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Potential protective effects of red yeast rice in endothelial function against atherosclerotic cardiovascular disease

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[ABSTRACT] Atherosclerotic cardiovascular disease (ASCVD) is the deadliest disease in the world, with endothelial injury occurring throughout the course of the disease. Therefore, improvement in endothelial function is of essential importance in the prevention of ASCVD. Red yeast rice (RYR), a healthy traditional Chinese food, has a lipid modulation function and also plays a vital role in the improvement of endothelial reactivity and cardiovascular protection; thus, it is significant in the prevention and treatment of ASCVD. This article reviews the molecular mechanisms of RYR and its related products in the improvement of endothelial function in terms of endothelial reactivity, anti-apoptosis of endothelial progenitor cells, oxidative stress alleviation and anti-inflammation.

[KEY WORDS] Red yeast rice; Xuezhikang; Atherosclerotic cardiovascular disease; Endothelial cells; Molecular mechanism

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Introduction

Atherosclerosis cardiovascular disease (ASCVD) has been one of the leading causes of mortality in developed countries, with increasing morbidity in developing countries. ASCVD has resulted in the highest death rate out of all diseases in China and is a great burden to society. The most fundamental pathological change in ASCVD is atherosclerosis (As), where endothelial injury continues throughout the course of the disease. Therefore, it is important to maintain endothelial function. It has been reported recently that red yeast rice (RYR) is both a lipid modifier and a healthy functional food in the prevention and treatment of ASCVD that inhibits as by suppressing apoptosis, increasing the number of endothelial progenitor cells, improving endothelial reactivity, attenuating oxidative stress and reducing inflammation. This article reviews recent studies on the mechanisms of the aforementioned functions of RYR products and provides further information regarding the cardiovascular protective role of RYR in the prevention and treatment of ASCVD.

Components of RYR

RYR is made by fermenting the fungus *monascus purpureus* on wet rice. Due to its health-enhancing qualities, it has been used as a healthy food and herbal medicine in China for over 1000 years. Apart from rice starches and sugars, its functional components are varied: polyketides, monounsaturated fatty acids, phytosterols, isoflavones, condensed tannins,

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Coenzyme Q10, microelements and pigments, including ankaflavin, monascin, rubropunctatin, monascorubrin, rubropunctamine and monascorubramine. Monacolin, one of the polyketides, is the principal component, the content of which depends on the mold strain. Among the monacolins, monacolin K is the most investigated, as it is possibly identical to lovastatin [1-2]. Dimerumic acid and γ-aminobutyric acid are reported to be parts of the products fermented with Monascus [3].

Marketed domestic pharmaceuticals of RYR are mainly Xuezhikang capsules, Zhibituo tablets and Zhibitai capsules [4], and international products include Red Yeast Rice (manufactured by Sylvan Bioproducts, Inc., Kittanning, Pennsylvania, USA) [5], Cholestin (produced by Pharmanex, UT, USA) [6] Colesia (a combined nutraceutical containing red yeast rice, phytosterols and L-tyrosol, IBSA Farmaceutici, Milan, Italy) [7], *etc*. Notably, Xuezhikang (XZK) is one of the most widely used drugs of its kind in China. Despite being a partially purified extract of red yeast rice, its multiple components produced from the fermentation of Monascus purpureus on polished grained rice work in concert with monacolins to bring additional health benefits (the composition of XZK is listed in Table 1) [2, 8-9].

Table 1 Composition of XZK

Ingredients	Percentage content (300 mg per capsule) [2, 8-9]
13 natural statins	2%
Monacolin K	0.29%−0.33%
Monacolin L	0.034%−0.045%
Dehydromonacolin K	0.041%−0.065%
Unsaturated fatty acids	8% (approximately)
Palmitic acid	18.61%
Linoleic acid	48.13%
Oleic acid	28.78%
Stearic acid	4.49%
Amino acids (approximately 20 kinds)	8.57% (approximately)
γ-aminobutyric acid	29.77% (approximately)
Flavone and flavonol	0.045%
Ergosterin	0.3%
Alkaloid trace elements	0.35%
in water-soluble form	0.3%
in fat-soluble form	0.05%
Monascin	Unknown

RYR and cardiovascular outcomes

RYR has historically been known as a functional lipid modulator, and its effectiveness has been shown in a double-blind, 6-month clinical trial (n = 40) that tested a combination of RYR and coenzyme Q10 [10]. For participants in the treatment group, the low-density lipoprotein cholesterol (LDL-C) level was lowered by 26.3%. This outcome coincided with the results in the China Coronary Secondary Prevention Study (CCSPS) [11]. The CCSPS was a multi-centered, randomized and placebo-controlled study, where XZK was used as a drug representative of red yeast rice. With 4 870 Chineses coronary heart disease (CHD) patients aged 18 to 75 years old with a previous history of myocardial infarction, the CCSPS study lasted for an average of 4 years, and the results showed that patients administered with XZK benefited from a decrease in total cholesterol (TC) by 13.2%, LDL-C by 20.2% and triglyceride (TG) by 15.0% (differences between groups are of statistical significance, $P < 0.0001$).

In addition to the obvious hypolipidemic effects, a subgroup analysis of CCSPS conducted by Ye P. *et al* [12] with 1 445 CHD patients showed a 36.9% decrease in coronary events and a 31% decrease in coronary death with less adverse events. Similar results in other subgroup analyses such as reductions in unstable angina, acute myocardial infarction, nonfatal myocardial infarction and sudden cardiac death support the myocardial protective role of XZK[13-18]. Notably, the hypotensive impacts of XZK have also been shown in some subgroup studies [19-20]. Further proving this benefit, left ventricular hypertrophy was improved in one study conducted on 90 hypertensive patients [21] (Table 2).

RYR and endothelial function improvement beyond lipid reduction

In terms of the target population, sample size, baseline lipid level and follow-up time, the CCSPS study is quite comparable with the CARE (the Cholesterol and Recurrent Events, 1996) study [22-23], in which patients benefited from a 19%−27% reduction in TC, 23% reduction in LDL-C and 23% reduction in TG after pravastatin intake. XZK in the CCSPS study lowered lipid levels to a lesser extent compared with pravastatin in the CARE study but seemed to show more benefits in reducing cardiovascular events, with a 45.1% reduction in the CCSPS study ($P < 0.0001$) compared to a 24% reduction in the CARE study ($P = 0.0003$).

Given the above results, continuous attention has been focused on RYR, not only because of its function of lipid profile but also due to its cardiovascular benefits [24]. Since the effect of RYR is partially attributed to the presence of natural statins, it has been hypothesized that relatively high concentrations of other natural compounds may work in coordination with the statins to provide additional health benefits. Since it occurs throughout the process of ASCVD, endothelial dysfunction plays a pivotal role in its pathogenic mechanisms. Hence, improvement in endothelial function is essential, given that endothelial injury contributes to an increased risk of coronary events.

One of the most common consequences of endothelial dysfunction is a negative influence on the barrier function of vessels. Nitric oxide (NO) and endothelin 1 (ET-1) are active substances secreted by the endothelium [25] that are normally in

Table 2 Clinical trials on the cardiovascular benefits of RYR products

Study	Study Subjects	Treatment Group	Control Group	Clinical Benefits	Effects of RYR and its Related Products	Study Design	Duration
Ye P *et al.*, 2007 [12]	1445 Chinese patients with CHD aged 65 to 75	conventional therapy plus Xuezhikang 600 mg twice daily (n = 735)	conventional therapy plus placebo twice daily (n = 710)	CHD protection	↓ total CHD events, total CHD death, nonfatal AMI, total stroke	Double-blinded RCT	4 years in average
Li JJ *et al.*, 2009 [13]	1530 Chinese elderly (over 65 years old) hypertensive patients with previous myocardial infarction	conventional therapy plus Xuezhikang 600 mg twice daily (n = 772)	conventional therapy plus placebo twice daily (n = 758)	Anti-hypertension and CVD protection	↓ SBP, DBP, coronary events and non-fatal MI	Double-blinded RCT	4.5 years in average
Yang XK *et al.*, 2009 [14]	100 Chinese patients with stable angina	conventional therapy plus Xuezhikang 600 mg twice daily (n = 55)	conventional therapy (n = 45)	Protection for ischemic heart disease	↓ TIBand ischemic events (unstable angina, acute myocardial infarction and sudden cardiac death)	RCT	24 months
Lu ZL *et al.*, 2005 [15]	591 Chinese patients with coronary heart disease diabetes mellitus	conventional therapy plus Xuezhikang 600mg twice daily (n = 306)	conventional therapy plus placebo twice daily	Coronary and heart protection	↓ coronary events (nonfatal and fatal acute myocardial infarction, sudden coronary death and other coronary death) and coronary death (fatal acute myocardial infarction, sudden coronary death and other coronary death)	RCT	4 years on average
Du BM *et al.*, 2006 [16]	2704 Chinese myocardiac infarction patients (over past 5 years till past 28 days) with hypertension	conventional therapy plus Xuezhikang 600mgtwice daily (n = 1363)	conventional therapy plus placebo twice daily(n = 1341)	Coronary and heart protection	↓ coronary events(nonfatal and fatal acute myocardial infarction , sudden coronary deaths and other coronary death) and coronary death(fatal acute myocardial infarction, sudden coronary death and other coronary death)	RCT	4 years on average
Lu Z *et al.*, 2008 [17]	4870 Chinese patients (aged18 to 70 years old), each with a documented previous myocardial infarction (MI) in 65 Chinese hospitals	conventional therapy plus Xuezhikang 600 mg twice daily (n = 2429)	conventional therapy plus placebo twice daily(n = 2441)	Protection against CVD	↓ major coronary events (consisted of nonfatal MI or death from coronary or cardiac causes), coronary disease mortality, CV mortality and need for coronary revascularization.	Double-blinded, parallel-group RCT	4.5 years on average
Huang B *et al.*, 2007 [18]	128 Chinese patients with acute coronary syndrome	conventional therapy plus Xuezhikang 600 mg twice daily (n = 64)	conventional therapy (n = 64)	Protection against ischemic heart disease	↓ TIB and ischemic events (unstable angina, acute myocardial infarction and sudden cardiac death)	RCT	12 months
Li JJ *et al.*, 2010 [19]	2704 Chinese hypertensive patients with previous myocardial infarction	conventional therapy plus Xuezhikang 600 mg twice daily (n = 1363)	conventional therapy plus placebo twice daily (n = 1341)	Anti-hypertension	↓ SBP and DBP	RCT	4.5 years on average
Zhu ZT *et al.*, 2010 [20]	110 Chinese hypertensive patients	antihypertensive drugs (difference of drug dose between 2 groups was of no statistical significance) plus Xuezhikang 600 mg twice daily(n = 56)	antihypertensive drugs (based on angiotensin-converting enzyme inhibitors/calcium- channel blockers combination) (n = 54)	Anti-hypertension	↓ 24 h SBP, 24 h DBP, PPI, 24 h PP; SIBDP and SISBP were higher than the control group.	RCT	6 months
Gong C *et al.*, 2010 [21]	90 Chinese primary hypertensive patients with left ventricular hypertrophy	basic treatment, valsartan (80 mg, once a day) and Xuezhikang 600 mg twice a day (n = 32)	1. basic treatment (n = 28) 2. basic treatment and Valsartan80 mg once daily (n = 30)	Anti-hypertension and improvement in left ventricular hypertrophy	↓ SBP, DBP, TO and LVMI ↑ TS	RCT	24 months

↓: decrease; ↑: increase; SBP: systolic blood pressure; DBP: diastolic blood pressure; MI: myocardial infarction; CHD: coronary heart disease; TIB: total myocardial ischemia burden; PP: pulse pressure; PPI: pulse pressure index; SISBP: smoothness index for systolic pressure; SIDBP: smoothness index for diastolic pressure; CV: cardiovascular; TS: slope coefficient; TO: the original heart rate; LVMI: left ventricular mass index; CV: cardiovascular; PPI: pulse pressure index (PPI = 24 h PP/24 h SBP); TO = [(RR1 + RR2)-(RR-1 + RR-2)]/(RR-1 + RR-2)×100%, in the formula, RR1 and RR2 denote the RR interval of the prime 2 sinus rhythmic contractions immediately following a ventricular premature beat.

a balanced state. NO helps with vasodilatation and inhibition of platelet aggregation and adhesion. ET-1, a strong vasoconstrictor, acts to mobilize some inflammatory cells and release proinflammatory mediators. When a deficiency in the secretion capacity of the endothelium occurs, this balance will be broken, and vasomotor malfunction occurs, leading to endothelial injury. WANG WH *et al.* conducted a randomized controlled trial (RCT) on 105 Chinese patients with acute coronary artery syndrome (ACS), and the results fit with the theory that intake of XZK is associated with higher levels of NO and lower levels of ET-1 [26]. Several small sample size clinical trials may also support this finding [27-28].

Endothelial progenitor cells (EPCs), which participate in the maintenance of vascular homeostasis angiogenesis under harmful conditions, are crucial to endothelial repair and restoration [29]. A study conducted by Spigoni V *et al.*[29] documented that 12 weeks of intervention with nutraceuticals containing RYR resulted in changes in EPC numbers, which showed no statistical significance ($P > 0.05$), and the placebo arm showed a decrease in EPCs.

Flow-mediated dilation (FMD) is a common and noninvasive method to evaluate endothelial function [30]. A recent meta-analysis of clinical data shows that a 1% improvement in FMD is associated with a 12% decline in CV risk [31]. Studies focused on patients with hyperlipidemia since it is widely acknowledged that changes in the lipid profile contribute to improvements in endothelial function [7, 32]. Interestingly, WANG WH *et al.* demonstrated improvement in FMD (3.16% ± 0.47% *vs* 7.03% ± 0.40%) in ACS patients with hyperlipidemia and also showed comparable changes (3.67% ± 0.56% *vs* 7.16% ± 0.63%) in patients with normal blood lipid levels [26]. Beyond this outcome, this study implied that the increase in FMD, conducive to endothelial function restoration, may be less relevant to blood lipid levels, and further investigation pointed to XZK, a medication which was used in this RCT that revealed its possible direct effect on endothelial protection [26]. To support this protection, the mean change in FMD was found to be 1.9% ± 4.2% in a trial where 57 patients with metabolic syndrome completed 18 weeks of treatment [33].

With regard to the endothelial reactivity parameters, pulse volume displacement (PVD) was increased by 6% with supplementation with red yeast rice and Coenzyme Q10 [10]. Another commonly used measurement of endothelial-dependent vasodilatation is pulse wave velocity (PWV), which changes in accordance with declines in large arterial elasticity that are caused by adverse effects on arterial structure and contractile and relaxant function [34]. Cicero AF *et al.* found PWV was decreased by 4.7% after treatment with red yeast rice [10] and PVD changed 18.59% after red yeast rice combination treatment [35].

From current clinical outcomes, we may conclude that the anti-atherosclerotic benefits of RYR result from its positive influence on endothelial protection (Table 3). This article aims to review the latest reports on the molecular mechanisms of RYR products in the improvement of endothelial reactivity, increase of endothelial EPCs, alleviation of inflammation, attenuation of oxidative stress, and protection of overall endothelial function.

Molecular mechanisms of RYR products in endothelial function improvement

Endothelial dysfunction is a complex process that mainly involves increases in endothelial nitric oxide synthase (eNOS), EPCs, oxidative stress and inflammation. As an initiating step in ASCVD, attention should be given to endothelial dysfunction, as it is vital to the pathogenic mechanisms of this disease [36].

As the functional component of RYR, Monacolin K (MK) is identical to lovastatin [1] and is an inhibitor of β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) reductase [37]. Therefore, some of the cardiovascular benefits are similar to those of statins, which are HMG-CoA reductase inhibitors, and the other benefits are comprised of other functional and natural components, namely, monascus, unsaturated fatty acid, ergosterol, amino acid, flavonoid, phytosterol, alkaloid and microelements. Taken together, RYR products protect humans from cardiovascular diseases and ASCVD through endothelial improvement by different molecular mechanisms (Fig. 1).

RYR and eNOS

eNOS has a homologous dimeric structure, and when its calcium/calmodulin binding sites are occupied by caveolin-1 (Cav-1), NO production will be reduced [38], after which vasodilatation and endothelial dysfunction will occur. Hence, an improvement in endothelial dysfunction is closely associated with the activity of eNOS. RYR upregulation of eNOS may be achieved through several mechanisms. The most widely acknowledged mechanism is MK, which is a functional component of RYR that is a HMG-CoA reductase inhibitor, which is proven to reinforce eNOS activity *via* the PI3K/PKB/Akt signaling pathway [39].The second mechanism is the separation of the eNOS-Cav-1 complex, which makes it feasible for the active form of eNOS to catalyze NO production in endothelial cells and further regulate relaxation of vascular endothelia [40]. This conclusion was derived from rat models fed with high-fat diets and treated with XZK, which showed an increase in Cav-1 expression in the walls of the aortaand increased eNOS expression in endothelia [40]. Moreover, rats treated with XZK had higher levels of eNOS than those treated with lovastatin [40]; this outcome indicated that XZK (an extract of RYR) is more effective than HMG-CoA reductase inhibitors in terms of eNOS upregulation and endothelial improvement, and the unsaturated fatty acids and ergosterol in RYR extracts (i.e. XZK) may synergistically enhance eNOS.

Therefore, it is reasonable to conclude that RYR products have beneficial impacts on endothelial function not only *via* upregulation of eNOS but also through other functional pathways whose underlying mechanisms have yet to be studied.

RYR and EPCs

RYR extracts have been found to effectively increase the number of EPCs [41-42]. EPCs are key players in the process of

Table 3 Clinical trials on the endothelial protection of RYR

Study	Duration	Study Design	Study Subjects	Treatment Group	Control Group	Outcome (Treatment Group vs Control Group)
Cicero AFG *et al.*, 2017 [7]	2 months	Double-blind RCT	50 Italian polygenic Hypercholesterolemia Italian patients resistant to Mediterranean diet	Colesia®, 2 pills per day (n = 25)	Placebo, 2pills per day (n = 25)	↑ FMD
Cicero AF *et al.*, 2016 [10]	6 Months	RCT	79 Italian patients with moderate hypercholesterolemia, non-smokers	Monacolin 10 mg plus 30 mg Coenzyme Q10 (n = 40)	Placebo (n = 39)	↑ PVD
Zhu ZT *et al.*, 2010 [20]	6 months	RCT	110 Chinese patients with essential hypertension	Xuezhikang 600 mg, twice daily plus antihypertensive therapy (n = 56)	Antihypertensive therapy (n = 54)	↓ PWV
Wang WH *et al.*, 2004 [26]	12 weeks	Double-blinded RCT	105 Chinese patients with acute coronary artery syndrome (ACS): 51 normal blood lipid patients (NBL) and 53 hyperlipidemic (HL) patients	Xuezhikang, 0.6 g twice daily (n = 53, NBL = 26, HL = 27)	Placebo (n = 52, NBL = 25, HL = 27)	↑ FMD and NO for both NBL and HL patients; ↓ ET-1 for both NBL and HL patients
Li JJ *et al.*, 2007 [27]	3 months	RCT	36 Chinese patients with cardiac syndrome X	Xuezhikang 1200 mg·d^{-1} (n = 18)	Placebo (n = 18)	↓ mean ET-1
Huang YS *et al.*, 2006 [28]	8 weeks	RCT(uncertain)	112 Chinese patients with coronary heart disease	Xuezhikang capsules 600 mg twice daily plus conventional therapy (n = 56)	Probucol 500 mg twice daily plus conventional therapy (n = 56)	↑ NO and NO/ET-1 ratio; ↓ ET-1
Spigoni V *et al.*, 2017 [29]	12 weeks (11−13 weeks)	RCT	41 Italian patients with hypocholesteremia	A combination pill of nutraceuticals[##] once daily (n = 30)	Placebo once daily (n = 9)	↑ EPCs identified as KDR+/CD133+/CD34+ and EPCs identified as KDR+/CD34+; Compared with control group, these increases were of no statistical significance
Affuso F *et al.*, 2010 [32]	6 weeks	Double-blind RCT	48 Italian patients with hypercholesterolemia	Nutraceutical combination[**], daily oral dose(n = 24)	Placebo, daily oral dose (n = 24)	↑ FMD
Affuso F *et al.*, 2012 [33]	18 weeks	Prospective, single centered RCT	64 Italian patients with metabolic syndrome (MetS)	A single tablet[#] (n = 29)	Placebo (n = 30)	↑ FMD
Cicero AF *et al.*, 2016 [35]	12 weeks (including 4 weeks' wash-out period)	Crossover, double-blind RCT	25 moderate hypercholesterolemic, non-smoking, pharmacologically untreated Italian subjects	Monacolin 10 mg plus a mix of antioxidants[*], 1 pill per day(n = 12)	Placebo, 1 pill per day (n = 13)	↑ PVD

↓: decrease; ↑: increase; FMD: flow-mediated dilation; PVD: pulse volume displacement; PWV: pulse wave velocity; Colesia®: an active product containing red yeast rice (5 mg monacolins/pill), 400 mg phytosterols/pill, and 2.5 mg L-tyrosol/pill; [*]: includes green tea extract, 10 mg, coenzyme Q10 20 mg, astaxanthin 2 mg, resveratrol 20 mg and quercetin 50 mg; [**]: includes policosanol 10 mg, red yeast rice 200 mg and berberine 500 mg; [#]: a single tablet contains berberine 500 mg, red yeast rice with monacolin K 3 mg and policosanol 10 mg; [##]: a single pill contains berberine 200 mg, monacolin K 3 mg, chitosan 10 mg and coenzyme Q10 10 mg

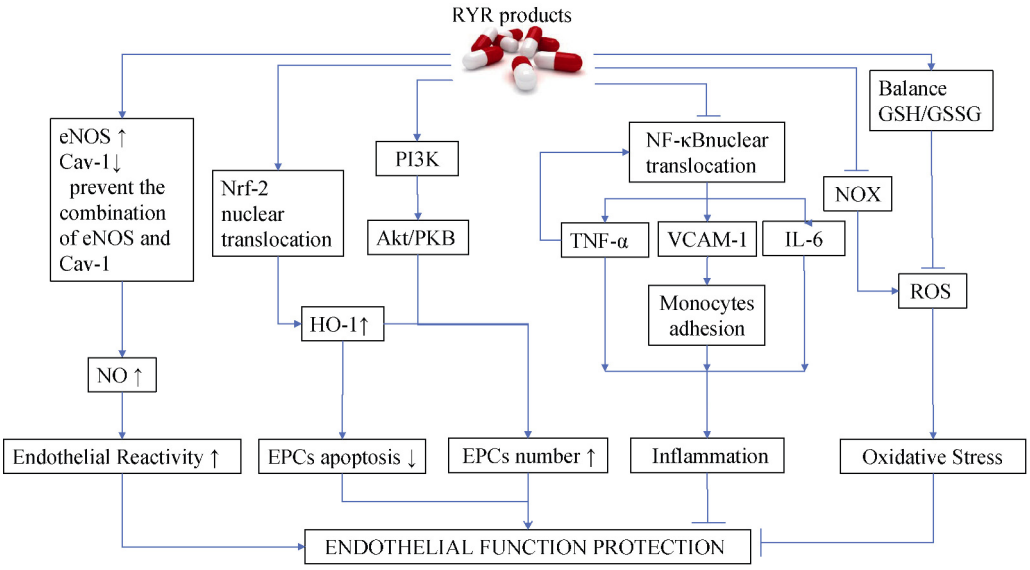

Fig. 1 Possible mechanisms of the effects of RYR products in improving endothelial function. →: promote; ⊣ : inhibit; eNOS: endothelial nitric oxide synthase; Cav-1: caveolin-1; NO: nitric dioxide; Nrf-2: nuclear factor erythroid 2-related factor; HO-1: heme oxygenase-1; EPC: endothelial progenitor cell; TNF-*α*: tumor necrosis factor *α*; VCAM-1: vascular cell adhesion molecular-1; IL-6: interleukin 6; NF-*κ*B: nuclear factor-kappa B; GSH: glutathione; GSSG: oxidized glutathione; ROS: reactive oxygen species; NOX: nicotinamide adenine dinucleotide phosphate oxidase

endothelial repair and replacement, as they substantially contribute to endothelial homeostasis and neoangiogenesis in response to different detrimental cues [43]. Decreased EPCs damages endothelial homeostasis and thus disrupt normal endothelial function. RYR contains chemicals that are identical to prescription statin medication, such atorvastatin, which is a HMG-CoA reductase inhibitor and can activate the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathway to increase the number of EPCs [44], achieving the goal of endothelial protection.

A study showed that the senescence and apoptosis of EPCs induced by high glucose was attenuated by RYR extract [45]. *In vitro* incubated human EPCs treated with RYR extracts displayed a higher level of heme oxygenase 1 (HO-1) expression along with declined senescence damage of EPCs [45]. It was also reported that nuclear factor erythroid 2-related factor (Nrf-2) nuclear translocation, together with mRNA and protein levels of HO-1, increased in a dose-dependent manner after treating these EPCs with RYR (0-50 μg·mL^{-1}) [45]. HO-1 resides inside cells as a core anti-apoptotic molecule and exerts an inhibitory effect on the senescence and apoptosis of EPCs. HO-1 expression is mediated through the accumulation of Nrf-2 in the nucleus. These data suggest that HO-1 activation mediated by Nrf-2 up-regulation may play a pivotal role in the anti-senescence effects of RYR extract on EPCs [45].

RYR and inflammation

The Canakinumab anti-Inflammatory thrombosis outcome study (CANTOS) demonstrated anti-inflammatory therapy targeting at interleukin 1*β* (IL-1*β*)-interleukin 6 (IL-6) brought benefits to ASCVD patients. A wide variety of inflammatory cytokines involved in the process from inflammatory response to As are the major contributors to endothelial injury, among which IL-6 and tumor necrosis factor *α* (TNF-*α*) are important mediators of vascular inflammation. In addition to being positively correlated with high sensitivity C reactive protein (hsCRP), IL-6 can induce the production of hsCRP and trigger the inflammatory response, promoting the infiltration of a large number of leukocytes and monocytes. Studies have reported that hyperlipidemic rats treated with RYR showed a decrease in TNF-*α* and IL-6 [46-47], and researchers also found that in ApoE$^{-/-}$ rats with abdominal aortic aneurysm, hsCRP level decreased after administration of RYR products [27, 46, 48].

Nuclear factor *κ*B (NF-*κ*B) is a nuclear transcription factor that regulates expression of a genes critical for inflammation. Nuclear translocation of activated NF-*κ*B stimulates the expression of IL-6 and TNF-*α*, whereas the latter presents with a positive feedback to NF-*κ*B. Transcriptional regulation involving NF-*κ*B activation has been implicated in TNF-*α* induced endothelial dysfunction [49]. LIN CP *et al.* investigated the effects of monascus-fermented rice metabolites (i.e. monacolin K, ankaflavin and monascin) on TNF-*α*-treated human aortic endothelial cells, gel-shift assays indicated NF-*κ*B activation was inhibited and the rest results showed suppression in vascular cell adhesion molecular-1 (VCAM-1) and E-selectin as well as cellular binding between the human monocytic cells U937 and HAECs [49]. Statins decrease the adhesion of monocytes to endothelial cells.

To summarize, RYR suppresses both the activation of NF-*κ*B and adhesion between monocytes and endothelial cells alleviate inflammation directly and indirectly: the suppression of NF-*κ*B, on one hand inhibited the release of inflammatory cytokines such as TNF-*α* and IL-6 and cut the positive feed

back of TNF-α, on the other, disrupted the adhesion of monocytes to endothelial cells.

RYR and oxidative stress

As a trigger of inflammation and endothelial dysfunction, oxidative stress plays an important role in the process of as. Oxidative stress is intensified when the oxidant and antioxidant status are no longer balanced inside human bodies; in other words, the redox buffering pair is no longer in balance, and reactive oxygen species (ROS) accumulate beyond the body's ability to scavenge them.

Glutathione (GSH)/oxidized glutathione (GSSG) are an important redox buffering pair, and the balance of these two components affects the GSSG mobilization capacity and counteracts the effects of oxidation *in vivo*. A previous study has shown that XZK attenuated oxidative stress by regulating the balance of GSH and GSSG [28], effectively enhancing endothelial function and delaying the process of As. Further, RYR elevated levels of GSH eliminate reactive oxygen *in vivo* and reduce cellular injury by inhibiting HMG-CoA reductase [50-51]. The selenium present in RYR extracts has been reported to help with the activity of glutathione peroxidase 1 [52] after a drop in GSSG occurs.

The evidence shows that cholestin, a dietary supplement made from red yeast rice, attenuated intracellular ROS generation by endothelial cells [6]. ROS have been implicated in the pathogenesis of most stages of atherosclerosis. Li P *et al.* [53] observed that XZK inhibited the activity of Nicotinamide adenine dinucleotide phosphate oxidase (NOX) in macrophages and reduced the production of ROS. NOX is a major source of ROS [54]. Wang J *et al.* [54] treated diabetic rats with a XZK dose of 300 $mg \cdot kg^{-1} \cdot d^{-1}$ and observed decreased expression of the cytomembrane subunitgp91^{phox}, which is a major component of NOX and oxidative stress. This outcome indicated that XZK can alleviate oxidative stress by down-regulating NOX. Furthermore, RYR extracts upregulated HO-1 to improve its antioxidant effect, as HO-1 is a key molecule in the resistance to oxidation [45]. *In vitro* experiments showed that RYR upregulated HO-1 expression and reduced the ROS levels in EPCs, alleviating oxidative stress [45]. One possible mechanism for this could be that RYR increases the nuclear translocation of Nrf-2, which promotes the expression of HO-1 [55]. Tien AJ *et al.* [55] demonstrated that the NF-κB/ICAM-1 signaling pathway was blocked by MK in rat models with carotid arterial occlusion, thus relieving oxidative stress.

We may draw the conclusion that RYR can balance GSH/GSS and ROS to attenuate oxidative stress. In addition, it is possible to conclude that the multi-functional components of RYR products may work synergistically in ROS reduction, the evidence of which may be found from the animal experiments showing the positive effect of magnesium on the decrease in ROS [56-57]. Reduced ROS resulted in increased NO, which maintains normal vasodilatory function, and this release could be another underlying mechanism in how RYR products restore endothelial function by ROS reduction.

Conclusions

Studies have shown that RYR products aid in the treatment of cardiovascular diseases due to their effectiveness and safety in lowering lipid levels. This review has set forth the mechanisms of different cardiovascular protective effects of RYR products. The authors deem that RYR products that are categorized as medicine and dietary supplements have profound impacts in the primary and secondary prevention of ASCVD, and this is in accordance with Chinese expert consensus on the use of Xuezhikang [58], whose major change cannot be neglected regarding recommendation of XZK's usage in the primary prevention of ASCVD. However, the functional components and toxicity risks of RYR products may vary based on fermentation conditions and the fungal strains elaborating the monacolins. There are many studies that have been published regarding their safety [1]. To tackle this problem, strengthened quality control and supervision are needed, and high-performance liquid chromatography could be considered as available tool to precisely control the product quality. Furthermore, additional epidemiological studies with larger sample sizes are required to ensure consistent benefits in a holistic picture.

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