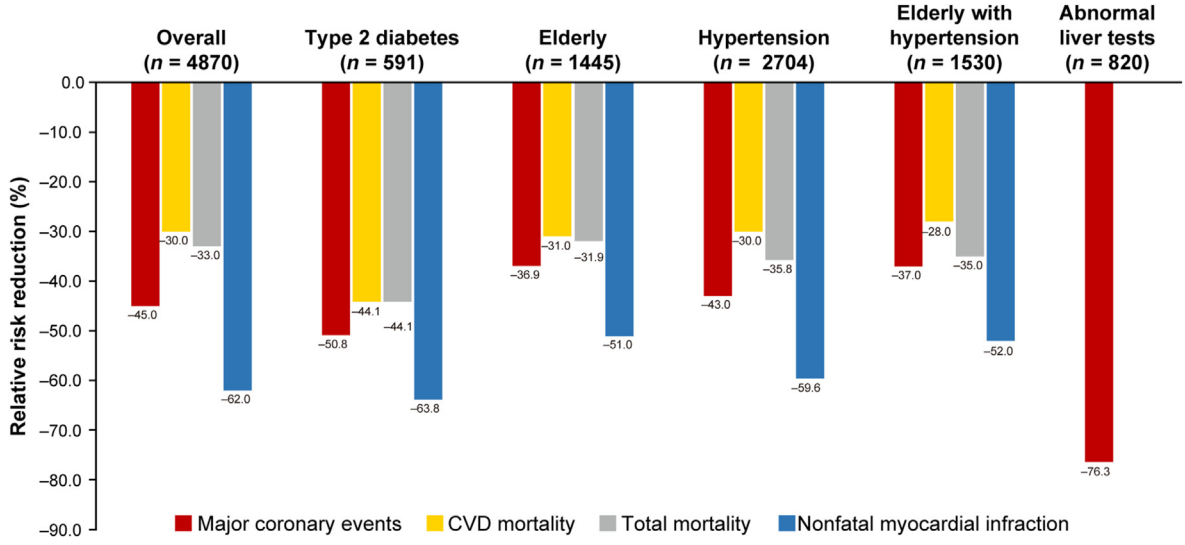

Figure 3 Risk reductions with Xuezhikang *vs.* placebo in the China Coronary Secondary Prevention Study. The reduction in relative risk was calculated based on the number of events in the Xuezhikang group compared to the placebo group. The overall patient population included Chinese patients with previous myocardial infarction. CVD, cardiovascular diseases.

7. Applications in various clinical settings

The wide spectrum of clinical benefits of Xuezhikang supported by studies in humans include lipid modification[43,106,124,125,135,136], regulation of the coagulation-fibrinolysis balance[79], anti-inflammation[49,57,71,72,74,137], improvement of vascular and heart functions [82−84,137], and eventually protection against CVDs[106,138]. The diverse activities of Xuezhikang have led to discussions of its utilization in patients with different conditions. The diverse activities of Xuezhikang have led to discussions of its utilization in patients with different conditions. Notably, its efficacy in lowering blood cholesterol, mitigating inflammation, inhibiting oxidative stress, suppressing platelet activity, and enhancing endothelial function positions it as an effective intervention for both primary and secondary prevention of CVDs[49,71−74,79,106]. Xuezhikang is recommended as a moderate-intensity statin given the extent to which it can reduce LDL-C (17.6%−28.5% in clinical studies), and its efficacy in lipid modification has been validated in Asian and Caucasian populations alike[35,43,106,124,125,135,136]. Aside from the large-scale CCSPS mentioned above, the anti-CVD efficacy of Xuezhikang was also supported by results from a large-scale real-world study (n = 34,723), in which Xuezhikang reduced the risk for stroke by 35% compared with that in the non-RYR group and the benefit was observed regardless of the type of stroke[138]. In patients with hypertension, Xuezhikang has shown the ability to reduce arterial stiffness, improve left ventricle diastolic function, left ventricular hypertrophy, and heart rate turbulence, which add to its anti-inflammatory and lipid-lowering effects, and therefore it provides multiple cardioprotective benefits in these patients[82−84]. In addition, Xuezhikang shows promise as a potential medication for the prevention and treatment of NAFLD given the clinical evidence showing its anti-inflammatory activities in patients with NAFLD and preclinical evidence of its ability to reduce hepatic fat accumulation, steatosis, and collagen deposition with a high-fat diet[57,87]. Preclinical evidence suggested that Xuezhikang may have potential applications in the management of diabetes[87,92], kidney damage secondary to diabetes and/or hyperlipidaemia[58,101], and brain injury after cardiac arrest[60].

A reduction in LDL-C by ≥50% is desired for patients at high risk or very high risk for CVDs. However, substantial lipid lowering with high-intensity, high-dose statins may come at the cost of greater risks of side effects[34,139]. Combining a low-dose statin with a new lipid-lowering drug is a possible solution to avoid statin intolerance and overcome statin non-adherence, which is recommended by the European Society of Cardiology (ESC) working group[4]. Xuezhikang, which is without the safety concerns of statin intolerance, with a lower-dose statin, is a therapeutic strategy of great interest to researchers. Combining Xuezhikang with 5 mg/day rosuvastatin has been shown to result in greater reductions in LDL-C (by 53% *vs* 48%) and triglycerides (by 21% *vs* 2%) than double doses of rosuvastatin (10 mg/day), with no noticeable safety signals identified[140]. Moreover, a preliminary study in patients with unstable angina pectoris revealed that Xuezhikang in combination with rosuvastatin *vs*. rosuvastatin alone, in addition to the more effective lowering of blood cholesterol, resulted in more pronounced reductions in carotid atherosclerotic plaque area and intima-media thickness and improvements in endothelial functions and inflammation, suggesting that the combination treatment stabilized carotid atherosclerosis plague and inhibited atherosclerosis progression[141]. Combining Xuezhikang with non-statin lipid-lowering agents was also studied. This research has shown that the combination of Xuezhikang plus ezetimibe could confer a greater extent of cholesterol reduction than monotherapy[142,143], and a low dose of Xuezhikang and ezetimibe demonstrated lipid-lowering and anti-inflammatory effects similar to those achieved with a high-dose of Xuezhikang[144]. In addition, Xuezhikang plus antihypertension drugs were shown to improve vascular and heart functions in patients with hypertension, again suggesting that a combination treatment strategy that includes Xuezhikang can provide cardioprotective benefits[84,145].

8. Safety profile

In clinical trials, adverse events in the Xuezhikang group were infrequent and the incidence rates were no higher than those in the control group[43,106,124,125,135,136,146]. Most adverse events with Xuezhikang were gastroenterological symptoms, mainly mild to moderate, and no serious adverse events related to Xuezhikang were reported[106,124,125,146]. There were no events of creatine phosphokinase elevation to a level of >5 × upper limit of normal, myopathy, or rhabdomyolysis, and incidences of clinically meaningful changes in laboratory tests, including liver enzymes, did not differ between Xuezhikang and control groups[38,106,124,125]. Concomitant use of Xuezhikang with antidiabetic or antihypertensive medications did not pose additional safety concerns[130,132]. In patients with pre-existing abnormal liver tests, the level of alanine aminotransferase during 4.5 years of follow-up was similar between Xuezhikang and placebo groups, without signs of impairment in liver functions[134]. A real-world study that analysed data from 34,504 patients showed that Xuezhikang was associated with a lower risk for incident diabetes compared with lovastatin[147]. Xuezhikang was as well-tolerated in elderly patients as in young patients[131] and appeared to be as safe in Caucasians as in Asian patients[43,106,124,125,135,136]. Altogether, the potential safety issues associated with statins, for instance, muscle toxicity, liver toxicity, and new-onset diabetes, did not emerge during treatment with Xuezhikang in clinical trials and real-world clinical practice. Therefore, Xuezhikang is a relatively safe treatment option for long-term use, in particular for patients with statin intolerance and those with pre-existing muscle or liver test abnormalities[139].

9. Challenges and future directions

Several unanswered questions about Xuezhikang warrant further investigation. Firstly, there is currently only one cardiovascular outcome study on Xuezhikang[106], highlighting the need for more large-scale studies to assess its impact on cardiovascular outcomes. Secondly, although two small sample randomized, controlled clinical trials of Xuezhikang included white and other racial groups[125,136], previous studies mainly included Asian patients. Therefore, its efficacy and safety, especially its effect on CVD prevention, await further study in non-Asian populations. Moreover, while Xuezhikang is commonly used in the Chinese population, its application in other demographic groups, such as children, the oldest older, and individuals with conditions like familial hypercholesterolemia remains understudied. Furthermore, no studies have evaluated the effects of individual components in this composite drug. It remains unclear whether these components exert distinct effects individually or if their actions are dependent on each other. Besides, the effects of Xuezhikang in combination with other medications, in addition to more effective lipid-

lowering, is an appealing area for future studies. Adding Xuezhikang to other medications may bring manifold cardioprotective benefits, effectively lower the risk for CVDs, and improve other clinical outcomes in patients with different medical conditions. Finally, the potential impact of Xuezhikang at high-dose usage on lipid profile and clinical outcomes may also be needed to address.

10. Perspectives and guideline recommendations

The approval of Xuezhikang, a natural product extract, has opened a new avenue for the discovery of lipid-lowering treatment, making an effective intervention for primary and secondary CVD prevention without known safety risks available[106,138]. Xuezhikang has two advantages over pure single-agent statins. First, attributed to its different bioactive ingredients and their synergistic actions, Xuezhikang provides pleiotropic benefits not limited to cholesterol reduction, confers cardio-protection, improves vascular and heart functions, and inhibits atherosclerosis progression. These multi-fold effects are not commonly seen with single-agent lipid-lowering drugs[6]. Second, Xuezhikang appears to obviate the safety concerns with statins, likely due to the activity of other components in the pill, which is important for long-term use, treatment adherence, and in particular for patients with statin intolerance[106,124,125].

Several cardiovascular guidelines have endorsed Xuezhikang as a recommended treatment for lipid modification and CVD prevention[34,35,148–155] (Table 2). For instance, the 2019 ESC/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias recommend RYR nutraceuticals as lifestyle interventions to reduce blood cholesterol levels, particularly for individuals ineligible for statin therapy. Of significance, these guidelines have recognized that Xuezhikang is the only RYR extract for which its anti-CVD efficacy is supported by a randomized controlled trial[34]. In the 2023 Chinese guidelines for lipid management, as well as the 2016 Chinese guideline for the management of dyslipidaemia in adults, the Chinese guidelines for the treatment of coronary disease, the Chinese guidelines on the primary prevention of cardiovascular disease, among others, Xuezhikang is recommended as a moderate-intensity, relatively safe lipid-lowering treatment for the prevention of CVDs[35,150,152–155]. Consequently, Xuezhikang has emerged as a foundational lipid-lowering treatment widely used in clinical settings and has become a cornerstone intervention for CVD prevention across Asia.

Table 2 Guidelines that include red yeast rice in treatment recommendations.

Guideline	Year	Ref.
Chinese Guidelines for Diagnosis and Treatment of Chronic Stable Angina	2007	148
ESC/EAS Guidelines for the Management of Dyslipidaemias	2011	149
Chinese Guideline for the Management of Dyslipidaemia in Adults	2016	150
2016 ESC/EAS Guidelines for the Management of Dyslipidaemias	2016	151
Chinese Guidelines for the Treatment of Coronary Disease	2018	152
Chinese Guideline on the Diagnosis and Treatment of Stable Coronary Artery Disease	2018	153
Chinese Guidelines for Diagnosing and Treating Acute Myocardial Infarction by Integrative Medicine	2018	154
2019 ESC/EAS Guidelines for the Management of Dyslipidaemias	2019	34
Chinese Guidelines on the Primary Prevention of Cardiovascular Disease	2019	35
Chinese Guidelines for Lipid Management	2023	155

ESC, European Society of Cardiology; EAS, European Atherosclerosis Society.

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Author contributions

Cheng Yang: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. Yongjian Wu: Supervision, Writing – original draft, Writing – review & editing. Jie Qian: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. Jian-Jun Li: Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Conflicts of interest

The authors declare no conflicts of interest.

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