Clinical Pharmacology: Advances and Applications

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REVIEW

Monascus purpureus Red Yeast Rice: A Review of the in vitro and in vivo Pharmacological Activities, Studies in Humans, and Case Reports

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Abstract: Red yeast rice (RYR) is an Asian indigenous medicine that ferments *Oryza sativa* grains using the Monascus fungi, specifically *Monascus purpureus*. Monacolins, pigments, phenols, sterols, and benzopyrans, such as the mycotoxin citrinin, were proven to be present in RYR, contributing to its numerous effects. This study aims to provide a thorough overview of the in vitro and in vivo pharmacological activities of *M. purpureus* red yeast rice, its studies in humans, and a summary of recent case reports. A literature search was conducted on the PubMed database, using the keywords: "pharmacology activity of red yeast rice" filtered to free full text and articles published from 2014 to 2024 for in vitro and in vivo studies, to ensure the newest developments. In vitro and in vivo pharmacological activity studies of RYR and/or metabolites have confirmed antidyslipidemia, anti-inflammatory, and anticancer activities, whereas studies in humans have evidenced its activity in improving lipid profiles. Furthermore, case reports on red yeast rice supplements, published between 2020 and 2025, revealed Fanconi syndrome and kidney dysfunction as the main adverse events, mostly reported from Japan.

Keywords: angkak, antidyslipidemia, complementary and alternative medicine, *Monascus* fungi, pharmacological activity, red koji

Introduction

Red yeast rice (RYR) (Figure 1) is an Asian conventional food and medicine that ferments *Oryza sativa* grains using *Monascus purpureus*. Bioactive compounds such as monacolins, pigments, flavonoids, lignans, terpenoids, and polysaccharides were reported to be present in RYR and contribute to its numerous biological effects, which are mainly as lipid-lowering agents.[1–8] The other biological effects of RYR are described as follows: a multicenter study in 5000 patients demonstrated that long-term treatment with purified extract of RYR significantly reduced cardiovascular events and total mortality by 30% and 33%, as reported by Lu et al in 2008.[6] Nutraceutical supplementation containing RYR, berberine, policosanol, astaxanthin, coenzyme Q10 and folic acid is linked with improvement of lipid and glucose profile when given in a long-term period.[7] A randomized clinical trial by Cicero et al reported the effects of RYR combined with antioxidants on lipid profile, high-sensitivity-C-reactive protein (a biomarker for inflammation), and endothelial function in moderately hypercholesterolemic patients. After RYR treatment, there was a decrease in total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and high-sensitivity-C-reactive protein, and an increase in high-density lipoprotein-cholesterol (HDL-C) and endothelial function, suggesting both the anti-inflammatory and antidyslipidemic properties of RYR.[8] A systematic review of the traditional uses, chemistry, pharmacology, and quality control of RYR described its numerous pharmacological properties, such as hypolipidemic, anti-atherosclerotic, anti-cancer, neuroprotective, anti-osteoporotic, anti-fatigue, anti-diabetic, and anti-hypertension.[9]

Received: 10 June 2025
Accepted: 23 August 2025
Published: 3 September 2025

Figure 1 *Monascus purpureus* red yeast rice.

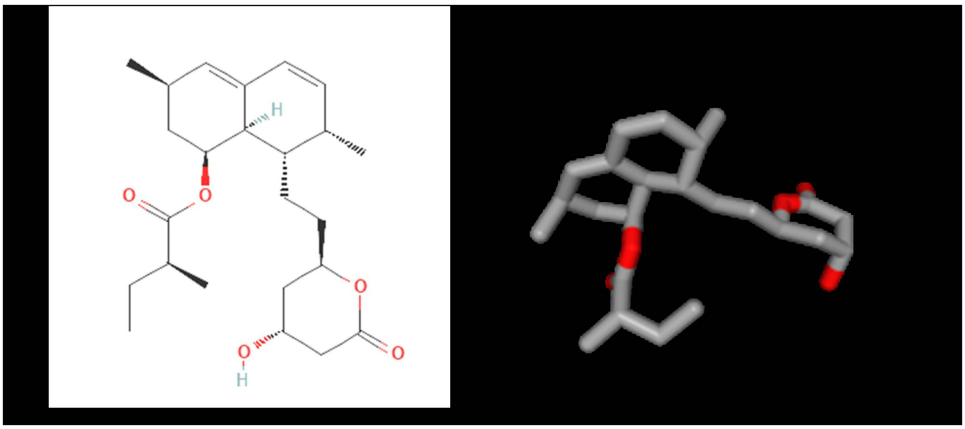

Figure 2 The structure of monacolin K (PubChem CID: 53232, molecular formula $C_{24}H_{36}O_5$) in a two-dimensional (left) and a three-dimensional (right) presentation.

Studies revealed that RYR contains distinct types of monacolin, of which is monacolin K (Figure 2), whose structure is identical to lovastatin, a hydroxymethyl glutaryl (HMG)-CoA reductase inhibitor.[10–12] The enzyme HMG-CoA reductase converts its substrate, hydroxymethylglutaryl-CoA (HMG-CoA), to mevalonate in the hepatocytes. This reaction is the first and rate-limiting step in cholesterol biosynthesis. A popular inhibitor of HMG-CoA reductase, belonging to the statin family of drugs, such as lovastatin, competitively interacts with the substrate in the catalytic site and induces a conformational alteration in the structure of the enzyme.[13] The interaction of statins with HMG-CoA reductase reduces the intracellular synthesis of cholesterol and blood cholesterol levels, because most of the blood cholesterol originates from the hepatic cells rather than from the foods.[14]

Plant statins are synthesized in the polyketide pathway, which is an important biosynthetic route, mainly occurring in fungi and some plants. When interacting with HMG-CoA reductase, these statins occupy the L-domain of the enzyme and build polar interactions with the amino acid residues within the cis-loop.[15] The L-domain of the HMG-CoA reductase catalytic site exists in the form of a "cis-loop" shape (amino acid residues 684–692), allowing Ser684, Asp690, Lys691, and Lys692, which are responsible for the binding to the enzyme's substrate, HMG-CoA.[16]

Considering that RYR contains many substances reflecting its pharmacological activities, this narrative review is organized into five main sections: chemical aspects of RYR, in vitro pharmacological activity studies of RYR, in vivo pharmacological activity and toxicity studies of RYR, studies in humans, and case reports of RYR.

Chemical Aspects of Red Yeast Rice (RYR)

RYR was broadly explored and reported for its numerous chemical constituents, of those were monacolins,[3,4,12,17–19] pigments,[20–22] benzopyrans such as the mycotoxin citrinin,[12,23–25] phenolics,[26,27] amino acids such as (+)-monascumic acid and (-)-monascumic acid,[28] sterols such as ergosterol,[29] and other constituents.

Ma et al in 2000 reported that a fermentation using *M. purpureus* on steamed rice resulted in monacolins, fatty acids, and trace elements.[3] Several monacolins were found in RYR, serving the potential of RYR as a nutraceutical.[4] The acidic form of monacolin K, at a level of 9.5 mg/g, was identified and quantified in *M. purpureus* RYR using high-performance chromatography (HPLC) with a photodiode array detector (PDA) SPD-20A ultraviolet (UV) detector at 237 nm, as described by Yuan et al in 2023. The authors reported that using the HPLC separation and analytical technique, no citrinin was detected in the RYR product.[12] Another study by Dhale et al in 2007 in Mysore, India, reported the presence of dihydromonacolin-MV in the methanol extract of *M. purpureus* RYR, which was separated using silica gel column chromatography (CC), and the chemical structure was confirmed by spectroscopic analysis by UV, infrared (IR), proton nuclear magnetic resonance (1H-NMR), carbon nuclear magnetic resonance (13C-NMR), two-dimensional heteronuclear single-quantum correlation (2D-HSQCT) NMR, and mass spectroscopy (MS).[18] Huang et al in 2006 reported the levels of monacolin K in some RYRs collected from nine locations in Fujian Province using HPLC with a PDA detector and tandem MS. The HPLC chromatogram of monacolin K was identified at 238.6 nm, with the molecular ion of the predominant peak of MS being m/z 427, representing monacolin K (molecular weight of 404) occurring in its lactone form, and the levels ranged from 0.31 to 3.8 mg/g.[19]

Campoy et al in 2006 declared their findings on five new pigments in *M. purpureus* IB1, as proven by the spectrophotometric and HPLC analysis, with high concentrations of azaphilone pigments.[20] Furthermore, the pigments of *Monascus* RYR applied to yoghurts were found to be physicochemically stable over a two-week depository at 4 °C, as reported by Chen et al in 2012.[21] Huang et al in 2015 reported an HPLC analysis of orange pigments in RYR, namely rubropunctatin and monascorubrin, conducted using two different detectors, a UV detector and a fluorescence detector (FLD), which measures the fluorescence emitted by the pigments when they are exposed to a Xenon radiation source.[22]

Another high-accuracy method was employed for citrinin analysis in RYR products by LC-MS/MS. It was described by the authors, Ji et al, in 2015, that citrinin was positively detected within the tested samples, at levels of 0.14 to 44.24 mg/kg.[23] Interestingly, a year before, in 2014, Jiménez-López et al developed a fluorometric opto-sensor for the analysis of citrinin in RYR products, with optimum excitation/emission at 330/494 nm, showing good fulfillment for validation parameters.[24] A recent work by Tangni et al in 2021 about the analysis of citrinin in RYR and wheat flour using LC-MS/MS revealed that this substance was homogenously distributed and stable in the tested samples.[25]

Moreover, phenol compounds were found in trace amounts in RYR,[26] while in another study, the ethyl acetate fraction of RYR was confirmed to contain the highest phenolic compounds and flavonoids among other fractions.[27]

Akihisa et al in 2005 successfully isolated azaphilones (monascin, ankaflavin, rubropunctatin, monascorburin, rubropunctamine, and monascorburamine), furanoisophthalides (xanthomonasin A and xanthomonasin B), and monascumic amino acids from RYR.[28] Ergosterol was also found in fungi *M. purpureus* BCRC 38113, as pronounced by Cheng et al in 2010.[29]

https://doi.org/10.2147/CPAA.S542721

In vitro Pharmacological Activity Studies of RYR

In vitro pharmacological activity studies of RYR and/or metabolites were reported in 7 articles (Table 1), describing anti-type I allergy (antiasthma) activity,[30] anticancer activity against human hepatocarcinoma cells,[31] alleviating vascular complications of diabetes,[32] anticancer activity against MCF-7 cells,[33] anti-inflammation,[34] antifungal,[35] and antibacterial.[36] The details are described as follows:

Table 1 In vitro Pharmacological Activity Studies of RYR

Name of RYR	Name of Substance/Metabolite	Name of Cells/Bacteria/Fungi and the Standard Drug	Results	Reference
Monascus-fermented products	Monascin (MS) and ankaflavin (AK)	RBL-2H3 cells	Inhibition of PMA/ionomycin-induced mast cell degranulation and TNF-α secretion.	[30]
Extract of *M. purpureus* CWT715 fermented from sorghum liquor biowaste	Metabolites and pigments were obtained as follows: *M. purpureus* CWT715 was inoculated in DSR medium and incubated at 30 °C for 1–7 d. The mycelia and broth were collected and then freeze-dried. The dried powder was dissolved in PBS, sonicated for 2 h, and centrifuged at 8000× *g* for 20 min. After centrifugation, the supernatant was collected. The concentration of extracellular pigments was estimated by measuring the absorbance of filtrates at 400 nm (yellow pigment), 470 nm (orange pigment), and 500 nm (red pigment).	SK-Hep-1 cells (BCRC 67005) were purchased from the Food Industry Research and Development Institute, Hsinchu, Taiwan. Control drug was not described.	Significant anticancer activity against SK-Hep-1 cells.	[31]
M. purpureus-fermented rice (RYR) (LipoCol Forte) was obtained from NatureWise Biotech & Medicals Corporation (Taipei, Taiwan) and extracted at room temperature	Not described	The protocol was approved by the China Medical University (Taichung, Taiwan) Institutional Review Board. Peripheral MNCs were isolated from volunteers by Histopaq-1077 (Sigma, USA). Isolated MNCs were plated in endothelial growth medium (EGM-2 MV; Cambrex, USA), with supplements on fibronectin-coated plates. After culturing, the medium was replaced, and nonadherent cells were removed. Culture medium was changed every 3 days, and the late outgrowth proangiogenic cells (PACs) under passage 3 were used for the study. No standard drug was described in this study.	RYR extract has the potential to alleviate vascular complications of diabetes.	[32]
M. purpureus-fermented rice	Mevinolin (a synonym of lovastatin), a member of the statin family, is abundant in RYR. In this study, pure mevinolin was purchased from Sigma Aldrich Chemical Co. (St. Louis, MO, USA).	MCF-7 cells were obtained from Vacsera (Giza, Egypt). The cells were maintained in RPMI-1640 supplemented with 100 μg/mL streptomycin, 100 μg/mL penicillin, and 10% (w/v) heat-inactivated FBS in a humidified, 5% (v/v) CO_2 atmosphere incubator at 37°C. Doxorubicin was used as the standard drug.	Mevinolin in RYR has significant anticancer activity against MCF-7 cells.	[33]

(*Continued*)

Table 1 (Continued).

Name of RYR	Name of Substance/Metabolite	Name of Cells/Bacteria/Fungi and the Standard Drug	Results	Reference
Xuezhikang, an extract of RYR, was provided by the WBL Peking University Biotech Co., Luye Pharma Group (Beijing, China).	Not described	RAW264.7 cells were obtained from the Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China), cultured in DMEM (Thermo Fisher Scientific) supplemented with 10% FBS (Biological Industries, Beit-Haemek, Israel) and antibiotics (100 U/mL penicillin and streptomycin) in a humidified incubator containing 5% CO_2 at 37°C. Cells were passaged for fewer than 2 months after resuscitation and were used at the third through tenth passage for this study. The control drug, atorvastatin, was obtained from Pfizer Ltd. (New York, NY, USA).	RYR extract has anti-inflammatory and antitumor properties on RAW264.7 cells.	[34]
The EtOAc extract of mangrove-derived fungus *M. purpureus* wmd2424, a filamentous fungal strain collected from the Chiayi mangrove wetland.	Five monascuspurins of new xanthonoid, cyclohexenone, γ-lactone, isoquinoline, and azaphilone skeleton compounds were isolated and confirmed via HRESI-MS and 1D- and 2D-NMR spectroscopy.	A panel of laboratory control strains belonging to the Bioresource Collection and Research Center (BCRC) in Hsinchu, Taiwan, namely, *Aspergillus niger* (BCRC-31512), *Penicillium italicum* (BCRC-30567), *Candida albicans* (BCRC-21538), and *Saccharomyces cerevisiae* (BCRC-20822). Antifungal susceptibility testing of the isolated compounds was performed with the following strains: *Aspergillus niger, Penicillium italicum*, *Candida albicans*, and *Saccharomyces cerevisiae* using the disk diffusion method and the following CLSI guidelines were applied: M44-A and M44-S2 for yeasts and M-51P for filamentous fungi. A standard disk of ketoconazole was used as a positive control, while a disk imbued with 50 μL of pure DMSO was used as a negative control. The diameters of the inhibition zones were measured in millimeters using a slide caliper. Each test was performed in triplicate, and the results were analyzed for statistical significance.	The compounds exhibited moderate antifungal activities against *Aspergillus niger, Penicillium italicum, Candida albicans*, and *Saccharomyces cerevisiae*.	[35]
M. purpureus DBM 4360 and *Monascus* sp. DBM 4361 isolated from non-sterile dried RYR samples	Monascus pigments (monascin, rubropunctatin and rubropunctamine) and citrinin were analysed by UHPLC, using a C18 (2.2 μm, 150×4.6 mm) column; the mobile phase: 0.025% H_3PO_4 in water and acetonitrile (30:70), isocratic elution at a flow rate of 1 mL/min, injection volume 5 μL, with a PDA detector for the pigments and a fluorescence detector for citrinin.	*Escherichia coli* MG 1655, *Pseudomonas aeruginosa* PAO1, *Bacillus subtilis* ATCC 6633, and *Staphylococcus aureus* ATCC 25923	Antibacterial activity against Gram-positive bacteria.	[36]

Abbreviations: AK, ankaflavin; DSR, distiller's sorghum residue; ERK, extracellular signal-regulated kinase; EtOAc, ethyl acetate; FBS, fetal bovine serum; H_3PO_4, phosphoric acid; HRESI-MS, high-resolution electrospray ionization-mass spectrometry; HO-1, heme oxygenase-1; IκBα, inhibitor of NF-κB alpha; JNK, c-Jun N-terminal kinase; 7-KC, 7-ketocholesterol; MAPK, mitogen-activated protein kinase; MNCs, blood mononuclear cells; MS, monascin; NF-κB, nuclear factor-kappaB; Nrf2, nuclear factor erythroid-2-related factor; PACs, bone marrow-derived proangiogenic cells; PARP, poly (ADP-ribose) polymerase; PBS, phosphate-buffered saline; PKC, protein kinase C; PMA, phorbol myristate acetate; RBL-2H3, a basophilic leukemia cell line; ROS, reactive oxygen species; RYR, red yeast rice; SK-Hep-1, a highly metastatic human hepatocarcinoma cells; XZK, xuezhikang (RYR extract);

Chang et al in 2015 reported that the secondary metabolites of RYR, namely monascin and ankaflavin, inhibited phorbol myristate acetate (PMA)/ionomycin-induced mast cell degranulation and tumor necrosis factor (TNF)-α secretion by suppressing the phosphorylation of protein kinase C (PKC) and mitogen-activated protein kinase (MAPK) family extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 in RBL-2H3 cells, suggesting their potential to alleviate type I allergy (asthma).[30] The extract of *M. purpureus* CWT715 fermented from sorghum liquor biowaste showed significant inhibition of the proliferation of SK-Hep-1 cells in a concentration-dependent manner by 31% ($p < 0.001$) and 36% ($p < 0.001$) at 24 h and 48 h of incubation, respectively, and demonstrated anti-migration and anti-invasion activities related to the induction of nm23-H1 protein expression. SK-Hep-1 cells are malignant human hepatocarcinoma cells. The nm23-H1 is a protein involved in cell migration, adhesion, and growth.[31] *M. purpureus*-fermented rice (RYR) (LipoCol Forte) was reported to induce the nuclear transfer of Nrf2, stimulate heme oxygenase-1 (HO-1) mRNA and protein levels in bone marrow-derived proangiogenic cells (PACs). Moreover, RYR inhibits glucose-induced PAC senescence and ROS production in a concentration-dependent manner.[32] Another study described that mevinolin (a synonym of lovastatin) is found abundantly in RYR. In this study, mevinolin induced apoptosis (IC_{50} of mevinolin = 2.08 μg/mL; IC_{50} of doxorubicin = 0.42 μg/mL) and DNA degradation responses in MCF-7 cells, markedly increased caspase-3 activity, although weaker compared to doxorubicin, thus confirming its anticancer properties. Mevinolin also inhibited HMG-CoA reductase and farnesyl pyrophosphate transferase in the same cells.[33] In another study, Xuezhikang, an extract of RYR, inhibited the upregulation of apoptosis, the expression of apoptotic markers (cleaved caspase-3 and cleaved PARP), and NF-κB activation.[34] Interestingly, the ethyl acetate extract of mangrove-derived fungus *M. purpureus* wmd2424 contained five monascuspurins secondary metabolites, as confirmed by high-resolution electrospray ionization-mass spectrometry (HRESI-MS) and 1D- and 2D-NMR spectroscopy. These isolated monascuspurins exhibited moderate antifungal activity against *Aspergillus niger, Penicillium italicum, Candida albicans*, and *Saccharomyces cerevisiae*.[35] Moreover, *M. purpureus* DBM 4360 and *Monascus* sp. DBM 4361 was isolated from non-sterile dried RYR samples and revealed the best antibacterial activity against *Escherichia coli* MG 1655, *Pseudomonas aeruginosa* PAO1, *Bacillus subtilis* ATCC 6633, and *Staphylococcus aureus* ATCC 25923, and did not form the mycotoxin citrinin.[36]

In vivo Pharmacological Activity Studies of RYR

In vivo pharmacological activity studies of RYR and/or metabolites were reported in 6 articles (tabulated in Table 2), employing various types of rodent models, such as ApoE$^{-/-}$ C57BL/6 mice,[34] C57BL/6J mice,[37] Sprague-Dawley rats,[38–40] and Wistar rats,[41] describing an inhibitory activity towards intraplaque hemorrhage and vulnerable plaque progression,[34] antidyslipidemia or hypocholesterolemia,[37,38,40,41] anti-inflammatory,[37] increasing the bone mineral density and decreasing osteocalcin and tartrate-resistant acid phosphatase activity.[39] The details are described as follows:

Xuezhikang, an extract of RYR, was administered to the left common carotid artery partial ligation (LCCA) female ApoE$^{-/-}$ C57BL/6 mice. Atorvastatin at 10 mg/kg daily was used as the control drug. This study delineated that the RYR extract significantly decreased intraplaque hemorrhage, reduced multilayer discontinuity of blood vessels, and lowered the plaque rupture with thrombus ($p < 0.05$ vs control group), suggesting its comparable effective activity with atorvastatin. However, no marked differences in the LDL-C and HDL-C levels between groups were found.[34] In another study, monascin and ankaflavin contained in *M. purpureus* NTU 568-RYR were reported to significantly reduce the serum AST and ALT activity, total cholesterol, and triglyceride levels, prevent hepatic fat accumulation, effectively activate antioxidant enzymes, reduce the severity of lipid peroxidation, and directly reduce pro-inflammatory cytokine (TNF-α, IL-6, and IL-1β) levels, thereby reducing NF-κB and its downstream iNOS and COX-2 expressions in C57BL/6J mice fed with the Lieber–De Carli liquid alcohol diet for 6 weeks.[37] An extract of Chinese RYR showed stronger hypotriglyceridemic activity compared to simvastatin, as proven by LDL-C lowering power, and more upregulation of apoA5 via the PPARα signaling pathway in male Sprague-Dawley rats.[38] RYR extract markedly improved bone mass and reduced osteocalcin levels and tartrate-resistant acid phosphatase activity in ovariectomized female Sprague-Dawley rats.[39] Furthermore, RYR and monascus pigment markedly reduced the TC, TG, and LDL-C levels in the blood and improved lipid metabolism in a hyperlipidemia model of male Sprague-Dawley rats without specific pathogens.[40] RYR

Table 2 In vivo Pharmacological Activity Studies of RYR

Name of RYR	Name of Substance/ Metabolite	Animals, Design of Experiment, Control Drug (Dosage)	Pharmacological Activity and Results	Reference
Xuezhikang (XZK), an extract of RYR, was provided by the WBL Peking University Biotech Co. (Beijing, China)	Not described	Seven-week-old female ApoE$^{-/-}$ C57BL/6 mice were purchased from Jackson Laboratory (Bar Harbor, ME, USA). At the age of eight weeks, a combined partial ligation of the LCCA and left renal artery was carried out under a dissecting microscope. The mice were divided into four groups: 1. Control (saline, n = 16) 2. Atorvastatin (10 mg/kg/d, n = 16) 3. XZK-600 (600 mg/kg/d, n = 19) 4. XZK-1200 (1200 mg/kg/d, n = 21)	The extract was as effective as atorvastatin, and no hepatotoxicity or nephrotoxicity was observed upon administration of the extract at the dose that effectively inhibited vulnerable plaque progression.	[34]
M. purpureus NTU 568-RYR	Monascin (MS) and ankaflavin (AK)	C57BL/6J mice were fed with the Lieber–De Carli liquid alcohol diet for 6 weeks. Silymarin (200 mg/kg bodyweight/day) was used as the control drug.	MS and AK demonstrated anti-dyslipidemia, anti-inflammatory, and antioxidant properties.	[37]
Xuezhikang (XZK), an extract of Chinese RYR, was provided by the WBL Peking University Biotech Co. (Beijing, China)	Not described	Male, 8-week-old, Sprague-Dawley rats (n = 40) were purchased from Shanghai Slac, China. The rats were divided into four groups (n = 10): 1. control group 2. fructose group (fructose-induced hypertriglyceridemia group) 3. Statin group (1 mg/kg/d) 4. XZK (80 mg/kg/d)	XZK has greater hypotriglyceridemic performance than simvastatin, which is attributed to more apoA5 up-regulation by this agent via the PPARα signaling pathway.	[38]
RYR extract (Hongqu)	Monacolin K	Fifty female Sprague-Dawley rats were randomly divided into: 1. sham-operated group 2. OVX with vehicle 3. OVX with fluvastatin 4. OVX with RYR extract dose-1 5. OVX with RYR extract dose-2 6. OVX with RYR extract dose-3	RYR extract markedly increased the bone mineral density and decreased the levels of bone turnover markers, including osteocalcin and tartrate-resistant acid phosphatase activity in OVX rats.	[39]

(*Continued*)

Table 2 (Continued).

Name of RYR	Name of Substance/ Metabolite	Animals, Design of Experiment, Control Drug (Dosage)	Pharmacological Activity and Results	Reference
Monascus strain SHM1105-RYR	Monacolin K and monascus pigment	A hyperlipidemia model of male Sprague-Dawley rats without specific pathogens was used in this study. The rats were purchased from Beijing Sibeifu Experimental Animal Co., Ltd. [license number: SCXK (Shanghai) 2012-0002]. All animal procedures were performed following the Guidelines for Care and Use of Laboratory Animals (Ministry of Science and Technology of China, 2016) and approved by the Animal Ethics Committee of Tianjin University of Science and Technology. After one week of adaptive feeding, the rats were randomly divided into five groups according to their BW. 10 rats served as the normal control group (CK, n = 10), and the remaining 40 were randomly divided into four groups, namely the high-fat model group (HFS, n = 10), the lovastatin group (LOV, n = 10), red yeast rice group (RYR, n = 10), and monascus pigment group (PIG, n = 10). Lovastatin was used as the control drug	Intervention with RYR and monascus pigment significantly reduced the serum TC, TG, and LDL-C levels, and improved lipid metabolism in rats by regulating steroid hormone biosynthesis, glycerolipid metabolism, and the arachidonic acid metabolism pathway.	[40]
RYR extract (containing > 3% monacolin K) was purchased from Giellepi S.p.A (Milano, Italy).	Monacolin K	Male Wistar rats (Harlan Laboratories Ltd., Fullinsdorf, Switzerland), weighing 180–200 g, were divided into five groups (n = 10): 1. Normolipidemic controls were kept on a standard diet (Harlan) for 30 d. 2. Hyperlipidemic controls received the hypercholesterolemic diet for 30 d. 3. Bergamot polyphenolic fraction (BPF) (10 mg/kg/rat daily), same route. 4. RYR extract (1 mg/kg/rat daily, respectively), same route. 5. RYR extract (3 mg/kg/rat daily, respectively), same route.	RYR at 1 and 3 mg/kg doses significantly reduced LDL-C but had deplorable effects on TG, HDL-C, GPX, MDA, and PCSK9 expression. BPF increased HDL-C levels and reduced PCSK9 levels.	[41]

Abbreviations: AK, ankaflavin; BW, body weight; GPX, glutathione peroxidase; HDL-C, high-density lipoprotein-cholesterol; LCCA, left common carotid artery; LDL-C, low-density lipoprotein-cholesterol; MDA, malondialdehyde; MS, monascin; OVX, ovariectomized; PCSK9, proprotein convertase subtilisin/kexin type 9; RYR, red yeast rice; TC, total cholesterol; TG, triglyceride; XZK, xuezhikang (RYR extract).

extract (containing > 3% monacolin K) significantly reduced LDL-C but had deplorable effects on TG, HDL-C, GPX, MDA, and PCSK9 expression.[41]

Studies in Humans

Studies of RYR in humans were described in 10 articles (summarized in Table 3), which mostly evidenced its activity in improving lipid profiles.[5,8,11,42–48]

A systematic review and meta-analysis study of the effectiveness and safety of RYR extract for cardiovascular risk reduction, involving 20 randomized trials on 6663 hypercholesterolemic sufferers, confirmed that RYR treatment at doses of 1200–4800 mg/day for 1 month significantly decreased the LDL-C levels ($p < 0.0001$). The long-term intake of

Table 3 Human Studies of RYR

Name of Product	Type of Study, Demographic of Patients or Participants, Design of Experiment	Dose, Duration of Intervention, and Results	Ref
RYR	A systematic review and meta-analysis study of the effectiveness and safety of RYR extract for cardiovascular risk reduction, involving 20 randomized trials on 6663 hypercholesterolemic patients	RYR treatment at a dose ranging from 1200–4800 mg/day for 1 month decreased the LDL-C levels by −90.3 mg/dL (−1.02 mmol/L) ($p < 0.0001$). The chronic administration of monacolins could be responsible for mild to moderately severe side effects, but it is usually well tolerated. The incidence of kidney injury, liver injury, and muscle symptoms was found to be at an acceptable rate (< 5%).	[5]
RYR product containing 10 mg monacolins from *M. purpureus* and a mix of antioxidants (100 mg of green tea dry extract, 20 mg of coenzyme Q10, 2 mg of astaxanthin, 20 mg of resveratrol, and 50 mg of quercetin) (Laborest S.p.A., Nerviano, Milan, Italy). The RYR extract used was certified to be highly purified in monacolins, without chromatographically detectable levels of dehydromonacolins, decalin derivatives, and contaminants.	A crossover, double-blind, placebo-controlled randomized clinical trial was carried out on 25 moderately hypercholesterolemic, nonsmoking, pharmacologically untreated subjects in the Medical and Surgical Sciences Department of the University of Bologna. Inclusion criteria were as follows: age between 18 and 70 years and LDL-C level between 130 and 190 mg/dL, confirmed in at least two sequential checks before signing the consent form. Exclusion criteria were as follows: personal history of cardiovascular disease or risk equivalents; TG > 400 mg/dL and/or HDL-C < 35 mg/dL; BMI > 30 kg/m^2; use of lipid-lowering drugs or drugs affecting lipid metabolism; and known thyroid, liver, renal, or muscle diseases. The study was fully conducted per the Declaration of Helsinki, the study protocol was approved by the Ethical Committee of the University of Bologna, and written informed consent was obtained from all patients before their inclusion in the study. After 4 weeks of diet and physical activity, patients were allocated to treatment either with an identical placebo pill or with the RYR product. The patients were asked to observe a 4-week washout period, and they were then assigned to the alternative treatment for a further period of 4 weeks. Clinical and laboratory data were obtained at baseline, at the end of the first treatment period, after the washout, and again after the second treatment period. The following parameters were evaluated via standardized methods: TC, HDL-C, TG, LDL-C, apolipoprotein B, apolipoprotein AI, glucose, creatinine, liver transaminases, creatine-phosphokinase, hs-CRP, and endothelial function.	During RYR treatment, patients experienced a more favourable percentage change in TC, LDL-C, non-HDL-C, hs-CRP, and endothelial function.	[8]

(*Continued*)

Table 3 (Continued).

Name of Product	Type of Study, Demographic of Patients or Participants, Design of Experiment	Dose, Duration of Intervention, and Results	Ref
RYR	This was a multicenter, prospective, open-label, controlled study conducted in five facilities in Japan. The study protocol was approved by the Institutional Review Board (IRB) of Chiba University Hospital (ID number: G23073), which assessed all the participating study sites and served as a centralized IRB (ID numbers: N26010, N26011, N26012, N26013). The patients without known cardiovascular disease and unsatisfactory LDL-C (3.96 ± 0.19 mmol/L), controlled only by diet therapy, were enrolled from May 2012 to October 2016, and all of them provided signed written informed consent. The study was conducted in full compliance with the articles of the Declaration of Helsinki and was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry. A sample size calculation showed that a minimum of 16 patients were needed to establish an LDL-C reduction of 0.65 mmol/L in the RYR group than in the control group (power: 0.80, significance level: 0.05). Patients were screened for eligibility at the first visit. The eligibility criteria were: LDL-C between 3.62 mmol/L and 4.65 mmol/L, no history of cardiovascular diseases, age between 20 and 80 years, compliance with diet therapy, and an understanding of the study and provision of written informed consent. The exclusion criteria were: familial hypercholesterolemia; LDL-C 63.9 mmol/mol; severe liver, kidney, or heart disease; allergy to food, including rice; excessive alcohol intake; pregnancy or lactation, or the possibility or scheduling of pregnancy; and other determination of inappropriateness for participation by a physician. Subsequently, diet therapies were conducted in line with the American Heart Association Step One diet, which allows ≤ 30%, 50–60%, and 10–20% of total daily calories as fat, carbohydrates, and protein, respectively, during the run-in period for 4 weeks. After the run-in period, the eligible patients were randomly assigned to: 1. The RYR group (200 mg/day) containing 2 mg monacolin K 2. The control group (diet therapy) for 8 weeks.	LDL-C decreased significantly in the RYR group than in the diet therapy group (median [interquartile range]: control −0.20 [−0.62, 1.19] mmol/L vs RYR −0.96 [−1.05, −0.34] mmol/L, p=0.030). The RYR group also exhibited significant decreases in total cholesterol, apolipoprotein B, and blood pressure. No severe treatment-related adverse effects on muscles, liver, or renal function were observed.	[11]
RYR	A retrospective observational study in 56 hypercholesterolemic patients with musculoskeletal pain. The patients were categorized into: 1. CYP3A4: patients treated with lovastatin, atorvastatin, or simvastatin (n = 21; female 57.1%)) 2. NO-CYP3A4: patients treated with rosuvastatin or pravastatin (n = 19; female 31.6%)) 3. RYR: patients treated with RYR (n = 16; female 68.8%) The musculoskeletal pain was assessed through the NMQ.	Patients treated with RYR showed a slight decrease in cholesterol levels, however, cholesterol levels were lower in CYP3A4 and NO-CYP3A4, compared with RYR. The RYR and CYP3A4 groups had a higher prevalence of reported knee pain than the NO-CYP3A4. Patients receiving treatment with statins and RYR should be monitored to prevent musculoskeletal pain. Appropriate information about the potential adverse effects of RYR on the musculoskeletal system should be provided to clinicians and patients.	[42]

(*Continued*)

Table 3 (Continued).

Name of Product	Type of Study, Demographic of Patients or Participants, Design of Experiment	Dose, Duration of Intervention, and Results	Ref
200 mg RYR extract corresponding to 3 mg of monacolins	A double-blind, randomized, placebo-controlled, crossover trial in 40 children affected by heterozygous FH (n=24) and FCH (n=16), aged 8–16 years. RYR extract was given daily for 8 weeks	RYR supplement, compared with the placebo, significantly reduced TC by 18.5% ($p < 0.001$), LDL-C levels by 25.1% ($p < 0.001$), and apolipoprotein B by 25.3% ($p < 0.001$). No significant differences were observed in HDL-C and apolipoprotein A–I levels. No adverse effects were detected when liver and muscular enzymes (AST, ALT, and CK) were determined.	[43]
An extract of Chinese RYR	A randomized trial was conducted in 1530 hypertensive geriatric patients with previous MI. The patients were assigned to a placebo (n = 758) or RYR (n = 772) daily for 4.5 years.	The supplementation with RYR was associated with a reduction in the risk of CHD (−31.0%; $p = 0.04$), all-cause mortality (−31.9%; $p = 0.01$), stroke (−44.1%; $p = 0.04$), the need for a coronary artery bypass graft, or a percutaneous coronary intervention (PCI) (−48.6%; $p = 0.07$), and malignancies (−51.4%; $p = 0.03$).	[44]
RYR	A meta-analysis of 13 randomized, placebo-controlled clinical trials, including 804 dyslipidemic subjects.	Consuming RYR for periods ranging from 4 weeks to 12 months revealed significant weighted mean improvements in the lipid profile as compared to placebo (TC −0.97 (95% CI −1.13, −0.80) mmol/l, $p < 0.001$; LDL-C −0.87 (95% CI −1.03, −0.71) mmol/l, $p < 0.001$). No serious adverse events were reported.	[45]
A nutraceutical mixture containing monacolin K	A longitudinal study included 30 hypercholesterolemic statin- and ezetimibe-untreated patients, with SCORE values <10%, who received 3-month-long supplementation with a nutraceutical mixture containing monacolin K, and vitamins C, B1, and K2. The status of cholesterol homeostasis was assessed by measuring serum concentrations of non-cholesterol sterols (NCS), which serve as cholesterol synthesis and absorption surrogate markers. Serum NCS were quantified by the HPLC-MS/MS method. Atherogenic indexes were calculated from lipid status parameters concentrations. The albumin degradation inhibition test was conducted to estimate the in vitro anti-inflammatory activity of the nutraceutical mixture, whereas in vitro antioxidant activity was measured in serum enriched with prooxidants and antioxidants.	Treatment with the supplement lowered TC, LDL-C, and TG concentrations ($p < 0.001$), as well as atherogenic indexes and SCORE values ($p < 0.001$, $p < 0.01$, respectively). Concentrations of cholesterol synthesis markers were decreased ($p < 0.001$), whereas levels of cholesterol absorption markers remained unchanged after the supplementation. The levels of desmosterol and lathosterol were significantly decreased. β-sitosterol and campesterol concentrations increased after supplementation. A significant reduction in every cholesterol homeostasis ratio except desmosterol/β-sitosterol was observed. Reduction in cholesterol synthesis went parallel with reductions in lipid status parameters and atherogenic indexes. In vitro analyses showed certain anti-inflammatory and antioxidant activity of the nutraceutical.	[46]
A new food supplement containing RYR, berberine, coenzyme Q10, and hydroxytyrosol.	A multicenter, randomized, double-blind, placebo-controlled study was conducted in 158 hypercholesterolemic patients, 4 weeks of treatment with a daily oral dose of the new food supplement, compared to placebo.	A significant change of LDL-C and TC levels from baseline, at week 4 was: −39.1 mg/dL ± 17.76 and −45.9 mg/dL ± 21.54, respectively, in the new food supplement group; 5.7 mg/dL ± 14.98 and 2.4 mg/dL ± 18.43, respectively, in the placebo group. The new food supplement was more effective in lowering LDL-C levels than the placebo. Three AEs were reported by five patients after the initiation of the study treatment: two in the new food supplement group (influenza and insomnia) and one in the placebo group (back pain). All AEs were mild in intensity, except for back pain (severe).	[47]

(*Continued*)

Table 3 (Continued).

Name of Product	Type of Study, Demographic of Patients or Participants, Design of Experiment	Dose, Duration of Intervention, and Results	Ref
A nutraceutical contained DIF1STAT (RYR, with monacolin K 2.5–2.9 mg/capsule, linear aliphatic alcohols titrated at 60% in octacosanols and niacin), *Olea europaea* total extract of pomace and leaves (titrated at 15% in oleuropein), *Camellia sinensis* extract and vitamins E, B_6, B_9, and B_{12}.	A double-blind, placebo-controlled randomized clinical trial aims to evaluate the modulating effect, in a setting of controlled nutritional habits, of a combined food supplement with DIF1STAT (based on red yeast rice with a very low content of monacolins, linear aliphatic alcohols and niacin) and *Olea europaea* on plasma lipids and endothelial function, in a group of 40 healthy, moderately hypercholesterolemic patients in primary cardiovascular prevention. 40 healthy adult volunteers, aged 25–65 years, with borderline LDL cholesterol levels (LDL between 150 and 190 mg/dl as confirmed in at least two sequential checks) in primary cardiovascular prevention. Patients in secondary prevention for cardiovascular diseases, age < 25 or > 65 years, triglyceridemia > 400 mg/dL, taking lipid-lowering drugs or nutraceuticals, with chronic gastrointestinal disorders and under therapy for this disease, with clinically relevant modification of renal function or with any medical or surgical condition that makes the patient's adherence to the study protocol complex or inconstant, were excluded from the study. The study included a 1-month-long run-in period of diet standardization, followed by a 2-month-long period of active treatment or placebo. Patients received standard quantitative and qualitative nutritional advice to correct their negative behavioral habits at the initial visit. To achieve an overall healthy diet for the length of the research, participants were highly advised to observe the general indications of a Mediterranean diet, limiting unhealthy consumption of dairy and red meat-derived items. Patients were highly advised to improve their physical fitness by exercising for at least 20 minutes, 3 to 5 days a week. The study fully complied with the ethical guidelines of the Declaration of Helsinki, and its protocol was approved by the Ethical Committee of the University of Bologna. All participants signed a written informed consent form to participate. After 4 weeks of diet standardization, the participants were randomly assigned to receive two indistinguishable placebo or active substance capsules (provided by Difass International, Cerasolo, Italy), one capsule per day, at the same time after dinner.	After 8 weeks of treatment, when compared to the placebo group, the active treated patients experienced significant improvements in different metabolic parameters and endothelial reactivity compared to placebo. The treated patients showed a statistically significant percentage change in TC (–12.25 delta% vs –1.8%, $p < 0.01$), LDL-C (–28.7 delta% vs –1.1%, $p < 0.01$), HDL-C (+4.99% vs +0.9%, $p < 0.05$), non-HDL-C (–16.02 delta % vs –1.5%, $p < 0.01$), SUA (–12.96 delta%, $p < 0.05$), and endothelial reactivity (+6.73% vs –1.4%, $p < 0.01$). In both groups, there was no case of intolerance, and the safety parameters were unchanged.	[48]

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, coronary heart disease; CK, creatine kinase; FCH, Familial Combined Hyperlipidemia; FH, Familial Hypercholesterolemia; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; NMQ, the Nordic Musculoskeletal Questionnaire; RYR, red yeast rice; SCORE, systematic coronary risk estimation; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride.

monacolins was thought to be responsible for the minor adverse events, but it was generally well tolerated and at an acceptable rate (< 5%).[5]

A crossover, double-blind, placebo-controlled randomized clinical trial was carried out on 25 moderately hypercholesterolemic, nonsmoking, pharmacologically untreated subjects. The patients were treated either with a placebo pill or with the RYR product. It was concluded that the RYR supplement treatment reduced hypercholesterolemia, hs-CRP, and markers of vascular remodeling.[8]

A multicenter, prospective, open-label, controlled study was conducted in five facilities in Japan, in 18 adults to geriatric patients, with LDL-C between 3.62 mmol/L and 4.65 mmol/L, no history of cardiovascular diseases, and compliance with diet therapy. It was described that patients administered with RYR indicated a marked decrease in LDL-C levels, total cholesterol, apolipoprotein B, and blood pressure, compared to those given the standard diet therapy. It was confirmed that the patients experienced no severe side effects on the musculoskeletal, hepatic, or renal systems.[11]

A retrospective observational study in 56 hypercholesterolemic patients with musculoskeletal pain (assessed using the Nordic Musculoskeletal Questionnaire) confirmed that patients treated with RYR showed a slight decrease in cholesterol levels but a higher incidence of reported knee pain. It was suggested that these patients (n = 16; female 68.8%) should be monitored to prevent musculoskeletal pain; therefore, the potential side effects of RYR on the muscles should be explained.[42]

A double-blind, randomized, placebo-controlled, crossover trial was performed in 40 children diagnosed with familial hypercholesterolemia and familial combined hyperlipidemia. Treatment with RYR extract was given daily for 8 weeks, resulting in a marked reduction of total cholesterol, LDL-C, and apolipoprotein B, without significant changes in HDL-C and apolipoprotein A–I levels. All of the patients showed no abnormalities in alanine aminotransferase, aspartate aminotransferase, and creatine kinase levels.[43]

Another study of randomized trial by Colletti et al was conducted in 1530 hypertensive geriatric patients with myocardial infarction. The patients were assigned to a placebo (n = 758) or an extract of Chinese RYR (n = 772) daily for 4.5 years. It was confirmed that RYR could reduce the risk of coronary heart disease, all-cause mortality, stroke, the number of coronary artery bypasses, percutaneous coronary interventions, and malignancies.[44]

A meta-analysis of 13 randomized, placebo-controlled clinical trials, including 804 dyslipidemic patients, reported that RYR supplementation from 1 month to 12 months significantly improved the lipid profile as compared to placebo, without serious side effects.[45]

Moreover, a longitudinal study included 30 hypercholesterolemic statin- and ezetimibe-untreated patients, with systematic coronary risk estimation values < 10%, receiving supplementation consisting of monacolin K, and vitamins C, B1, and K2 for 3 months, showed an improved lipid profile, as well as atherogenic indexes and systematic coronary risk estimation values. Regrettably, HDL-C levels did not significantly change.[46]

A multicenter, randomized, double-blind, placebo-controlled study, conducted in 158 hypercholesterolemic patients, treated daily for 4 weeks with an oral dose of a supplement containing RYR, berberine, coenzyme Q10, and hydroxytyrosol, resulting in a lower LDL-C levels than the placebo, but three mild side effects were reported: two in the RYR group (influenza and insomnia) and one in the placebo group (back pain).[47]

A double-blind, placebo-controlled randomized clinical trial to evaluate the modulating effect of a combined food supplement: DIF1STAT (RYR with monacolin K 2.5–2.9 mg/capsule and niacin), *Olea europaea* extract in oleuropein, *Camellia sinensis* extract, and vitamins E, B_6, B_9, and B_{12}, in 40 healthy adult participants, with borderline LDL cholesterol levels. At the end of treatment (week 8), when compared to the placebo group, the participants treated with the combined food supplement showed marked improvements in metabolic biochemical tests and endothelial reactivity.[48]

Case Reports of RYR Supplement

Case reports of RYR supplement were obtained from the PubMed database using the keywords "case reports of red yeast rice supplement", filtered to 5 years of publication date and free full-text, which resulted in 20 documents. After examining the title and abstract, 11 documents were selected.[49–59] Of these, ten documents reported Fanconi syndrome (a rare disorder that affects the proximal tubules of the kidney, leading to impaired reabsorption of glucose, phosphate, electrolytes, bicarbonate, and amino acids) and renal dysfunction, while one reported fulminant rhabdomyolysis (severe acute liver injury). All of the Fanconi syndrome and renal dysfunction cases were reported from Japan, mainly caused by an RYR supplement product, namely Beni Koji Choleste Help, Japan.[49–58] Details of the cases are described in the following paragraphs:

Yoshikawa et al, from Tokyo, Japan, presented two cases as follows: the first case was a 43-year-old male who presented with epigastric discomfort and was prescribed rebamipide (a *Clostridium butyricum* combination drug), famotidine (a histamine H_2 receptor antagonist), and metoclopramide (a dopamine receptor antagonist). Because of the

persistence of his symptoms, the patient revisited the clinic, and laboratory analysis showed an increase in sCr level. He confessed to having consumed a product containing RYR for 1 year. Laboratory examinations indicated probable renal tubular acidosis, hypophosphatemia-hyperphosphaturia, normoglycemic glucosuria, hypouricemia-hyperuricosuria, and aminoaciduria, confirming a diagnosis of Fanconi syndrome. The RYR product was discontinued on the day of admission, and the symptoms decreased.[49] In the second case described in the same article, a 54-year-old male with proteinuria, hematuria, glucosuria, sCr of 1.75 mg/dL, uric acid 1.5 mg/dL, blood glucose 102 mg/dL, and HbA1c 5.8%, was diagnosed with Fanconi syndrome. He had taken a supplement containing RYR for 4 years. The RYR was discontinued, and four months later, the Fanconi syndrome was resolved, but his sCr remained at the upper borderline.[49]

A similar case of Fanconi syndrome was reported by Kawai et al in 2024 from Yokohama, Kanagawa, Japan. The patient was a 56-year-old female with renal dysfunction, no relevant medical history, except for smoking, no evidence of renal disease or urinary abnormalities, and no family history of kidney disease. She admitted to having been taking an over-the-counter intestinal medication for 2–3 years, a beauty supplement, and an RYR supplement (Beni Koji Choleste Help, Japan). She began experiencing shortness of breath, vomiting, and loss of appetite 1 month priorly, but no abnormalities on upper gastrointestinal endoscopy. Urinalysis showed glucosuria, proteinuria, high urine β2-microglobulin (β2MG, a non-glycosylated polypeptide in all nucleated cells, which plays a significant role in adaptive immunity), and N-acetyl-glucosaminidase levels. Blood analysis showed an increase in sCr level, hypokalemia, hypophosphatemia, hypouricemia, and hyperchloremic metabolic acidosis, implying proximal tubule dysfunction, manifesting as renal tubular acidosis, renal diabetes, and hypophosphatemia, which positively supported the diagnosis of Fanconi syndrome. A renal biopsy revealed severe tubular injury and mild interstitial fibrosis, accompanied by sparse lymphocytic infiltration. The OTC drug and two supplements were discontinued, and the patient was given oral prednisolone 30 mg/day to suppress interstitial fibrosis. At 4 weeks of prednisolone administration, the sCr levels decreased to normal levels, the drug was discontinued, and the renal function of the patient was rapidly improved.[50]

Three cases of RYR-containing supplements were reported in an article by Chikasue et al in 2025 from Karume, Japan. In the first case, the patient was a 49-year-old female without any underlying diseases or abnormalities in the annual laboratory test checkup. After a 2-week of RYR supplement (Beni Koji Choleste Help, Japan), she experienced malaise, nausea, and appetite loss, leading her to discontinue the product. Laboratory tests showed elevated sCr levels, proteinuria, microhematuria, metabolic acidosis, and glycosuria, and thus, hemodialysis was initiated, followed by a kidney biopsy, which indicated diffuse tubular injury, loss of brush border, and tubular necrosis. Although there were no histological abnormalities in the glomerulus, massive $CD3^{+}$T lymphocyte infiltrates were observed, and oral prednisolone (50 mg/day) was given. Eventually, kidney function improved; thus, hemodialysis was stopped. The sCr, uric acid, and potassium levels improved.[51] The second case described in the same article involved a 55-year-old man with a history of surgery for adhesive intestinal obstruction, with no underlying kidney diseases detected, and normal sCr levels, before he took an RYR supplement (Beni Koji Choleste Help, Japan) for 6 months. The supplement caused abdominal distension, nausea, and appetite loss, an increase in sCr, proteinuria, microhematuria, hypouricemia, hypokalemia, and glycosuria, suggesting proximal renal tubular acidosis with Fanconi syndrome. In addition to discontinuing the RYR supplement, oral citrate treatment was initiated, which eventually improved the levels of sCr, uric acid, and potassium.[51] Case 3 involved a 60-year-old woman without underlying kidney disease, who showed a significant increase in sCr, proteinuria, hypouricemia, hypokalemia, glycosuria, and severe metabolic acidosis, after 7 months of taking an RYR supplement (Beni Koji Choleste Help, Japan), suggesting Fanconi syndrome. After the supplement was discontinued and daily treatment with citrate tablets was initiated, sCr, uric acid, and serum K were found to be within normal range.[51]

Another case was reported by Katayama et al from Tokyo, Japan, involving a 51-year-old woman with high sCr levels and unremarkable physical examination. The urinalysis revealed high levels of urinary β2-microglobulin and N-acetyl-β-D-glucosaminidase. Despite severe kidney dysfunction, her serum potassium, uric acid, and phosphate levels were low. She confessed to having been taking an RYR supplement (Beni Koji Choleste Help, Japan) for 10 months, three tablets/day to treat her dyslipidemia, lansoprazole (a proton pump inhibitor), metoclopramide, and rebamipide. She was treated for Fanconi syndrome with potassium gluconate (to increase potassium levels), alfacalcidol (a vitamin D analogue used to manage hypocalcemia), and phosphoric acid, leading to an improved sCr level to normal, and she was discharged. The patient resumed taking the RYR supplement for 18 days and was readmitted to the hospital because of recurrent acute

kidney injury with an increase in sCr levels and Fanconi syndrome. A kidney biopsy was performed, which revealed that 14.29% of the glomeruli were globally sclerotic. The patient was treated with sodium bicarbonate, and three weeks later, her sCr, urinary β2-microglobulin, and urinary N-acetyl-β-D-glucosaminidase levels were within normal range.[52]

In 2024, Miyazaki et al from Tokyo, Japan, reported an acute kidney tubular injury. The patient was a 47-year-old woman diagnosed with dyslipidemia, who started taking an RYR supplement (Choleste Help, Japan) at her discretion, 3 tablets/day with approximately a total of 300 tablets. Five days before admission, she felt nauseous and stopped taking the supplement. Laboratory analysis revealed elevated sCr levels, and urinary tests showed proteinuria, granular casts, tubular epithelial cells, and glycosuria. Urinalysis showed high levels of urinary β2-microglobulin and N-acetyl-β-d-glucosaminidase. Serum potassium and uric acid levels were low. A kidney biopsy showed tubular dilatation, epithelial desquamation, and hyaline casts, without diffuse interstitial infiltration, suggesting acute tubular necrosis. The patient was given oral corticosteroid therapy at a dose of 40 mg/day, and when the kidney function improved, the corticosteroid was stopped.[53]

Two cases after taking the RYR supplement were reported by Takeuchi et al from Kanagawa, Japan, which revealed renal dysfunction with low uric acid, potassium, and phosphorus levels, confirming a Fanconi syndrome. The renal biopsy findings of both cases indicated severe damage to the proximal tubules with few inflammatory cell infiltrations, diffuse loss of the brush border, flattening, and tubular lumen dilation. Immunofluorescence exhibited no deposition of immunoglobulin and complement. Electron microscopic findings indicated proximal tubular damage without crystal deposition.[54]

Another two cases of RYR supplements were reported by Uchiyama et al from Chiba, Japan, in 2024. In case 1, a 56-year-old woman with no significant past medical history, admitted that she had taken an RYR supplement (Beni Koji Choleste Help, Japan) 3 tablets/day for months, eventually developed hypertension, with a systolic blood pressure of 160 mm Hg. During a routine visit to the neurosurgeon, laboratory analysis revealed an elevated sCr level, a low eGFR level, marked proteinuria, increased urinary protein-to-creatinine ratio, glucosuria, hypouricemia, hypokalemia, hypophosphatemia, and metabolic acidosis with a low serum bicarbonate level, suggesting a Fanconi syndrome. The RYR supplement was stopped, and three days later her kidney function improved, but the urinary albumin-to-creatinine ratio and the urinary β2-microglobulin-to-creatinine ratio indicated the leakage of amino acids in the urine. Kidney biopsy showed 14.29% of glomeruli were globally sclerosed, tubular degeneration was prominent, and interstitial inflammatory cell infiltration was present. The next day, sCr level and eGFR improved, and proteinuria was reduced; therefore, oral corticosteroid was not given. One month later, the kidney function improved to normal.[55] In case 2, a 56-year-old man with controlled diabetes mellitus and no signs of diabetic retinopathy, on therapy of sitagliptin (50 mg/day), dapagliflozin (5 mg/day), glimepiride (0.5 mg/day), and metformin (1500 mg/day), confessed that he had begun consuming 3 tablets/day of an RYR supplement (Beni Koji Choleste Help, Japan) for several months. Four months after taking the RYR supplements, his appetite decreased, and the supplement was discontinued, but he developed nausea and vomiting and was taken to the hospital. Upon arrival, his sCr level was very high, with lactic acidosis and a high serum lactate level, which was considered an adverse event of metformin accumulation due to severe kidney injury. Abdominal computed tomography revealed normal kidneys, with a normal creatinine kinase level. Continuous hemodialysis was administered for three days, followed by intermittent hemodialysis up to day 17. Urinalysis revealed proteinuria, glucosuria, and hematuria, indicating Fanconi syndrome. Kidney biopsy revealed 13.64% of glomeruli were globally sclerosed and 18.18% of nodular glomerulosclerosis, which indicated diabetic nephropathy. Although he was anuric on day 0, his urinary volume increased gradually on day 8, sCr levels improved on day 14, and hemodialysis was discontinued on day 16. On day 25, prednisolone was initiated (30 mg/day), and the patient was discharged on day 30.[55]

A case of acute kidney injury and Fanconi syndrome of multiple supplements, including RYR Cholesterol Help, was reported by Oda et al from Mie, Japan, in 2024. The patient was a 62-year-old man who lost his appetite and experienced fatigue. He was prescribed vonoprazan fumarate (a pyrrole derivative and reversible potassium-competitive acid blocker, P-CAB). He confessed to taking multiple health supplements, including Taisho Chinese herbal gastrointestinal medicine, Red Yeast Rice Cholesterol Help, DHA & EPA, and a Chinese herbal laxative, in addition to P-CAB. After admission, all the supplements were stopped, and P-CAB was changed to rebamipide. Blood samples indicated kidney injury, hypokalemia, hypouricemia, hypophosphatemia, and elevated levels of markers of renal tubular injury. The urine β_2-

microglobulin value and the urine glucose level were high, and based on normal blood sugar and HbA1c levels and the presence of sugar in urine, it was determined that the glucosuria was from renal diabetes. The patient was diagnosed with acute kidney injury and Fanconi syndrome. Renal biopsy revealed global sclerosis in 14.29% of glomeruli and severe proximal tubular damage. He was treated with oral potassium and phosphorus preparations, which resulted in improvement and recovery of kidney function.[56]

Two other cases were reported by Shimokawa et al from Tokyo, Japan. The first case involved a 60-year-old woman with renal dysfunction and abnormal urinalysis results. She had suffered from endometriosis, a left ovarian cyst, and appendicitis, without any family history of kidney disease. Because her laboratory test showed elevated LDL-C levels, she began taking an RYR supplement (Beni Koji Choleste Help, Japan) for 4 months. During this time, her blood pressure increased and proteinuria developed; thus, the supplement was discontinued. Physical examination showed normal results, but laboratory analysis confirmed renal dysfunction, hypokalemia, hypophosphatemia, and hypouricemia. Autoimmune markers were negative. Urinalysis revealed proteinuria and glucosuria, without hematuria. A spot urine protein-to-Cr ratio was 1.51 g/g Cr, and β2-microglobulin was elevated, with a high N-acetyl-β-D-glucosaminidase index. Postadmission tests revealed aminoaciduria and tubulointerstitial dysfunction, consistent with Fanconi syndrome and acute kidney injury. Sodium restriction and calcium channel blocker therapy were initiated, but due to the persistence of hypertension, telmisartan (40 mg/day) was administered.[57] In the second case described in the same article by Shimokawa et al, a 58-year-old man with a history of hypertension presented with proteinuria and declining renal function. He had been on amlodipine (5 mg/day) for several years and revealed normal sCr levels without proteinuria. Two months earlier, the patient began consuming an RYR supplement (Benikoji CholesteHelp) to manage his dyslipidemia, but after a month, the supplement was discontinued because he felt fatigued and had a loss of appetite. Upon admission to the hospital, the laboratory findings confirmed renal dysfunction, hypophosphatemia, hypouricemia, and proteinuria. Moreover, an elevation of β2-microglobulin and the N-acetyl-β-D-glucosaminidase index, a reduction of phosphate reabsorption, and excessive urinary glucose excretion suggest Fanconi syndrome.[57]

Two cases were reported in 2025 by Koshida et al from Urayasu, Chiba, Japan. The first case involved a 42-year-old man with renal dysfunction. He confessed to having been taking supplements containing RYR for six months. The patient reported general fatigue, loss of appetite, frequent urination, and thirst exacerbation. A physical examination revealed normalities. Laboratory data indicated blood eosinophil and IgE levels were within the normal ranges, sCr 2.12 mg/dL, and eGFR 29 mL/min/1.73 m^2. Urinary findings indicated mild proteinuria, massive glycosuria, severely elevated β2 microglobulin, α1 microglobulin, and N-acetyl-β-D-glucosaminidase. The serum levels of uric acid, potassium, phosphorus, and bicarbonate indicated the proximal tubule injury. Abdominal computed tomography revealed no kidney atrophy. RYR supplementation was discontinued, and steroid pulse therapy (methylprednisolone 500 mg for 3 days) was initiated, followed by 30 mg/day prednisolone. Kidney biopsy contained 20 glomeruli, without any significant injuries, and no significant interstitial infiltration of inflammatory cells. Subsequently, the sCr level improved, and the impaired reabsorption of glucose, uric acid, potassium, bicarbonate, and phosphorus was also improved; therefore, the dose of prednisolone was tapered to 5 mg/week.[58] The second case described in the same article by Koshida et al from Urayasu, Chiba, Japan, involved an 83-year-old woman with diabetic kidney disease and renal dysfunction, for the evaluation of acute kidney injury. After taking supplements containing RYR for 2 months, her renal dysfunction worsened. In this case, the renal function did not recover after two months of supplement discontinuation, but serum levels of potassium, calcium, and phosphorus were improved, and urinary levels of N-acetyl-β-D-glucosaminidase, β2 microglobulin, and proteinuria were also improved.[58]

The last case was reported by Kurnik et al from Celje, Slovenia, involving a 68-year-old female patient with no history of chest pain, dyspnea, muscle weakness, or syncope. She suddenly experienced muscle weakness, followed by a brief episode of visual blackout and loss of consciousness, and was transported to the hospital. Electrocardiogram and chest X-ray findings were normal. Laboratory tests revealed slight hypokalemia, mildly elevated transaminases, D-dimer, and lactate levels. Polymerase chain reaction tests for respiratory infections were negative. The PCR test also confirmed SARS-CoV-2 infection was positive, but after the patient had already recovered from the acute phase. Despite no reported changes in diet or medication regimen over the past several months, the clinical examination revealed clear signs of volume depletion, including collapsed jugular veins, dry mucous membranes, absence of axillary sweat, and

prolonged skin turgor. She was treated with parenteral rehydration with potassium supplementation and continuous ECG monitoring. Follow-up laboratory tests showed an increase in serum lactate. Bedside echocardiography revealed a hypercontractile left ventricle and a completely collapsed inferior vena cava. Parenteral rehydration was continued without further potassium supplementation. The condition began to deteriorate with progressive muscle weakness and paresthesias primarily affecting the lower extremities. Clinical examination at that point showed flaccid paraparesis of both lower limbs. A urinary catheter was placed, collecting 1000 mL of dark urine. Follow-up laboratory tests showed a continued elevation in lactate, along with significantly increased levels of creatinine kinase and serum myoglobin (> 30,000 µg/L). The patient's condition continued to decline, with diffuse pain in both lower limbs and diminishing muscle strength in the upper extremities. The presentation of ascending paresis suggested the diagnosis of fulminant idiopathic rhabdomyolysis. ECG monitoring revealed worsening T wave elevation, although no cardiac dysrhythmias were observed. Empirical treatment was initiated with calcium gluconate and insulin therapy. A thorough investigation into the health and medical history, including interviews with family, revealed that the patient had started taking two supplements only two days before her collapse: Dr. Böhm Immun Complex (Apomedica, Austria) and Biostatine (Pharmalife Research, Italy), which contained RYR extract with monacolin K.[59]

Discussion

Red yeast rice (RYR) has shown numerous benefits for health. Various constituents have been found in RYR, such as monacolins,[3,4,12,17–19] pigments,[20–22] benzopyrans, such as the mycotoxin citrinin,[12,23–25,60] phenolics,[26,27] amino acids such as (+)-monascumic acid and (-)-monascumic acid,[28] sterols, such as ergosterol,[29] and other constituents.

Monacolin K is present in two forms: the lactone form, which is named monacolin K, and the hydroxyl acid form, named monacolin KA. Monacolin KA is thought to be the efficient form in the body because of its high absorbability.[61] The level ratio of monacolin K/monacolin KA varies broadly in numerous RYR products.[62] The chemical structure of monacolin K is identical to lovastatin, a hydroxymethyl glutaryl (HMG)-CoA reductase inhibitor,[10–12] thus explaining its hypocholesterolemia effects in animal models,[37,38,40,41] and in humans.[5,11,42–48] RYR supplementation has shown similar effects to taking lovastatin, although the potency may be lower, but the potential for adverse events should be taken to notice. Monacolin K is metabolized mainly by the hepatic CYP3A4,[63] which is the main enzyme contributing to the Phase I biotransformation of numerous endogenous compounds, such as steroid hormones, lipids, bile acids, and more than 50% of prescribed drugs.[64]

Besides the "good-for-health" constituents (monacolins, pigments, phenolics, and sterols) contained in RYR, *Monascus*-fermented rice also contains the mycotoxin citrinin. Citrinin has shown nephrotoxicity and teratogenicity,[60,63] and the development of renal tumors in rats.[63] Different types of *M. purpureus* produced various levels of citrinin, and *M. purpureus* E showed the highest levels.[60] Citrinin is easily absorbed by human intestinal epithelial cells and is a non-substrate of the permeability glycoprotein (P-gp),[65,66] a drug efflux transporter protein, involved in the removal of different chemical structures of drugs.[67,68] The strong binding of citrinin to P-gp makes it absorbable, yet it cannot be removed, thus leading to its accumulation in the body.[65,66] Citrinin was associated with several disorders, including Fanconi syndrome, leukemia, and fatty liver diseases,[65,66] which explains the incidence of the Fanconi syndrome cases reported from Japan.[49–58]

The Panel on Food Additives and Nutrient Sources added to Food (ANS) had reviewed the scientific evidence in response to a request from the European Commission. It was considered that the lactone form of monacolin K is structurally identical to lovastatin and that exposure to monacolins from RYR may cause similar effects with the therapeutic doses of lovastatin. The recommended daily intakes ranged from 2 to 48 mg of monacolin K, but most food supplements supply a recommended intake of 10 mg/day, following the European Food Safety Authority (EFSA) for health claims. It should be noted that monacolin K from RYR may cause severe adverse events on the musculoskeletal system, the kidney, and the liver.[69] Impressively, a systematic review of clinical trials of monacolin K supplementation in 769 adult patients with high cholesterol levels described an advantageous effect of monacolin supplementation on LDL-C and total cholesterol levels, despite the dose and period of supplementation. Monacolin K at a dose of 3 mg/day has shown potential anti-hypercholesterolemic effects, although the number of relevant studies is few. It was recommended that all patients taking monacolin K should be routinely monitored for vital organ functions.[70] A recently

published article of the 2024 update on the post-marketing nutrivigilance safety profile of RYR delineated that there was a very low incidence of suspected adverse effects associated with the RYR supplementation. The safety of patients taking the RYR supplements can be improved by increasing awareness of following the indications and warnings written on the labels.[71]

Limitations of the Study

During the review of the studies, we found limitations, such as the various types of rodent models and different genders of the animals employed in the in vivo studies, small sample sizes in human studies, the lack of standardization and quality control in commercial RYR products administered in human studies, different ranges of age (adults to geriatrics), varying effects observed between genders, short follow-up, geographic concentration of adverse events in Japan, the variety of the periods, and potential confounding factors in case reports, which require more in-depth exploration in clinical settings to confirm therapeutic potential in humans.

Conclusion

This review provides an overview of the complex and multifaceted roles of *Monascus purpureus*-fermented red yeast rice (RYR), which include the chemical aspects, in vitro and in vivo studies. In vitro studies reported anti-type I allergy (antiasthma), anticancer, alleviating vascular complications of diabetes, anti-inflammatory, and antimicrobial activity, while in vivo studies delineated inhibitory activity towards plaque progression, antidyslipidemia, anti-inflammatory, and anti-osteoporosis activity, and studies in humans have evidenced its activity in improving lipid profiles. However, case reports on the over-the-counter RYR supplements revealed Fanconi syndrome and kidney dysfunction as the main adverse events, all of which were reported from Japan. It should be noted that the safety profile of this supplement is mainly based on case reports, and patients taking the supplement did not consult their physicians, thus may lead to dosage errors and/or nonadherence. The cases were mostly complicated because of varying product composition and doses (in particular, the monacolin K and citrinin content), the variety of the periods of therapy, the multiple supplements taken, health history, and the presence of comorbidities. Patients taking multiple supplements or medications should consult with a healthcare professional to avoid drug-drug interactions, especially those categorized as vulnerable patients.

Acknowledgments

The authors thank the Rector of Universitas Padjadjaran via the Directorate of Research, Downstream, and Community Engagement for facilitating the APC. This review study is within the framework of the doctoral research of the first author at the Doctoral Program in Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, West Java, Indonesia.

Funding

The APC is funded by Universitas Padjadjaran via the Directorate of Research, Downstream, and Community Engagement.

Disclosure

The authors declared no potential conflicts of interest in the research, authorship, or publication of this article.

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