ENDOCRINOLOGY AND METABOLISM

Cite as: Archiv EuroMedica. 2026. 16; 4. DOI 10.35630/2026/16/Iss.4.17

Received 16 June 2026;
Accepted 30 July 2026;
Published 6 August 2026

SAFETY CONCERNS OF RED YEAST RICE SUPPLEMENTS: HEPATIC, RENAL, AND MUSCULAR TOXICITY IN THE CONTEXT OF VARIABLE MONACOLIN K CONTENT AND PRODUCT CONTAMINATION—A NARRATIVE REVIEW OF RECENT EVIDENCE

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ABSTRACT

Background

Red yeast rice (RYR) supplements are widely used for lipid lowering because they contain monacolin K, a compound structurally identical to lovastatin. However, RYR products are not consistently standardized and are subject to different regulatory requirements across jurisdictions, resulting in substantial variability in monacolin content,

product composition, and possible contamination. These factors raise concerns regarding unpredictable exposure and potential hepatic, renal, and muscular toxicity.

Aims

The aim of this narrative review was to summarize the current evidence on the safety of red yeast rice supplements, with particular attention to hepatic, renal, and muscular adverse effects associated with variable monacolin K content, product composition, and possible contamination.

Materials and methods

A narrative review was conducted using PubMed/MEDLINE and Google Scholar. Systematic reviews, randomized controlled trials, cohort studies, case series, case reports, and pharmacovigilance reports published from 2010 to May 2026 were evaluated. A total of 72 publications were included in the qualitative synthesis, together with 4 additional regulatory and contextual documents.

Results

Commercial RYR supplements showed substantial variability in monacolin content, composition, and product quality, with contamination reported in some products. Randomized controlled trials and meta-analyses generally indicated a favorable overall safety profile. However, pharmacovigilance reports, case series, and case reports described uncommon but potentially severe hepatic, muscular, and renal adverse events, including drug-induced liver injury, rhabdomyolysis, acute kidney injury, and Fanconi syndrome. The true frequency of these complications and the relative contributions of monacolin K, product variability, and specific contaminants remain uncertain.

Conclusions

Red yeast rice supplements may be associated with hepatic, muscular, and renal adverse effects. Severe complications appear to be uncommon, but their true frequency remains uncertain. Improved product standardization, clearer labeling, stronger post-marketing surveillance, and greater awareness among healthcare professionals and consumers are needed to improve the safety of RYR supplements.

Keywords: red yeast rice (RYR), monacolin K, statin exposure, dietary supplements, hepatotoxicity, nephrotoxicity, myopathy, adverse effects.

INTRODUCTION

Hypercholesterolemia, particularly elevated low density lipoprotein cholesterol, is a major modifiable risk factor for atherosclerotic cardiovascular disease [1]. Atherosclerotic cardiovascular disease remains a leading cause of death worldwide and represents a substantial public health burden [2]. Lowering low density lipoprotein cholesterol is therefore an important component of cardiovascular risk reduction [3].

Lifestyle modification, including dietary intervention, is the initial approach to lipid management. When target lipid levels are not achieved, pharmacological treatment may be required [4]. Statins are the most commonly used lipid lowering drugs. They inhibit 3 hydroxy 3 methylglutaryl coenzyme A reductase, reduce hepatic cholesterol synthesis, increase hepatic low density lipoprotein receptor expression, and lower circulating low density lipoprotein cholesterol concentrations [4, 5].

However, concerns regarding side effects often result in patients seeking alternative therapeutic strategies. In recent years, dietary supplements have gained increasing popularity among patients who decline pharmacotherapy [6]. Among these, red yeast rice is used by some patients as an alternative lipid lowering supplement, although its composition and safety are not consistently predictable. Red yeast rice has been used for centuries in traditional Chinese medicine. The therapeutic efficacy of red yeast rice in managing dyslipidemia is attributed to a complex profile of bioactive secondary metabolites produced during the fermentation of white rice with Monascus species, mainly Monascus purpureus [7]. These include monacolins, pigments, and γ-aminobutyric acid (GABA), which work through diverse mechanisms to modulate systemic lipid metabolism.

The most significant component of RYR is monacolin K (MK), which is structurally identical to lovastatin [8]. By inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, monacolin K prevents cholesterol synthesis and exerts lipid-lowering effects through the same mechanism as statins. However, RYR products show considerable variability in quality due to inconsistent regulation, which may have important clinical consequences, including potential adverse effects similar to those observed with statin therapy, such as hepatotoxicity, myopathy, rhabdomyolysis, and possible nephrotoxic effects [9]. The lack of standardization of RYR products affects product quality, dose estimation, and safety assessment, making it difficult to evaluate dose related exposure [9]. The variability in monacolin content and potential contaminants

complicates the interpretation of toxicity data, especially with regard to organ-specific adverse effects.

AIM

The aim of this narrative review is to summarize current evidence on the safety of red yeast rice supplements, with particular attention to hepatic, muscular, and renal adverse effects associated with variability in monacolin K content and product contamination.

The objectives are:

1. To assess the variability in monacolin K content and composition of commercially available red yeast rice supplements.
2. To summarize the available evidence on hepatic, muscular, and renal adverse effects associated with red yeast rice supplementation.
3. To examine the possible contribution of contaminants to the development of toxicity.

MATERIALS AND METHODS

This narrative review was conducted based on evidence from systematic reviews, randomized controlled trials, cohort studies, and case series evaluating the safety of red yeast rice (RYR) supplements in relation to hepatic, renal, and muscular toxicity associated with variable monacolin K content. The most recent literature search was conducted in May 2026. Two databases were searched: PubMed/MEDLINE and Google Scholar. The literature was selected using a combination of the following keywords: red yeast rice, monacolin K, statin exposure, dietary supplements, hepatotoxicity, nephrotoxicity, myopathy, and adverse effects. The complete search strings used were:

PubMed/MEDLINE: The search strategy used combinations of keywords connected with Boolean operators (AND/OR): (“red yeast rice” OR “monacolin K”) AND (hepatotoxicity OR nephrotoxicity OR myopathy OR rhabdomyolysis OR “kidney injury” OR “liver injury”) AND (“adverse effects” OR safety OR toxicity) AND (“statin exposure” OR statin-related) AND (“dietary supplements” OR nutraceuticals).

Google Scholar: The following search phrases were used: “red yeast rice” AND hepatotoxicity, “red yeast rice” AND nephrotoxicity, “red yeast rice” AND myopathy, “red yeast rice” AND rhabdomyolysis, “red yeast rice” AND “kidney injury”, “red yeast rice” AND “liver injury”, “monacolin K content” AND “red yeast rice”, “statin exposure” AND “red yeast rice”, and “dietary supplements” AND “red yeast rice”.

The inclusion criteria were: 1. studies evaluating RYR supplements or monacolin K content in relation to hepatic, renal, or muscular outcomes; 2. systematic reviews, randomized controlled trials, cohort studies, case series, and pharmacovigilance reports; 3. publications issued from 2010 to May 2026; and 4. full-text articles published in English.

The exclusion criteria were: 1. conference abstracts without available full text; 2. duplicate publications or reports based on overlapping cohorts; 3. publications issued before 2010; and 4. narrative reviews.

The PubMed/MEDLINE and Google Scholar searches using the combinations of search terms described above identified 3,372 records. After title and abstract screening, removal of duplicates, exclusion of non-English publications, and exclusion of overlapping reports, 3,300 records were excluded. A total of 72 publications were included in the qualitative synthesis. In addition, 4 documents, comprising 1 clinical guideline, 1 scientific opinion, and 2 regulatory documents, were used to provide regulatory context and recommendations related to red yeast rice-containing products.

Given the heterogeneity of study designs, outcome measures, and monacolin K dosing, the findings were synthesized qualitatively and organized thematically by toxicity type: hepatotoxicity, nephrotoxicity, and myopathy. Patterns relating the frequency and severity of adverse events to variability in monacolin K content and reported product quality or contamination were also examined.

RESULTS

1. Variability, composition, and contamination of red yeast rice supplements

1.1 Variability in monacolin K content

Numerous studies have demonstrated that product labeling does not provide an accurate indication of true monacolin content [10]. A landmark study published in 2010 re-

ported a 100-fold variation in monacolin concentrations among 12 brands despite identical label information [11]. Follow-up research conducted in 2014 confirmed this variability, revealing a 40-fold difference in monacolin K levels [12]. Comprehensive analyses further highlight this unpredictability: a study from 2017 found that daily monacolin K doses across 28 brands varied 120-fold, with some products containing no detectable monacolin K at all [13]. In another study, using NMR spectroscopy to measure statin content, researchers identified total statin concentrations ranging from 1.5 mg to 25.2 mg per daily dose across various supplements [14]. Analysis of 31 dietary supplements further showed that 42% of products did not report monacolin concentrations on their labels [7]. In addition, some studies have found that all tested samples failed to meet pharmaceutical Good Manufacturing Practice (GMP) criteria, which declare that the active constituent should be present within 95–105% of the declared amount [9].

1.2 Diversity of monacolins in red yeast rice supplements

In addition to variability in monacolin K content, RYR products also differ considerably in their monacolin composition [15]. Monacolin K exists in two molecular forms: the lactone form (MK) and the hydroxy acid form (MKA) [16]. The proportion of lactone and hydroxy acid forms can vary considerably depending on the fermentation process, drying conditions, and type of rice used [8]. Consequently, the lactone-to-hydroxy acid ratio directly affects the systemic bioavailability and lipid-lowering efficacy of monacolin K [17]. This distinction is clinically significant because the lactone form functions as a prodrug, while the hydroxy acid form is the active metabolite that inhibits HMG-CoA reductase [16]. The hydroxy acid form is much more readily absorbed by the body compared to its lactone counterpart [18]. Activation of the lactone form requires hydrolysis of the lactone ring, a process facilitated under alkaline conditions or by CYP3A4-mediated metabolism in the liver and small intestine [17]. A major challenge in the clinical application of red yeast rice (RYR) supplements is the lack of standardization between these two forms. In commercial RYR products, the proportion of the active hydroxy acid form may vary from as little as 5% to as much as 100% of the total monacolin K content [17].

A 2024 analysis of 27 supplements on the Italian market underscored this volatility, finding lactone-to-hydroxy acid ratios ranging from 2.5:1 to 114:1 [18]. As a result, certain supplements may be rich in the active form of monacolin K, whereas others contain minimal amounts, which may contribute to inconsistent absorption and clinical effects [18]. Although monacolin K is considered the main active component of red yeast rice, RYR contains a wide range of other bioactive metabolites and may influence lipid

metabolism differently. High-performance liquid chromatography (HPLC) and mass spectrometry have identified 14 distinct monacolin compounds in RYR, including monacolins K, J, L, M, and X, their hydroxy acid forms, dehydromonacolin K, dihydromonacolin L, and compactin [11]. The profile of these compounds largely depends on the yeast strains selected and the fermentation parameters applied during manufacturing [17].

A 2025 analysis found high variability in monacolins other than monacolin K across commercial products, representing 3% to 30% of total monacolin content, with an average of 23% [8]. The presence of multiple monacolin variants with varying potencies creates major challenges for both therapeutic consistency and medication safety [18].

1.3 Contamination of red yeast rice supplements

Beyond variability in potency, contamination has also been reported in RYR supplements and may represent an additional safety concern. During the fermentation of red yeast rice (RYR), Monascus species may produce citrinin (CTN), a toxic secondary metabolite. This occurs because citrinin and monacolin K, the cholesterol-lowering constituent of RYR, are generated through interconnected metabolic pathways [19]. Citrinin is classified by the European Food Safety Authority (EFSA) as a nephrotoxin and has also demonstrated hepatotoxic, embryotoxic, and fetotoxic effects in experimental studies. [20]. Despite extensive research, the molecular mechanisms responsible for toxicity associated with CTN remain incompletely understood. It is unclear whether its toxic and genotoxic effects are primarily mediated by oxidative stress or by increased mitochondrial membrane permeability [21].

In response to the toxicological risks associated with citrinin, the European Commission established a maximum level of 100 µg/kg for citrinin in food supplements based on red yeast rice (RYR) fermented with Monascus purpureus [22]. Regulatory restrictions have not fully eliminated the issue of CTN contamination in RYR products. All analyzed red yeast rice (RYR) supplements contained detectable levels of citrinin (100–25,100 µg/kg), with 36 out of 37 products exceeding the current EU maximum limit of 100 µg/kg [22]. Moreover, some products labeled as “citrinin-free” were found to contain this mycotoxin, raising concerns about quality control and the reliability of labeling claims [9]. Studies conducted in Asia revealed widespread CTN contamination, with a prevalence of 100% among tested samples in Malaysia [23] and contamination detected in up to 69% of raw materials examined in Taiwan [24]. In contrast, similar study conducted in Poland did not detect the presence of citrinin in the analyzed dietary supplements [20]. Collectively, these findings indicate that maintaining consistently low citrinin concentrations across commercial RYR supplements remains chal-

lenging, although contamination levels appear to vary substantially between countries and manufacturers.

More recently, attention has focused on another potential contaminant, puberulic acid (PA), a metabolite produced by Penicillium adametzioides that may be present during the RYR fermentation process. Several case reports and investigations have suggested that contamination of certain RYR supplements with puberulic acid may have contributed to cases of kidney injury [25-28]. However, the molecular mechanisms underlying the potential nephrotoxicity of PA remain poorly understood.

The main findings of studies investigating the quality, safety, and potential risks associated with red yeast rice (RYR) products are summarized in Table 1.

Table 1. Overview of studies evaluating the quality, safety, and potential risks associated with red yeast rice (RYR) products.

AUTHOR (YEAR)	STUDY DESIGN	COUNTRY	PRODUCT INVESTIGATED	PARTICIPANTS / CASES	MAIN SAFETY ISSUES	SUSPECTED TOXIC FACTOR	MAIN FINDING
Gordon et al. (2010) [11]	Analytical study	USA	Commercial RYR supplements (12 brands)	12 products	Product variability	Variable monacolin K content	Approximately 100-fold variation in monacolin concentrations despite similar labeling.
Avula et al. (2014) [12]	Analytical study	USA	Commercial RYR raw materials and dietary supplements	3 authentic RYR samples, 31 commercial RYR raw materials and 14 RYR dietary supplements.	Product variability; contamination	Variable monacolin K content; citrinin	Marked variability in monacolin content and detection of citrinin in commercial products.
Cohen et al. (2017) [13]	Analytical study	USA	Commercial RYR supplements	28 products	Product variability	Variable monacolin K content	Daily monacolin K intake differed by more than 120-fold; some products contained no detectable monacolin K.
Lachenmeier et al. (2012) [14]	Analytical study (nuclear magnetic resonance (NMR))	Germany	RYR food supplements	5 products	Product variability	Total statin content	Variability in total statin concentration; substantial inconsistency among products.
Vanhee et al. (2024) [16]	Quality-control study	Belgium	Online-purchased RYR supplements	35 products	Contamination; quality deficiencies	Citrinin; variable monacolins	Nearly all products contained citrinin, most exceeded the EU regulatory limit, and some labeled "citrinin-free" tested positive.
Rigillo et al. (2025) [8]	Comparative analytical study	Italy	Commercial RYR supplements	14 products	Variable composition	Diverse monacolin profile	Variability in monacolin composition beyond monacolin K
Samsudin, N.I.P., Abdullah, N. (2013) [23]	Analytical study	Malaysia	RYR dietary supplements	50 supplements	Mycotoxin contamination	Citrinin	CTN present in 100% of RYR dietary supplement Samples;

Liao CD et al. (2014) [24]	Analytical study	Taiwan	RYR (raw material), RYR dietary supplements, RYR processed products.	302 samples	Mycotoxin contamination	Citrinin	Citrinin contamination rates were 69.0% in raw red yeast rice, 35.1% in dietary supplements, and 5.7% in processed red yeast rice products.
Twarużek et al. (2021) [20]	Analytical study	Poland	RYR dietary supplements	15 commercial products	Mycotoxin contamination	Citrinin	None of the analyzed samples contained CIT above the established limit of detection
Allkanjari et al. (2022) [10]	Pharmacovigilance study	Italy	Herbal supplements for dyslipidemia (including RYR)	National ADR reports	Adverse reactions	Monacolins; product variability	RYR-containing supplements accounted for a substantial proportion of reported adverse reactions.
Shinzawa et al. (2025) [26]	Nationwide questionnaire survey	Japan	Beni-koji (RYR) tablets	Nationwide reported cases	Kidney injury	Suspected puberulic acid contamination	Characterized the nationwide outbreak of kidney injury associated with contaminated RYR products.
EFSA NDA Panel (2025) [18]	Scientific opinion	European Union	Monacolins from RYR	Comprehensive evidence review	Safety assessment	Monacolins	Concluded that safety concerns remain and supported continued regulatory restrictions on RYR monacolins.

2. Hepatic toxicity associated with red yeast rice supplementation

The primary bioactive constituent of RYR is monacolin K, which is chemically identical to the synthetic lovastatin [29]. Because they share the same mechanism of action, RYR also carries a similar risk profile to pharmaceutical statins, including the potential for statin-associated organ-specific toxicity [30]. Furthermore, the lack of standardization and labeling of monacolin content among commercially available red yeast rice products may contribute to unintentional exposure to doses exceeding established safety thresholds [31].

Current evidence from systematic reviews and meta-analyses suggests that hepatotoxicity associated with RYR use is rare. An analysis from 2021 of 855 reported adverse

events revealed that hepatic complications accounted for only 3% of all cases (n = 26), corresponding to an estimated incidence of 0.0011% among consumers exposed to red yeast rice (RYR) [32]. A large meta-analysis encompassing 53 randomized controlled trials and 8535 participants concluded that red yeast rice (RYR) supplementation was not associated with an increased overall risk of drug-induced liver injury (DILI) [33]. Another meta-analysis including data from 6663 patients found that the incidence of liver abnormalities was less than 5%, a rate comparable to that observed in placebo groups [34].

Although generally considered safe, several case reports have described acute DILI associated with RYR use, with clinical presentations ranging from mild elevations in liver enzymes to severe, potentially life-threatening hepatic injury [31, 33, 35, 36]. Reported cases include acute hepatitis, marked hypertransaminasemia, and mixed hepatocellular–cholestatic liver injury developing within one to six weeks after initiating RYR [31,35,36]. In all reported cases, discontinuation of RYR resulted in clinical improvement and gradual normalization of liver enzyme levels, supporting a probable causal relationship between RYR use and hepatotoxicity [31,35,36]. While cases of liver injury have been reported, available clinical trials and meta-analyses suggest that serious hepatic adverse events are uncommon. However, their true frequency and the relative contributions of monacolin K, product variability, and possible contaminants remain uncertain.

3. Muscular adverse effects related to red yeast rice supplementation

A meta-analysis of 53 randomized controlled trials evaluated the incidence of musculoskeletal disorders, non-musculoskeletal adverse events, and serious adverse events. According to the results, the daily administration of monacolin K was not associated with an increased risk of musculoskeletal disorders compared to control groups [33]. In another meta-analysis involving 6663 patients RYR supplements appeared to be well tolerated, with a low incidence of muscle-related side effects. The occurrence of these symptoms ranged from 0-23.8% in the RYR groups, compared with 0-36% in control groups [34]. There were no instances of rhabdomyolysis or myopathy in the included studies. No difference in the risk of developing myalgia was observed between the RYR and control groups [34].

An analysis of spontaneous reports from the Italian Surveillance System of Natural Health Products and the WHO-Vigibase indicated that the most commonly reported adverse reactions of RYR supplementation were musculoskeletal and connective tis-

sue disorders (36%), predominantly myalgia and elevations in creatine phosphokinase (CPK). While some patients showed mild CPK elevations, others reached levels up to ten times the normal concentration, with one documented case of rhabdomyolysis reaching a CPK level of 12245 U/L. Approximately 63% of these reactions occurred within the first two months of supplementation. Notably, some of the patients who experienced myopathy after RYR use had a previous history of statin intolerance [30]. A retrospective analysis of spontaneous reports collected by the Netherlands Pharmacovigilance Centre Lareb between 1991 and 2020 identified 94 cases of adverse drug reactions connected to use of the RYR [37]. The musculoskeletal and connective tissue disorders were the predominant adverse events, with 64 cases reported. Six cases of adverse reactions associated with RYR use were classified as serious, including two cases of rhabdomyolysis [37]. An analysis of FDA reporting systems conducted in 2023 demonstrated a very low incidence of reported rhabdomyolysis linked to RYR use [38]. Of the 43833 rhabdomyolysis cases recorded in the FDA Adverse Event Reporting System, only four were linked to RYR supplementation [38].

However, safety concerns have been raised, as several case reports have described muscle-related adverse effects associated with red yeast rice consumption, ranging from mild myalgia to severe rhabdomyolysis [39, 40, 41, 42]. Clinical evidence has linked RYR use to rhabdomyolysis, a severe pathophysiological process involving skeletal muscle breakdown and the release of intracellular contents into the circulation [43]. Patients typically present with generalized myalgia, proximal muscle weakness, and dark (tea-colored) urine [43]. Laboratory findings often show massive elevations in creatine kinase and myoglobin levels [43]. In severe cases, RYR supplementation-associated rhabdomyolysis has been complicated by acute kidney injury (AKI), life-threatening hyperkalemia, and, in rare instances, respiratory failure due to diaphragmatic muscle dysfunction [37].

4. Renal complications linked to red yeast rice use

The pathophysiology of renal injury appears to be mediated by mitochondrial impairment, oxidative stress, and inflammatory cytokines [44]. Insufficient tubular repair may result in fibrosis, ultimately resulting in the progression of chronic kidney disease [45]. Proximal tubular damage often manifests clinically as Fanconi syndrome (FS). This disorder is characterized by global dysfunction of solute transport in the proximal renal tubule, which may contribute to impaired reabsorption of substances such as glucose, amino acids, phosphate, uric acid, and bicarbonate [46]. These abnormalities are reflected in laboratory findings, including metabolic acidosis, hypophosphatemia,

hypokalemia, hypouricemia, and glucosuria [46]. FS is frequently accompanied by acute kidney injury (AKI) associated with a rapid decline in renal function [46].

In recent years, concerns have emerged regarding the potential kidney injury associated with intake of RYR supplements. In a meta-analysis involving 6663 patients reported the incidence of kidney injury was less than 5% in both the RYR and placebo groups. [34] Renal safety outcomes were also examined in another systematic literature review, which found that RYR use for 4–24 weeks was not associated with significant impairment of kidney function [47].

However, a large-scale survey of 192 patients with red yeast rice-associated kidney injury, 94.1% of patients were found to have reduced estimated glomerular filtration rate (eGFR <60 ml/min/1.73 m^2) [26]. Interestingly, creatine kinase levels were generally not elevated, implying that rhabdomyolysis was not the primary cause of AKI in most cases [26]. Laboratory findings were indicative of Fanconi syndrome. Histopathologically, tubulointerstitial lesions were observed in 50% of patients, while tubular necrosis was present in 32% of patients [26]. After withdrawal of supplement and initiation of treatment, improvement in parameters associated with Fanconi syndrome was observed. However, impaired renal function (eGFR <60 ml/min/1.73 m^2) persisted in 87% of patients at follow-up [26].

Emerging evidence from multiple case reports and case series, suggests an association between RYR consumption and renal impairment. These cases are mainly reported from Japan and are often linked to specific products [25, 27, 28, 42, 44, 48-65]. In many studies, renal biopsies have been crucial in defining the nature of the injury, which is predominantly localized to the proximal tubular cells [25, 28, 48, 51-54, 56-61, 63-66]. Histological examination frequently demonstrated features of acute tubular injury and necrosis, including loss of brush border, flattening of the tubular epithelium, tubular dilatation, thinning and cast formation, epithelial desquamation, or balloon formation [44, 49, 53, 57, 60, 62, 63, 66]. In some studies, severe vacuolar degeneration and mitochondrial fragmentation were observed within tubular cells [53, 59,63]. Beyond tubular damage, tubulointerstitial nephritis was frequently diagnosed, often involving inflammatory cell infiltration. While some cases showed mild or sporadic inflammation, others presented with significant interstitial fibrosis and tubular atrophy, indicating more chronic or severe damage [27, 44, 49, 51, 52, 54, 55, 57, 59, 62, 65]. A significant finding in two studies was the marked glycogen accumulation within the proximal tubular epithelium [51, 66]. Immunohistochemical analysis showed reduced expression of SGLT2, a transporter normally expressed in the S1 and S2 segments of the proximal tubules, while SGLT1 and GLUT2 expression remained unchanged [53]. These

findings indicate that tubular injury from red yeast rice supplementation predominantly may affect the S1/S2 segments, with reduced SGLT2 expression, as the primary cause of the observed glucosuria [53]. Kidney biopsy findings from two patients with RYR-associated nephrotoxicity demonstrated reduced expression of several proximal tubular transporters, including URAT1, Na^+/K^+-ATPase, and Na-Pi IIa [60]. This transporter downregulation is consistent with the biochemical features of acquired Fanconi syndrome and supports direct proximal tubular injury as the underlying mechanism of RYR-induced nephrotoxicity [60].

In clinical practice, renal injury associated with red yeast rice supplementation was not fully reversible in some cases, despite withdrawal of the supplement. The primary intervention in all reported cases was immediate discontinuation of the supplement [25, 28, 42, 44, 48-51, 53-56, 58-65]. Many patients also received corticosteroid therapy (e.g., prednisolone). However, the effectiveness of corticosteroid therapy in these cases remains unclear [26, 48, 49, 55, 56, 58, 60, 62, 64, 65]. In the most severe cases, hemodialysis or hemoperfusion was required [42, 49, 61].

The recovery of proximal tubular function appears to depend on the severity of kidney damage and the duration of exposure. In advanced cases, recovery may be incomplete, with irreversible interstitial fibrosis and progression to chronic kidney disease (CKD) [54, 63–65]. The main findings of studies investigating the clinical and pathological characteristics of red yeast rice-associated toxicity are summarized in Table 2.

Table 2. Clinical and pathological characteristics of red yeast rice-associated toxicity

TYPE OF TOXICITY	CLINICAL MANIFESTATIONS	LABORATORY FINDINGS	MORPHOLOGICAL FINDINGS	SUSPECTED CAUSE	KEY EVIDENCE
Hepatic	Asymptomatic elevation of liver enzymes, acute hepatitis, mixed hepatocellular–cholestatic injury	↑ALT, ↑AST, occasionally ↑bilirubin and ALP	Histology consistent with DILI (when available)	Monacolin K exposure (lovastatin analogue); possible contribution of variable monacolin content and contaminants	Systematic reviews/meta-analyses [33,34]; case reports [31,35,36]
Muscular	Myalgia, muscle weakness, myopathy, rhabdomyolysis; severe cases complicated by AKI, hyperkalemia or respiratory failure	↑CK, ↑myoglobin	Skeletal muscle rhabdomyolysis	Monacolin K exposure (statin-like inhibition of HMG-CoA reductase), particularly in statin-intolerant individuals	Systematic reviews/meta-analyses [33,34,43]; pharmacovigilance [30,37,38]; case reports [39-42]
Renal	AKI, Fanconi syndrome, glucosuria, electrolyte abnormalities; incomplete renal recovery in some patients	↓eGFR, glucosuria, hypophosphatemia, hypokalemia, hypouricemia, metabolic acidosis	Acute tubular injury/necrosis, proximal tubular injury, tubulointerstitial nephritis, tubular atrophy, interstitial fibrosis, mitochondrial abnormalities, glycogen accumulation, reduced SGLT2, URAT1, Na^+/K^+-ATPase and Na-Pi IIa expression	Possible contaminants in specific RYR products (e.g., puberulic acid, citrinin) and other unidentified nephrotoxic components	Systematic reviews/Meta-analyses [34]; observational study [26]; case series/case reports [25,27,28,42,44,48-66]

DISCUSSION

The use of functional foods and nutraceuticals has gained significant attention as a preventive strategy to improve health and manage chronic diseases. Many consumers perceive dietary supplements as healthier and safer alternatives to conventional medications, often underestimating their potential risks. Red yeast rice supplements are widely available without prescription in pharmacies, health food stores, and online retail platforms, which may contribute to unsupervised consumption and delayed recognition of supplement-related adverse events. In addition, limited awareness of the safety profile of RYR among both patients and healthcare professionals may delay the diagnosis of supplement-associated toxicity and complicate accurate adverse event reporting.

Different national regulatory systems have established varying requirements regarding monacolin K content, contaminant limits, and health claims. As a result, manufacturers may not be obligated to standardize monacolin K content or provide detailed information regarding the concentration and bioavailability of active compounds [11]. In the

European Union, under Commission Regulation (EU) 2022/860, it is required that the label indicate the number of individual portions corresponding to the maximum daily intake, and include a warning not to consume a daily intake of 3 mg or more of monacolins from RYR without a requirement to differentiate the active hydroxy acid form of monacolin K [67].

In accordance with EU regulatory frameworks, RYR supplements are contraindicated in pregnancy and lactation, in individuals under 18 or over 70 years of age, and in patients receiving concomitant statin therapy. Moreover, most clinical trials evaluating RYR are underpowered to detect rare or long-term adverse events, supporting caution regarding unsupervised over-the-counter use [67]. In the United States, the Food and Drug Administration (FDA) classifies red yeast rice (RYR) products containing more than trace amounts of monacolin K (MK) as unapproved new drugs, given that lovastatin is an approved pharmaceutical agent. Consequently, such products cannot be legally marketed with reference to specific MK content. This regulatory constraint has resulted in a market characterized by substantial variability in product potency, while limiting manufacturers' ability to provide transparent information regarding the dose of the active constituent [11]. Persistent gaps remain in the regulation of purity and contaminant control. Maximum allowable concentrations for citrinin, a nephrotoxic mycotoxin, are set at 100 μg/kg under EU Regulation 2023/915 and 50 μg/kg under China's QB/T 2847-2023, whereas regulatory guidance in the United States is non-binding [11, 67, 68]. Furthermore, internationally unified requirements for screening synthetic statin adulteration and regulating other potentially cytotoxic metabolites are lacking. Collectively, divergent regulatory frameworks across major global markets impede the standardization of RYR products. In the absence of a unified international standard harmonizing potency assessment, contaminant limits, and safety protocols, product heterogeneity is likely to persist, alongside continued uncertainty regarding consumer safety [11].

The lack of standardization among RYR dietary supplements presents a significant challenge for clinical practice, as substantial differences between labeled and actual monacolin content impair both therapeutic efficacy and patient safety. While red yeast rice (RYR) is commonly perceived as a natural alternative to statin therapy, our findings and the reviewed literature suggest that the composition of commercial products is highly unpredictable, with marked variability in monacolin content, molecular form, and overall potency compared with the preparations used in clinical research [9]. As a result, consumers cannot reliably determine whether they are receiving an amount comparable to a low-dose statin or a dose similar to that of a prescription medication. This

variability may result in unintentional pharmacological overdosing, when consumers receive pharmacologically statin-equivalent doses exceeding those anticipated from label information.

In addition to variability in composition, safety concerns are heightened by the potential presence of contaminants. Citrinin, a nephrotoxic and hepatotoxic mycotoxin produced during fermentation, has been detected in some RYR products, along with other contaminants such as puberulic acid (PA) [19]. Although these compounds have been proposed as potential contributors to RYR-associated renal toxicity, their individual roles have not been definitively established.

PA has been suggested as one possible factor involved in tubular injury. Experimental evidence indicates that PA may directly contribute to tubular cell injury, potentially through dysfunction of the tubular GLUT2 transporter resulting in glycogen accumulation [66]. This proposed mechanism resembles Fanconi–Bickel syndrome, a glycogen storage disorder caused by GLUT2 deficiency which ultimately results in proximal tubular dysfunction and Fanconi syndrome [66]. Consistent with this hypothesis, electron microscopy of biopsies from patients exposed to red yeast rice supplements demonstrated marked glycogen accumulation in proximal tubular cells [66].

Animal studies also support a potential nephrotoxic effect of PA. In rats, the kidney was identified as the primary target organ for PA-associated toxicity [69]. After administration of synthesized PA significant nephrotoxicity was observed at 10 mg/kg/day in males and 3 mg/kg/day in females, suggesting sex-related differences in sensitivity [69]. In these groups, elevated serum creatinine levels and increased urinary glucose were also observed [69]. While most PA-associated nephrotoxicity in rats' kidneys appeared to be reversible upon discontinuation of PA, prolonged or severe injury may progress to focal interstitial fibrosis, a marker of chronic kidney disease [69].

Other contaminants have also been proposed as possible contributors. Silica nanoparticles used as tablet additives have also been suggested as potential contributors to toxicity. In one study a kidney biopsy was performed in a patient who developed acute kidney injury and Fanconi syndrome after intake of RYR supplements. Histopathological examination demonstrated proximal tubular necrosis and vacuolization along with silicon-containing nanoparticles within the endosomes and lysosomes of proximal tubules in AKI patient [70].

Previous animal studies have suggested that reabsorbed silica nanoparticles might increase mitochondria ROS production and trigger oxidative stress, potentially con-

tributing to impaired kidney and liver functions [70,71]. In animal models, uninephrectomized rats supplemented with red yeast rice supplements exhibited significant nanoparticle accumulation and tubular damage [72]. However, no evident histological signs of tubular damage were found in normal rats. These findings suggest that individuals with pre-existing conditions that impair renal function, such as hypertension, diabetes, or glomerular lesions may be at increased risk of developing AKI associated with nanoparticles, as in uninephrectomized rats model [72]. However, the specific role of silica nanoparticles in RYR-related kidney injury has not been clearly defined. Taken together, the available experimental and clinical evidence raises the possibility that different contaminants may contribute to supplement-related kidney injury.

Many adverse effects reported with RYR supplementation resemble those observed during statin therapy, particularly hepatotoxicity, myopathy and nephrotoxicity. While randomized controlled trials and meta-analyses generally report low incidences of severe adverse events, numerous case reports and pharmacovigilance databases document clinically significant liver injury, rhabdomyolysis, and acute kidney injury associated with RYR use.

Limitations

Despite the low reported incidence of severe adverse events, the assessment of RYR safety remains challenging due to several limitations of the available data. The evidence on RYR-related adverse effects consists of case reports, case series, and spontaneous pharmacovigilance reports, which cannot determine incidence rates, and do not adequately account for confounding factors such as the use of other medications, underlying diseases, and product differences. Moreover, there is a significant variability across studies regarding follow-up period, supplement composition, monacolin K dosage, manufacturing methods, and outcome definitions. This variability complicates direct comparisons and limits the ability to draw definitive conclusions regarding long-term safety. The body of evidence on renal toxicity is particularly heterogeneous, with most cases originating from Japan and linked to specific products, which may limit the representativeness of these findings. Furthermore, the relative contributions of monacolin K, citrinin, puberulic acid, and excipients such as silica nanoparticles to individual adverse events remain incompletely characterized, and the precise molecular mechanisms underlying RYR-associated renal tubular injury require further elucidation in experimental models and clinical studies. Overall, the current evidence highlights the need for large-scale prospective studies and randomized controlled trials with longer

follow-up periods to evaluate long-term outcomes, as well as characterize the incidence of adverse events and identify patient populations at greatest risk.

CONCLUSIONS

The available evidence indicates that red yeast rice supplements may be associated with hepatic, muscular, and renal adverse effects. Severe complications appear to be uncommon, but their true frequency remains uncertain because the available data are heterogeneous and often based on case reports, case series, and pharmacovigilance reports. The main safety concern is the marked variability in monacolin K content, product composition, and contamination, which makes individual exposure difficult to predict. The relative contribution of monacolin K and specific contaminants to reported toxicity also remains unclear.

Improved product standardization, clearer labeling, stronger post-marketing surveillance, and greater awareness among healthcare professionals and consumers are needed to improve the safety of red yeast rice supplements.

DISCLOSURE

Author contributions

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All authors have read and approved the final version of the manuscript.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

Use of artificial intelligence

Artificial intelligence was used for language editing and stylistic correction.

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