nutrients

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Supplementary Materials:

Supplemental Table S1. Other components of monacolin K formulation in key randomized controlled trials of RYR versus placebo or statins in subjects with dyslipidemia.

Study	Other Components
Placebo comparator	
Heber, 1999 [44]	Rice starch, fiber, protein, moisture, natural pigment, ash, organic phosphorus, trace elements, dihydromonacolin, monacolin I, monacolin II (hydroxy-acid form), monacolin III, monacolin IV, monacolin V, monacolin VI, saturated (palmitic and stearic) fatty acids, mono- and polyunsaturated fatty acids
Zhao, 2003 [45] and Zhao, 2004 [46]	Eight other monacolins, unsaturated fatty acids, sterols, isoflavones, glycerides, trace elements, other substances
Lin, 2005 [47]	Protein, starch, fat (linoleic acid, oleic acid, palmitic acid, stearic acid, ergosterol), fiber, water, other statins, gamma-aminobutyric acid, alkaloids, glycosides, flavonoids, natural pigments, ethanol extracts, water extracts, citrinin, trace elements
Becker, 2009 [48]	Monacolin JA, monacolin J, monacolin XA, monacolin KA, monacolin LA, monacolin L, monacolin M, dihydromonacolin K, citrinin
Bogsrud, 2010 [49]	Other monacolins
Cicero, 2013 [50]	Highly purified, without detectable dehydromonacolins, decalin derivatives, contaminants
Verhoeven, 2013 [51]	Ubiquinone (co-enzyme Q-10), procyanidins, lecithin
Moriarty, 2014 [52]	Other monacolins, phytosterols
Heinz, 2016 [53]	Coenzyme Q10, astaxanthin, folic acid
Wang, 2019 [54]	Other monacolins, gamma-aminobutyric acid, pigments, dimerumic acid, citrinin
Minamizuka, 2021 [55]	Other monacolins, pigments, organic acids (including gamma-aminobutyric acid), amino acids
Statin comparator	
Halbert, 2010 [63]	Other monacolins, citrinin, trace metals
Ruscica, 2014 [59]	Berberine, policosanol, astaxanthin, coenzyme Q10, folic acid
Marazzi, 2017 [60]	Berberine, policosanol, astaxanthin, coenzyme Q10, folic acid
Cui, 2015 [58]	Other monacolins, unsaturated fatty acids, sterols, alkaloids, essential amino acids, flavonoids, trace metals

RYR = red yeast rice.

Supplemental Table S2. Summary of serum lipid outcomes in key randomized controlled trials of RYR versus placebo or statins in subjects with dyslipidemia.

Study	LDL-C (mmol/L)	TC (mmol/L)	HDL-C (mmol/L)	TG (mmol/L)	ApoA-1 (mg/L)	ApoB (mg/L)
Placebo comparator						
Heber, 1999 [44]	CFB: RYR –1.01; PBO –0.13 $p < 0.001$ vs. PBO	CFB: RYR –1.03; PBO –0.13 $p < 0.05$ vs. PBO	RYR BL 1.29, Wk 12 1.29 PBO BL 1.19, Wk 12 1.19 p = NS vs. PBO	CFB: RYR –0.10; PBO +0.03 $p = 0.05$ vs. PBO	NR	NR
Zhao, 2003 [45]; Zhao, 2004 [46]	XZK BL 3.32, Wk 6 2.38; %CFB −34% $p < 0.001$ vs. BL PBO BL 3.35, Wk 6 3.26; p = NS vs. BL	XZK BL 5.37, Wk 6 4.36; %CFB −20% $p < 0.001$ PBO BL 5.37, Wk 6 5.30; p = NS	XZK BL 1.15, Wk 6 1.35; %CFB +18% $p < 0.001$ PBO BL 1.15, Wk 6 1.15; p = NS	XZK BL 1.77, Wk 6 1.22; %CFB −32% $p < 0.001$ PBO BL 1.74, Wk 6 1.68; p = NS	%CFB +13%; $p < 0.001$	%CFB −27%; $p < 0.001$
Lin, 2005 [47]	%CFB: RYR −27.7%; $p < 0.001$ vs. BL and PBO PBO −1.5%	%CFB: RYR −21.5%; $p < 0.001$ vs. BL and PBO PBO −0.4%	%CFB: RYR +0.9%; p = NS vs. BL and PBO PBO +1.0%	%CFB: RYR −15.8%; $p < 0.05$ vs. BL and PBO PBO +1.0%	%CFB: RYR +3.4%; p = NS vs. BL and PBO PBO +2.3%	%CFB: RYR −26.0%; $p < 0.001$ vs. BL and PBO PBO −3.9%
Becker, 2009 [48]	%CFB: RYR −21.3%; PBO −8.7% $p = 0.011$	%CFB: RYR −14.9%; PBO –5.3% $p = 0.016$	%CFB: RYR +8.6%; PBO +7.9% p = NS	%CFB: RYR −7.2%; PBO −1.4% p = NS	NR	NR
Bogsrud, 2010 [49]	%CFB RYR vs. PBO: −23.0% $p < 0.001$	%CFB RYR vs. PBO: −15.5% $p < 0.001$	RYR BL 1.62, Wk 16 1.71 PBO BL 1.35, Wk 16 1.48 p = NS RYR vs. PBO	RYR BL 1.01, Wk 16 0.90 PBO BL 1.29, Wk 16 1.51 p = NS RYR vs. PBO	RYR BL 1.46, Wk 16 1.61 PBO BL 1.35, Wk 16 1.47 p = NS RYR vs. PBO	RYR BL 0.99, Wk 16 0.77 PBO BL 1.11, Wk 16 1.11 $p < 0.001$ RYR vs. PBO
Cicero, 2013 [50]	%CFB RYR vs. PBO: −22.0%; $p < 0.01$	%CFB RYR vs. PBO: −12.5%; $p < 0.01$	%CFB RYR vs. PBO: NS	%CFB RYR vs. PBO: NS	NR	NR
Verhoeven, 2013 [51]	%CFB: RYR −22.2%; PBO +1.65% $p < 0.001$	%CFB: RYR −14.6%; PBO +1.2% $p < 0.001$	%CFB: RYR +3.0; PBO −0.3% p = NS	%CFB: RYR −13.8%; PBO +5.0% $p = 0.05$	NR	NR
Moriarty, 2014 [52]	%CFB: RYR 1200 mg	LS mean %CFB: RYR 1200 mg −17.8%; $p <$	LS mean %CFB: RYR 1200 mg +4.3%; p =	LS mean %CFB: RYR 1200 mg	LS mean %CFB: RYR 1200 mg +5.8%; $p <$	LS mean %CFB: RYR 1200 mg −19.0%; $p <$

	−26.4%; $p < 0.001$ vs. BL and PBO RYR 2400 mg −27.0%; $p < 0.001$ vs. BL and PBO PBO +0.5%, p = NS vs. BL	0.001 vs. PBO RYR 2400 mg −18.5%; $p < 0.001$ vs. PBO PBO +0.4%	NS vs. PBO RYR 2400 mg +5.2%; p = NS vs. PBO PBO −2.2%	−8.0%; p = NS vs. PBO RYR 2400 mg −5.9%; p = NS vs. PBO PBO +12.0%	0.001 vs. PBO RYR 2400 mg +3.9%, p = NS vs. PBO PBO 0%	0.001 vs. PBO RYR 2400 mg −21.2%; $p < 0.001$ vs. PBO PBO +2.9%
Heinz, 2016 [53]	%CFB: RYR −14.8%; $p < 0.001$ vs. PBO PBO −2.7%; p = NS vs. BL	%CFB: RYR −11.2%; $p < 0.001$ vs. PBO PBO −1.0%; p = NS vs. BL	%CFB: RYR +0.7%; p = NS vs. PBO PBO +0.2%; p = NS vs. BL	%CFB: RYR −5.0%; $p < 0.01$ vs. BL; p = NS vs. PBO PBO −0.4%	NR	NR
Wang, 2019 [54]	Median (mg/dL): RYR MK BL 153, 3 m 122; $p < 0.05$ vs. BL, RYR GABA, and PBO RYR GABA BL 151, 3 m 156; $p = 0.009$ vs. BL; p = NS vs. PBO PBO BL 154, 3 m 152; p = NS vs. BL	Median (mg/dL): RYR MK BL 237, 3 m 192.5; $p < 0.001$ vs. BL, $p < 0.05$ vs. RYR GABA and PBO RYR GABA BL 235, 3 m 237; p = NS vs. BL and PBO PBO BL 230, 3 m 234; p = NS vs. BL	Median (mg/dL): RYR MK BL 51, 3 m 54; p = NS vs. BL, RYR GABA, and PBO RYR GABA BL 56, 3 m 52; p = NS vs. BL and PBO PBO BL 50, 3 m 49; p = NS vs. BL	Median (mg/dL): RYR MK BL 133, 3 m 113; p = NS vs. BL, RYR GABA, and PBO RYR GABA BL 112, 3 m 104; p = NS vs. BL and PBO PBO BL 148, 3 m 161; p = NS vs. BL	NR	NR
Minamizuka, 2021 [55]	Median CFB: RYR −0.96; control −0.20 $p = 0.030$	Median CFB: RYR −0.92; control 0.00 $p = 0.014$	Median CFB: RYR −0.13; control 0.03 $p = 0.082$	Median CFB: RYR 0.24; control −0.05 p = NS	NR	Median CFB (g/L): RYR −0.18; control 0.03 $p = 0.011$
Statin comparator						
Xiaobin, 2007 [62]	%CFB: XZK NA; ATV NA $p < 0.01$ vs. BL for each; p = NA XZK vs. ATV	%CFB: XZK NA; ATV NA $p < 0.05$ vs. BL for each; p = NA XZK vs. ATV	%CFB: XZK NA; ATV NA $p < 0.05$ vs. BL for each; p = NA XZK vs. ATV	%CFB: XZK NA; ATV NA $p < 0.01$ vs. BL for each; p = NA XZK vs. ATV	NR	NR
Gheith, 2008 [61]	NR	Mean (mg/dL) XZK BL 457, 1 yr 303; FLV BL 436, 1 yr 302; PBO BL 463, 1 yr 348; $p = 0.003$ for FLV vs. PBO	NR	NR	NR	NR

Liu, 2011 [66]	%CFB: significantly lowered for all groups; intergroup comparisons (XZK, LRRMP, LOV) p = NS	%CFB: significantly lowered for all groups; intergroup comparisons (XZK, LRRMP, LOV) p = NS	%CFB: not significantly lowered for all groups	%CFB: significantly lowered for all groups; intergroup comparisons (XZK, LRRMP, LOV) p = NS	NR	NR
Li, 2011 [65]	Reduced vs. control in both groups p = 0.05	Reduced vs. control in both groups p = 0.05	NR	Reduced vs. control in both groups p = 0.05	NR	NR
Halbert, 2010 [63]	%CFB: RYR −30.2%; PRV −27.0% ΔLDL-C (CFB RYR vs. PRV): −10.7 mg/dL; p = NS	%CFB: RYR −23.0%; PRV −19.6% ΔTC (CFB RYR vs. PRV): −9.6 mg/dL; p = NS	%CFB: RYR −3.8%; PRV +0.2% ΔHDL-C (CFB RYR vs. PRV): −2.5 mg/dL; p = NS	%CFB: RYR −7.8%; PRV −7.0% ΔTG (CFB RYR vs. PRV): 0.5 mg/dL; p = NS	NR	NR
Ruscica, 2014 [59]	Armolipid Plus® BL 3.91, Wk 8 3.09 PRV BL 3.97, Wk 8 3.07 p < 0.0001 for both vs. BL p = NS Armolipid Plus® vs. PRV	Armolipid Plus® BL 6.2, Wk 8 5.4 PRV BL 6.41, Wk 8 5.38 p < 0.0001 for both vs. BL p =NS Armolipid Plus® vs. PRV	Armolipid Plus® BL 1.04, Wk 8 1.09 PRV BL 1.10, Wk 8 1.11 p = NS PRV vs. BL p < 0.05 Armolipid Plus® vs. BL p = NS Armolipid Plus® vs. PRV	Armolipid Plus® BL 2.44, Wk 8 2.21 PRV BL 2.55, Wk 8 2.43 p = NS for both vs. BL p = NS Armolipid Plus® vs. PRV	NR	NR
Marazzi, 2017 [60]	%CFB: RYR + LDS −26.8%; LDS −4.3% p <0.0001 for Armolipid Plus® + LDS vs. LDS	%CFB: RYR + LDS −17.5%; LDS −3.5% p < 0.0001 for Armolipid Plus® + LDS vs. LDS	%CFB: RYR + LDS +8.8%; LDS +3.7% p = 0.02 for Armolipid Plus® + LDS vs. LDS	%CFB: RYR + LDS −10.2%; LDS −7.9% p = NS for Armolipid Plus® + LDS vs. LDS	NR	NR
Kou, 1997 [56]	%CFB: XZK −28.0%; SMV −29.5% p = NS XZK vs. SMV	%CFB: XZK −23.0%; SMV −23.3% p = NS XZK vs. SMV	%CFB: XZK +5.0%; SMV +14.3% p = NS XZK vs. SMV	%CFB: XZK −28.1%; SMV −29.5% p = NS XZK vs. SMV	NR	NR

Chen, 2002 [57]	%CFB: XZK −28.2%; SMV −22.7% p = NS XZK vs. SMV	%CFB: XZK −21.8%; SMV −21.3% p = NS XZK vs. SMV	%CFB: XZK +6.2%; SMV +5.7% p = NS XZK vs. SMV	%CFB: XZK −18.1%; SMV −1.6% p < 0.001 XZK vs. SMV	NR	NR
Xue, 2017 [64]	%CFB: RYR −33.4%; SMV −30.9% p < 0.001 for both vs. BL p = NS RYR vs. SMV	%CFB: RYR −18.5%; SMV −19.6% p < 0.001 for both vs. BL p = NS RYR vs. SMV	%CFB: p = NS for both vs. BL	%CFB: p = NS for both vs. BL	NR	NR
Cui, 2015 [58]	LDL-C (mg/dL): XZK BL 152, Wk 8 119; p <0.05 vs. BL SMV BL 151, Wk 8 118; p < 0.05 vs. BL	TC (mg/dL): XZK BL 200, Wk 8 170; p < 0.05 vs. BL SMV BL 201, Wk 8 156; p <0.05 vs. BL	HDL-C (mg/dL): XZK BL 41, Wk 8 49; p < 0.05 vs. BL and SMV SMV BL 42, Wk 8 44; p = NS vs. BL	TG (mg/dL): XZK BL 189, Wk 8 146; p < 0.05 vs. BL and SMV SMV BL 191, Wk 8 168; p < 0.05 vs. BL	NR	NR

Apo = apolipoprotein; ATV = atorvastatin; BL = baseline; CFB = change from baseline; FLV = fluvastatin; GABA = gamma-aminobutyric acid; HDL-C = high-density lipoprotein cholesterol; HDS = high-dose statin; LDL-C = low-density lipoprotein cholesterol; LDS = low-dose statin (ATV 5–10 mg/d, RSV 5 mg/d, or SMV 10–20 mg/d); LOV = lovastatin; LRRMP = lipid-reducing red rice minute powder; LS = least squares; MK = monacolin K; NA = not available; NR = not reported; NS = not significant; PBO = placebo; PRV = pravastatin; QD = once daily; RYR = red yeast rice; SMV = simvastatin; TC = total cholesterol; TG = triglycerides; Wk = week; XZK = Xuezhikang.

Supplemental Table S3. Summary of RYR safety reported by meta-analyses.

Authors	Study Dates	Number of Studies	RYR Dosage[a]	Comparators	Principal AE Findings
Gerards et al. [10]	Up to November 2014	20	RYR 1200–4800 mg/d (MK 4.8–24 mg/d)	Inactive control (13); statin (3); non-statin active control (4)	Incidence of liver abnormalities and kidney injury: 0–5%: did not differ between RYR and control Incidence of muscle symptoms: 0–23.8% with RYR, 0–36% with controls Rhabdomyolysis: not observed
Li et al. [11]	Up to September 2021	15	RYR or XZK 200–2400 mg/d	Placebo (9); statins (3); phytosterols (1); nattokinase (1); nutraceuticals (1)	Incidence of AEs with RYR was similar to control (RYR alone: RR 1.18; 95% CI 0.91 to 1.54; $p = 0.21$. RYR combination: RR 1.63; 95% CI 0.22 to 11.83; $p = 0.63$)
Fogacci et al. [86][b]	Up to 2019	53	RYR 100–4800 mg/d	Placebo (47); statins (6); non-statin active control (2)	RYR was not associated with musculoskeletal disorders (OR=0.94, 95% CI 0.53 to 1.65) Risk of non-musculoskeletal disorders reduced (OR=0.59, 95% CI 0.50 to 0.69) Risk of serious AEs reduced (OR=0.54, 95% CI 0.46 to 0.64) Results were consistent across subgroups
Shang et al. [95]	Up to September 2011	22[c]	XZK 600–1800 mg/d	Conventional therapy (11); statin + conventional therapy (6); statin (4)	Most commonly reported AEs: intestinal disturbances, dizziness, high serum alanine aminotransferase, high serum creatine kinase, high serum creatinine, high blood urea nitrogen, and skin itch AEs were not significantly different between XZK and control
Cicero et al. [76]	Up to February 2021	12	Armolipid Plus®	Placebo (11); low-dose statin (1)	Armolipid Plus® produced a slight but clinically insignificant increase in serum ALT without affecting AST or CPK Armolipid Plus® was not associated with increased risks of musculoskeletal disorders or gastrointestinal disorders

[a]Some studies included combinations of RYR with nutraceuticals or a statin; [b]Two studies had placebo and a statin as control; [c]Studies in patients with coronary heart disease.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; OR = odds ratio; RR = relative risk; RYR = red yeast rice; XZK = Xuezhikang.

Supplemental Table S4. Summary of RYR adverse drug reaction reports collected by surveillance systems.

Surveillance System	Collection Period	Total Number of Case Reports, *n*	Total Number of ADRs, *n*	Causality of ADRs, *n*	Most Frequently Reported Adverse Drug Reactions by SOC, *n* (%)					
					Musculo-skeletal	Gastro-intestinal	Hepato-biliary	Skin and Subcutaneous	General	Nervous System
Italian Surveillance System of Natural Health Products [96]	2002–2015	52	55	Certain 1; probable 31; possible 18; unlikely 3; unassessable 2	20 (36)	12 (22)	10 (18)	9 (16)	–	2 (4)
Netherlands Pharmacovigilance Centre Lareb [97]	2007–2020	94	187	Certain 2; probable/likely 24; possible 61; unlikely 7	64 (34)	33 (18)	3 (2)	6 (3)	23 (12)	16 (9)
Post-marketing product-based (Armolipid®/Armolipid Plus®) database [75]	2004–2019	542	855	–	148 (17)	293 (34)	26 (3)	–	–	–

ADRs = adverse drug reactions; RYR = red yeast rice; SOC = system organ class.