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DRUG SAFETY

Adverse reactions to dietary supplements containing red yeast rice: assessment of cases from the Italian surveillance system

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Keywords adverse reactions, dietary supplements, monacolin, *Monascus purpureus*, red yeast rice, statins

AIMS

Red yeast rice (RYR) is contained in dietary supplements for patients with dyslipidemia. RYR supplements contain monacolin K, which is chemically identical to lovastatin, a licensed drug with a well-known risk profile. We aim to describe the safety profile of RYR by analysing spontaneous reports of suspected adverse reactions (ARs).

METHODS

Within the Italian Surveillance System of Natural Health Products, suspected ARs were collected and evaluated by a multidisciplinary group of experts to assess causality using the WHO-UMC system or the CIOMS/RUCAM score, for hepatic reactions. The public version of the WHO-Vigibase was also queried.

RESULTS

From April 2002 to September 2015, out of 1261 total reports, 52 reports concerning 55 ARs to RYR dietary supplements were collected. ARs consisted in myalgia and/or increase in creatine phosphokinase (19), rhabdomyolysis (1), liver injury (10), gastrointestinal reactions (12), cutaneous reactions (9) and other reactions (4). Women were involved in 70% of cases. In 13 cases, the reaction required hospitalization, and 28 patients were taking other medications. Dechallenge was positive in 40 reactions (73%), rechallenge was positive in 7. Causality resulted as *certain* (1), *probable* (31, 56%), *possible* (18, 34%), *unlikely* (3) or *unassessable* (2). Similar distribution emerged from the WHO-Vigibase.

CONCLUSIONS

The potential safety signals of myopathies and liver injury raise the hypothesis that the safety profile of RYR is similar to that of statins. Continuous monitoring of dietary supplements should be promoted to finally characterize their risk profile, thus supporting regulatory bodies for appropriate actions.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Red yeast rice (RYR) is a dietary supplement used in patients with dyslipidemia. It contains monacolin K, which, being identical to lovastatin, is associated with the same risks.
- RYR is often used by statin-intolerant patients, although there are no studies testing its safety profile as compared to statins.

WHAT THIS STUDY ADDS

- Our case-by-case assessment highlighted myopathies and liver injury as potential safety issues, thus suggesting that the safety profile of RYR is similar to statins.
- The proportion of serious reports (27%), the relatively rapid time to onset and the lack of concomitant/predisposing medications in several cases call for continuous monitoring of RYR-containing food supplements to define their risk profile.

Tables of Links

TARGETS	
Enzymes [2]	
Angiotensin-converting enzyme	HMG-CoA reductase

LIGANDS	
atorvastatin	pantoprazole
caffeine	resveratrol
lovastatin	venlafaxine
omeprazole	

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Introduction

Dietary supplements, often containing herbal substances, are widely used in Western countries. In Europe, as well as in the United States, the regulatory status of dietary supplements does not allow the claim of therapeutic properties. Thus, they are marketed as self-medication products promoted to maintain and improve well-being and overall health. The general perception of their safety by the public, due to their 'natural' components, induces an under-evaluation of their risk profile. However, a recent survey estimated that 23 000 visits per year to emergency department in the United States for adverse reactions (ARs) were related to dietary supplements [3]. Several case reports and general articles on ARs to these products have been published [4–7].

Red yeast rice (RYR), also known as 'red Koji' or 'Hongqu', is a remedy belonging to Traditional Chinese Medicine, largely used nowadays as dietary supplement in Western countries. It is produced by fermenting steamed rice with a food fungus of the *Monascus* genus, mainly *Monascus purpureus* (Aspergillaceae family); during fermentation the naturally produced pigments give the characteristic red colour to the rice and monacolins are produced. As part of the Chinese diet, red Koji is used as food additive to increase the colour of meat, fish and soybean products; moreover, it is recognized as a folk medicine for improving food digestion and blood circulation [8].

Several studies have shown the lipid-lowering effects of RYR in humans, especially in comparison with placebo in patients intolerant to statins [9–13], although only a minority of trials compared head-to-head RYR with statins or ezetimibe [14–16], and some quality issues (e.g., allocation concealment and blinding) have been raised [17]. These properties of RYR are due to its monacolins content, a family of naturally occurring substances that inhibit hydroxymethylglutaryl-coenzyme A reductase, the rate-limiting step in cholesterol synthesis. Monacolins content in RYR is usually around 0.4% w/w; of this about 90% consists of monacolin K (also known as mevinolin) which is chemically identical to lovastatin. Other chemical components of RYR are fatty acids and the pigments monascidin A, ankaflavin, monascorubrine and monascorubramine. A further pigment citrinin, a nephrotoxic mycotoxin, can be produced by some strains of *Monascus* [8, 18, 19]. A dose of RYR containing about 5–7 mg of monacolin K is considered as effective in lowering cholesterol as 20–40 mg of pure lovastatin, probably owing to the presence of other active monacolins or to an increased bioavailability of lovastatin when given as RYR [12, 20, 21].

RYR is considered well tolerated and is often proposed as an alternative therapy in statin-intolerant patients [9–13]. It should be acknowledged that clinical trials are usually underpowered and not fully representative to detect ARs, as demonstrated by a recent systematic review with meta-analysis of 20 studies, which concluded that the safety is uncertain due to different methodological issues of included studies, likely to result in underestimation of ARs [22]. Nevertheless, different suspected ARs following RYR consumption have been reported, mainly consisting in myopathies and liver injury [23–29]. Notably, between 2009 and 2013, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) received 30 reports of ARs potentially associated with the consumption of food supplements containing RYR. Of these, 25 were fully assessed for causality: in 12 cases

causality was very likely or likely, and concerned predominantly muscle and liver damage [30]. Notably, the identification of potential risks of these products is challenging because food supplements are not usually registered in pharmacovigilance databases where suspected adverse drug reactions are collected. Therefore, specific spontaneous reporting systems represent a key source to promptly identify potential safety signals.

In this context, the present study analysed the suspected ARs induced by RYR products, collected within the Italian Surveillance System of Natural Health Products from April 2002 (its inception) to September 2015, keeping in mind that well-documented anecdotal reports (and case series) can provide convincing evidence of a causal association [31].

Methods

Data source

In 2002 the Italian Surveillance System of Natural Health Products was set up to collect adverse reactions to natural products. The system, coordinated by the Italian National Institute of Health, born as a pilot project, has been a national surveillance system since 2012; it operates separately from the Italian pharmacovigilance network, which collects spontaneous reports of suspected ARs to registered medicines.

The surveillance system consists in the collection and evaluation of spontaneous reports of suspected ARs that occurred after the consumption/administration of: dietary supplements; herbal preparations and galenic formulations; other herbal preparations not included in the former paragraphs and other preparations of natural origin but non-plant (e.g., royal jelly or propolis, snake extracts); and homeopathic products.

Reports can be sent from anybody observing a suspected adverse reaction associated with these products, by an *ad hoc* form available on the websites of the involved institutions (National Institute of Health, Ministry of Health, Italian Medicines Agency). All reports are registered in a database at the National Institute of Health. Labels of the products are provided by the Ministry of Health. Diagnoses are coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 4). For serious cases, follow-up of patients is obtained from the hospital physician. The reporting form is provided in Supplementary material 1.

As an aid to better characterize the reporting profile from an international perspective, we queried the public version of the WHO-Vigibase (www.vigiaccess.org), given its (virtually worldwide) catchment area in terms of adverse drug reactions (ADRs). The Italian Surveillance System of Natural Health Products does not currently submit reports to WHO UMC, although there is the intention to share these data in the near future. For this reason, no duplicates are likely to exist in our sample.

Causality assessment

A Scientific Committee, including experts in toxicology, pharmacology, pharmacognosy, phytotherapy, botany, paediatrics and homeopathy, was appointed for the evaluation of the reports and the detection of risk signals. A Steering Committee with experts in pharmacovigilance, pharmacoepidemiology and regulatory aspects supports the activities of the Scientific Committee.

The causality assessment is performed using an evaluation scale adapted from the World Health Organization (WHO) causality categories reported in the WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems [32]. Feedback is provided to the reporter. When needed and possible, the product is acquired and analysed at the National Institute of Health. Among the possible analyses, search for contaminants, adulterants or undeclared drugs can be performed.

In this study, all reports associated with RYR products were extracted through a search strategy using active substances or specific product names and analysed according to the WHO-UMC system for standardized case causality assessment [33]. For hepatic reactions, causality assessment was performed, when possible, using the CIOMS/RUCAM score, a quantitative, liver-specific, validated scale for hepatotoxicity, used in the assessment of both herb- and drug-induced liver injury (DILI) [34]. The evaluation was performed by two independent authors who, in case of disagreement, discussed the case to reach consensus.

As suspected products contained other components in addition to RYR, the causality assessment concerned the whole supplement, not just its single components. Nevertheless, the possible role of the other components in the reaction has been considered and discussed. According to the WHO, an ADR was considered as 'serious' when it resulted in death, or was life-threatening, or required hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity [35].

Results

Data overview

From April 2002 to September 2015, out of a total of 1261 reports, 52 (4.1%) concerning 55 suspected ARs to dietary supplements containing RYR were collected within the Italian Surveillance System of Natural Products. Three cases (namely *1*, *2* and *3*) have been published previously [23]; however, they are included, in order to give a complete picture of the ARs collected within the system. The reports concerned 37 women (71%) and 14 men (in one case gender was not reported), aged between 35 and 85 years (mean: 64 years); in two cases age was not reported. The most frequently reported supplement was Armolipid plus® (29 cases, 55%), followed by Colestat® (5 cases, 10%). These products contained other components besides RYR, mainly policosanols (as such or as *Saccharum officinarum* extract), coenzyme Q_{10}, folic acid and astaxanthin; some supplements contained green tea, resveratrol, fish oil, vitamins E, B_6 and B_{12} and *Berberis aristata* dry extract (in Armolipid plus® and Colest 500®): the exact composition is reported in Table 1. The reason for use of RYR preparations, as indicated on the reporting forms, was hypercholesterolemia in all cases. The total daily dose of monacolin K of the food supplements involved was 3 mg in all but four reports.

Table 1

Adverse reactions to red yeast rice

Case n.	Age/Sex	Red yeast rice related product	Adverse reaction	Latency (day)/ Duration of treatment (day)	Laboratory data[a]	Seriousness	Other medications/ Predisposing conditions	Outcome Dechallenge/ Rechallenge	Causality assessment[b]
Musculoskeletal and connective tissue disorders									
1	53/F	Colestat®	CPK increased	120/120	CPK 288	NR	None/None	Recovered Positive/Not done	Probable
2	49/M	Statinat®	CPK increased	60/60	CPK 386	NR	None/None	Recovered Positive/Not done	Probable
3	60/M	Armolipid plus®	CPK increased	NR/165	CPK 356	NR	None/Statins intolerance	NRNR/Not done	Possible
4	53/F	Armolipid plus®	Generalised muscle aches	46/97	CPK 185	NR	Oestradiol transdermal patch/None	Recovered Positive/Not done	Possible
5	80/F	Colesterase®	CPK increased	20/20	CPK 206	NR	Lansoprazole, ramipril, carvedilol, cardioaspirin, nitroglycerin/None	Recovered Positive/Not done	Possible
6	65/M	Red yeast rice	Muscular pain	90/90	CPK increased	NR	None/Statins intolerance	Recovered with sequelae Positive/Not done	Probable
7	63/F	Colesterase®	CPK increased	77/77	CPK 177	NR	Ramipril, tiotropium bromide, mianserin, torsemide, salmeterol, fluticasone, theophylline, amlodipine/NR	Recovered Positive/Not done	Possible
8	65/F	Armolipid®	Cramps and myalgia of lower extremities	17/31	None	Not serious	None/None	Recovered NR/NR	Probable
9	67/F	Armolipid plus®	CPK increased, myopathy, asthenia	24/31	CPK about 1520	Not serious	Levothyroxine, venlafaxine, acetylsalycilic acid/ Basal increase of CPK (about 500 before taking the supplement); previous statins myopathy	Recovered Positive/Not done	Possible
10	55/F	Colestat®	Myalgia	18/18	CPK 202	NR	Levothyroxine, nebivolol, calcitriol/None	Recovered Positive/Not done	Probable
11	45/F	Armolipid plus®	Nocturnal leg muscle cramps	14/24	CPK and electrolytes: normal	NR	None/ None	Recovered Positive/Not done	Probable
12	70/F	Armolipid plus®	Myalgia, CPK increased	90/90	CPK 439	Not serious	Venlafaxine, levothyroxine, bisoprolol, levosulpiride/ Statins intolerance	Improvement Positive/Not done	Possible

(*Continues*)

Table 1

(Continued)

Case n.	Age/Sex	Red yeast rice related product	Adverse reaction	Latency (day)/ Duration of treatment (day)	Laboratory data[a]	Seriousness	Other medications/ Predisposing conditions	Outcome Dechallenge/ Rechallenge	Causality assessment[b]
13	NR/F	Armolipid plus®	CPK increased	>365/>365	Blood tests	NR	NR/ Tendency to elevation of CPK after taking statins	NRNR/Not done	Possible
14	68/F	Armolipid plus®	Localised muscle pain	52/62	CPK 732	NR	Calcifediol/None	Recovered Positive/Not done	Probable
15	48/NR	Armolipid plus®	Rhabdomyolysis	120/120	CPK 12.245, AST 287 (at admission).CPK 809, AST 97 (5 days after discontinuation)	Hospitalization	None/Rhabdomyolysis after taking simvastatin	Recovered Positive/Not done	Certain
16	57/F	Armolipid plus®	CPK increased	60/60	CPK 10 upper normal levels	Not serious	None/None	Recovered Positive/Not done	Probable
17	57/F	Ezimega plus®	Muscle ache, muscle fasciculation, muscle cramps	9/9	Not done	Not serious	Valsartan, nebivolol/None	Recovered Positive/Not done	Probable
18	69/F	Armolipid plus®	Myalgia of lower extremities	25/25	NR	Not serious	Moexipril + hydrochlorothiazide/NR	Recovered Positive/Not done	Possible
19	59/F	Normolip 5®	Myalgia	210/210	CPK increase	Not serious	None/None	Recovered Positive/Not done	Probable
20	45/F	Armolipid plus®	Myalgia in the legs	54/54	NR	Not serious	None/None	Recovered Positive/Not done	Probable
Hepatobiliary disorders									
21	68/F	Armolipid plus®	Pancreas and hepatic enzymes increased	About two weeks/ about two weeks	AST 386, ALT 991, γ-GT 525, amylase 99, ALP 275, LDH 624	Not serious	None/None	Recovered Positive/Not done	Probable
22	51/M	Policol 400®	Acute cholestatic hepatitis	23/28	AST 155, ALT 315, γ-GT 1243, ALP 351, TB 13, ferritin 833	Hospitalization	Olivis, Nuovo 3D, Omega 3 (fish oil)/None	Recovered Positive/Not done	Probable
23	42/F	Armolipid plus®	Acute hepatitis	30/31	AST > 1500; ALT 361; LDH 4284	Hospitalization	Atenolol, levothyroxine, potassium canrenoate/None	NR Positive/Not done	Probable
24	35/M	Armolipid plus®	Toxic acute hepatitis	About 60/about 60	AST 2416 ALT 3566 ALP 394 γ-GT 372 Liver biopsy	Hospitalization	None/None	Recovered Positive/Not done	Probable

(*Continues*)

Table 1

(Continued)

Case n.	Age/Sex	Red yeast rice related product	Adverse reaction	Latency (day)/ Duration of treatment (day)	Laboratory data[a]	Seriousness	Other medications/ Predisposing conditions	Outcome Dechallenge/ Rechallenge	Causality assessment[b]
25	36/M	Colest 500®	Hepatitis acute	76/76	ALT 1123, AST 984 TB 1.33 Viral serology: negative Liver ultrasound: steatosis	Hospitalization	Enervit Omega 3/ Modest alcohol abuse	Recovered Positive/Not done	Probable
26	49/F	Armolipid plus®	Acute hepatitis, heartburn, hepigastralgia	50/50	AST 1930ALT 1613 TB normal viral and autoimmune serology, hepatobiliar ultrasound: negative; rhabdomyolysis: excluded	Hospitalization	None/None	Recovered Positive/Not done	Probable
27	68/F	Armolipid plus®	Transaminases increased	About 365/about 365	ALT 168AST 87 TB 0.5 γ-GT 53 ALP 109 Viral serology: negative	Not serious	Levothyroxine, ursodeoxycholic acid/Statins intolerance, gallstones	Recovered Positive/Not done	Possible
16	57/F	Armolipid plus®	AST increased	60/60	AST (2 upper normal levels). Values reduced one week after discontinuation	Not serious	None/None	Recovered Positive/Not done	Probable
28	75/F	COLEX-MU®	Other disorders of liver	NR/NR	AST 229 ALT 392 TB 3.37	Hospitalization	Indacaterol, mometasone furoate/None	Unknown (spontaneous discharge) NR/NR	Unassessable
29	53/M	Armolipid plus®	Transaminases increased	Not available/Not available	ALT 85AST 135	Not serious	NR/NR	Recovered Positive/Reaction recurred without rechallenge	Unlikely
Gastrointestinal disorders									
30	67/F	Colestat®	Headache, nausea	2/2	None	Not serious	None/None	Persistent reaction Positive/Not done	Possible
31	47/F	Armolipid®	Abdominal pain, meteorism, diarrhoea	2/2	NR	Not serious	None/None	Persistent reaction Positive/Not done	Possible
32	32/M	Colestat®	Nausea	28/28	None	Not serious	Gloria Vis® (*Vitis vinifera*)/None	Not available Not available/Not done	Unassessable

(*Continues*)

Table 1

(Continued)

Case n.	Age/Sex	Red yeast rice related product	Adverse reaction	Latency (day)/ Duration of treatment (day)	Laboratory data[a]	Seriousness	Other medications/ Predisposing conditions	Outcome Dechallenge/ Rechallenge	Causality assessment[b]
33	85/F	Armolipid plus®	Digestion impaired	25/25	NR	Not serious	Amyloride, hydrochlorothiazide/NR	Improvement Positive/Not done	Possible
34	55/M	Armolipid plus®	Nausea, vomiting	1/1	NR	Serious	Citalopram/None	Improvement Positive/Positive	Probable
35	36/M	Armolipid plus®	Mucous and hemorrhagic diarrhoea	11/11	NR	Not serious	Ramipril, benzodiazepines/None	Recovered Positive/Positive	Probable
36	50/M	Armolipid plus®	Diarrhoea, griping abdominal	NR/NR	NR	Not serious	Olmesarta n medoxomil, benzodiazepines/None	Recovered Positive/Positive	Probable
37	68/F	Armolipid plus®	Dyspepsia, nausea, vomiting	1/2	NR	Not serious	None/None	Recovered Positive/Positive	Probable
38	43/F	Armolipid plus®	Vomiting	26/26	Hematic glucose, γ-GT, lipase, kalium, hemoglobin, birilubin, creatinin	Hospitalization	None/None	Recovered Positive/Positive	Probable
39	78/M	Armolipid plus®	Nausea, dyspepsia	24/29	None	Not serious	None/None	Recovered Positive/Not done	Probable
40	75/F	Esterol 3®	Retrosternal burning	1/2	NR	Not serious	Warfarin, ramipril, bisoprolol, levothyroxine, amiodarone, eplerenone/NR	Recovered Positive/Not done	Possible
18	69/F	Armolipid plus®	Abdominal pain, chest pain	25/25	NR	Not serious	Moexipril + hydrochlorothiazide/NR	Recovered Positive/Not done	Possible
Skin and subcutaneous tissue disorders									
41	57/F	Statinat®	*Pemphigus vulgaris*	58/43	Anti-DSG1 and anti-DSG3 antibodies; biopsy	Hospitalization	None/*Pemphigus vulgaris* eight years before	Recovered after pharmacological therapy Not applicable (Reaction occurred after discontinuation of treatment)/Not done	Unlikely
42	63/F	Armolipid plus®	Eruption of limbs, wheals	<1/3	None	Not serious	Lormetazepam/None	Recovered with sequelae Positive/Not done	Probable
43	75/F	Armolipid plus®	Severe urticaria, rash, oedema of lips	NR/NR	NR	Hospitalization	Cardioaspirin, amiloride + hydrochlorothiazide,	NRPositive/Not done	Unlikely

(*Continues*)

Table 1

(Continued)

Case n.	Age/Sex	Red yeast rice related product	Adverse reaction	Latency (day)/ Duration of treatment (day)	Laboratory data[a]	Seriousness	Other medications/ Predisposing conditions	Outcome Dechallenge/ Rechallenge	Causality assessment[b]
							triazolam, metoprolol, lansoprazole, risedronate, flu vaccine five days before onset of reaction/ None		
44	42/M	Armolipid plus®	Pruritus cutaneous	4/4	NR	Not serious	None/None	Recovered Positive/Not done	Probable
45	66/F	Colestat®	Generalized urticaria and itching	4/4	NR	Hospitalization	Levothyroxine, atenolol, calcium + colecalciferol, amiloride + hydrochlorothiazide, risedronate, cyclobenzaprine, serratiopeptidase/None	Recovered Positive/Not done	Possible
46	NR/F	Armolipid plus®	Skin erythema desquamative, thrombosis	2/2	NR	NR	None/None	NR Positive/Not done	Probable
5	80/F	Colesterase®	Urticaria	20/20	None	NR	Lansoprazole, ramipril, carvedilol, cardioaspirin, nitroglycerin/None	Recovered Positive/Not done	Possible
47	80/F	Armolipid plus®	Generalized urticaria	2/2	None	Not serious	Enalapril + hydrochlorothiazide/None	Improvement Positive/Not done	Possible
48	NR/F	Altacol®	Drug eruption with eosinophilia and sistemi symptoms (DRESS)	10/8	HB 9 AST 60 γ-GT 131 Eosinophil granulocytes 15.8% Platelets 58 000 IGM: positive for *Herpes simplex*	Hospitalization	Pantoprazole, levothyroxine/None	Recovered Positive/Not done	Possible
Other miscellaneous reactions									
49	78/F	Armolipid plus®	INR increased	71/78	INR 3,70	Not serious	Warfarin, calcium, calcitriol/None	Recovered Not done, warfarin dose was reduced/Not done	Probable
50	64/M	Arkosterol®	Nausea , vertigo, hazy vision	2/2	None	Not serious	None/None	Recovered Positive/Positive	Probable

(*Continues*)

Table 1

(Continued)

Case n.	Age/Sex	Red yeast rice related product	Adverse reaction	Latency (day)/ Duration of treatment (day)	Laboratory data[a]	Seriousness	Other medications/ Predisposing conditions	Outcome Dechallenge/ Rechallenge	Causality assessment[b]
51	73/F	Riscol 5®	Tingling of extremity	7/7	NR	Not serious	None/None	NR Positive/Not done	Probable
52	70/F	Fisiostatin®	Tachycardia	2/7	NR	Hospitalization	None/None	NR Positive/Not done	Probable

[a]CPK (creatine phosphokinase), ALT (alanine aminotransferase), AST (aspartate aminotransferase), ALP (alkaline phosphatase), γ-GT (gamma glutamyl transpeptidase), LDH (lactate dehydrogenase) and amylase values are expressed in U/L; TB (total bilirubin) values are expressed in mg dl^{-1}; HB (hemoglobin) value is expressed in g dl^{-1}; ferrtin value is expressed in μg l^{-1}

[b]Causality assessment was performed using WHO scale in all cases except for cases *26* and *27* for which the CIOMS/RUCAM score was applied

NR, Not reported; DSG, desmoglein;

Composition of red yeast rice supplements, except vehicles (dose, when reported, refers to one tablet):

Altacol® (Konpharma): red yeast rice (1.5% monacolin), policosanols, resveratrol, coenzyme Q_{10}, folic acid, vitamin E, fish oil.

Arkosterol® (Arkopharma): red yeast rice (*Monascus purpureus*), sugar cane (*Saccharum officinarum*) dry extract (90% policosanols).

Armolipid® (Rottapharm): red yeast rice (monacolin 3 mg), microalgae dry extract (astaxanthin 0.5 mg), *Saccharum officina rum* (10 mg policosanol), folic acid, coenzyme Q_{10}.

Armolipid plus® (Rottapharm): *Berberis aristata* dry extract (berberin 500 mg), red yeast rice (monacolin 3 mg), microalgae (*Hoematococcus pluvialis*) dry extract (astaxanthin 0.5 mg), *Saccharum officinarum* dry extract (10 mg policosanol), folic acid, coenzyme Q_{10}.

Colest 500® (OTI): *Berberis aristata* dry extract (berberin 500 mg day^{-1}), red yeast rice (monacolin K 3 mg day^{-1}), policosanols 10 mg day^{-1}, astaxanthin (5 mg day^{-1}), folic acid, coenzyme Q10, vitamin B_{12}.

Colestat® (Difass Interational S.rl.): *Monascus purpureus* dry extract (1.5% monacolin K), linear aliphatic alcohols (60% octacosanol), *Camellia sinensis* dry extract (40% poliphenols), vitamin E, vitamin B_6, vitamin B_{12}, folic acid, niacin.

Colesterase® (WP S.r.l.): red yeast rice, policosanols, vitamin E

Colex-mu® (MU S.r.l.): *Monascus ruber* dry extract (1.5% monacolin); *Cynara scolymus* (artichoke); *Plantago ovata* (ispagul), alga klamath.

Ezimega plus® (Bio Futura Pharma): red yeast rice dry extract (3% monacolin), policosanols from *Saccharum officinarum*, resveratrol, fish oil (EPA and DHA), coenzyme Q_{10}, vitamins B_6 and B_{12}, folic acid.

Esterol 3® (Laborest Italia): Omega 3 fatty acids (EPA-DHA), *Monascus purpureus*, quercetin, astaxanthin, vitamina D.

Fisiostatin® (Phyto Garda S.r.l): green tea (*Camellia sinensis*) dry extract (98% polyphenols of which 40% EGCG), red yeast rice (*Monascus purpureus*) (3% monakolin), Coenzyme Q10.

Normolip 5® (ESI): red yeast rice (5% monacolin), gamma-oryzanol, policosanols, coenzyme Q_{10}, chromium.

Policol 400® (Laboratorio della Farmacia): red yeast rice dry extract (3% monakolin K), red grape seeds dry extract (90% procyanidins), *Saccharum officina rum* dry extract (60% octacosanol), coenzyme Q_{10}, astaxanthin, folic acid.

Red yeast rice (1.5% lovastatin) (Ardanatura)

Riscol 5® (Errekappa): red yeast rice (titrated in monakolin K), resveratrol, policosanols.

Statinat® (Crinos – EG): red yeast rice (1.5% mevinolin), linear aliphatic alcohols (60% octacosanol), niacin, polyphenols from *Camellia sinensis*, vitamin E, vitamin B_6, vitamin B_{12}, folic acid.

Composition of other supplements, except vehicles:

Enerzona Omega 3 (Enervit): 60% EPA and DHA.

Glora Vis (Gloria Med Pharma): *Vitis vinifera* dry extract (procyanidis 95%), coenzyme Q10.

Olivis (Vis Medicatrix Naturae S.r.l.): olive (*Olea europaea*) dry extract (40% oleuropein), hawthorn (*Crataegus oxyacantha*) dry extract (40% flavonoids), mistletoe (*Viscum album*) dry extract, shepherd's purse (*Capsella bursa-pastoris*) dry extract, fumitory (*Fumaria officinalis*) dry extract.

Nuovo 3D (Phyto Garda S.r.l.): dandelion (*Taraxacum officinale*), greater burdock (*Arctium lappa*), java tea (*Ortosiphon stamineus*), common nettle (*Urtica dioica*), milk thistle (*Silybum marianum*), bearberry (*Arctostaphylos uva-ursi*).

In 14 cases (27%) the reaction was serious, including 13 cases that required hospitalization. Notably, hepatic reactions were serious in six out of ten cases. Twenty-eight patients were taking other medications consisting generally in conventional drugs (ACE inhibitors, thyroid hormone, selective serotonin reuptake inhibitors, oral contraceptives, antibiotics, benzodiazepines, calcium antagonists, vitamin D, beta-blocking agents and diuretics), but also in dietary supplements: fish oil, olive (*Olea europaea* L.) and *Vitis vinifera* L. (three cases). Conditions predisposing to RYR-associated reactions were generally absent or not reported. It has to be noted that in 12 out of 13 cases resulting in hospitalization, no concomitant medications or predisposing conditions were reported; only in one case was a poly-pharmacotherapy identified (≥ five drugs).

Based on the MedDRA terminology, the most frequently reported system organ classes (SOCs) were 'Musculoskeletal and connective tissue disorders' (20 reactions, 36%), 'Gastrointestinal disorders' (12, 22%), 'Hepatobiliary disorders' (10, 18%), 'Skin and subcutaneous tissue disorders' (9, 16%).

Overall, after causality assessment, association was evaluated as *certain* (1 reaction), *probable* (31 reactions, 56%), *possible* (18 reactions 34%), *unlikely* (3 reactions) or *unassessable* (2 reactions). Thus, for 56% of reactions, an at least probable causal association was assessed. A complete description of cases is reported in Table 1.

From the WHO-Vigibase, 75 reports were retrieved using RYR as active substance (search performed as of 13 September 2016): 56% were submitted from the Americas, 43% from Europe; 36% occurred in patients aged 45–64 years (28% in those aged >65) and 69% were females. The most frequently reported reactions were myalgia (22), followed by muscle spasm, chest pain, drug interaction (7 each), rhabdomyolysis, pain in extremity and dizziness (5 each). The full reporting frequency of ARs is provided in Supplementary material 2.

Case-by-case assessment

Musculoskeletal and connective tissue disorders. Muscular pain, with or without indication of creatine phosphokinase (CPK) increase, occurred in 19 patients, one case of rhabdomyolysis was also recorded. Muscle pain affected generally the lower extremities and cramps were sometimes present. The increase in CPK values was mild in some cases (*4*, *5*, *7*, *10*: about 200 U/L or less), high in others (*1*, *2*, *3*, *12*, *14*: from 288 to 732 U/L) and very high (up to ten times the normal concentrations) in two patients (*9*, *16*); in the rhabdomyolysis case, the CPK level reached 12 245 U/L. The latency of the reaction was variable, ranging between 9 days and more than one year; however, about one third of the reactions occurred within 30 days and 63% within two months. Several patients were taking medications, most of which are not known to be associated with muscular disorders, with exception of venlafaxine [36, 37]; this evidence was taken into account in the causality assessment. Noteworthy, some patients (*3*, *6* and *12*) were using RYR preparations as an alternative option, being intolerant to statins, while patients *9* and *13* previously experienced myopathy and CPK increase associated with statin use; patient *15*, who showed rhabdomyolysis, presented a previous identical reaction after taking statins; in these cases RYR use was considered a positive rechallenge.

The causality assessment, according to the WHO scale, resulted as *possible* in 8 cases (*3*, *4*, *5*, *7*, *9*, *12*, *13*, *18*), *probable* in 11 cases (*1*, *2*, *6*, *8*, *10*, *11*, *14*, *16*, *17*, *19*, *20*) and *certain* in case *15*.

Gastrointestinal disorders. Gastrointestinal reactions occurred in 12 patients and consisted mostly in dyspepsia, nausea, vomiting and abdominal pain, sometimes in diarrhoea. The reactions occurred within one or two days or after 3–4 weeks of treatment. The reactions were in general not serious, and only one case (*38*) needed hospitalization. Dechallenge was always positive (not available for case *32*). Nevertheless, in two patients (*30*, *31*) the reaction, even if improved, was persistent. Five patients (*34–38*) had a positive rechallenge. For case *32* the causality was judged as *unassessable*, due to lacking information about outcome and dechallenge; furthermore, the patient was taking another food supplement with unknown side-effects. Some cases were judged as *possible* because similar reactions were reported for concomitant drugs; for example, abdominal pain has been reported in more than 1% of hypertensive patients who received moexipril/hydrochlorotiazide [38], as with case *18*. In causality assessment a conservative approach was used, taking in account that gastrointestinal symptoms such as nausea, vomiting and impaired digestion do not represent specific medical disorders and are common side-effects of drugs. As a consequence, cases *37* and *38* were judged as *probable* and not *certain* despite the plausible time relationship to drug intake, the absence of other causes, a positive response to withdrawal and a positive rechallenge.

Hepatobiliary disorders. Hepatic reactions occurred in ten patients and consisted in acute hepatitis (six patients), that required hospitalization, or in increase of hepatic enzymes. These six cases fulfilled criteria for DILI, according to the international Expert Working Group [39]. In one patient (*16*) increase in AST occurred together with CPK increase. Nine cases were compatible with the definition of drug-induced liver injury, as recommended by the CIOMS [40, 41].

Time to onset was between two weeks and one year of treatment, 37% of the reactions occurred within one month and 75% within two months. Transaminases ranged from about twice to 80 times the upper normal level. In all cases, except for two in which it was not reported, dechallenge was positive. Patients were taking other drugs or dietary supplements, but generally these were not known to be associated with liver injury. The CIOMS/RUCAM score was only applied to cases *26* and *27*, for whom the follow-up was available. Case *26* regarded a 49-year-old woman who had consumed Armolipid plus® for 50 days. She was hospitalized for suspected myocardial infarction; the infarction was excluded, while an acute hepatitis was diagnosed with ALT and AST values corresponding to 46 and 57 times the upper normal concentrations, respectively. Total bilirubin was normal, viral and autoimmune serology was negative and other drug and non-drug causes of hepatitis were excluded; rhabdomyolysis was also excluded. The supplement consumption was suspended and the values decreased, returning to normal

after 17 days. The causality assessment resulted in a score of 7 (*probable*).

Case *27* was a 68-year-old woman who had a history of hypercholesterolemia, for which she had been taking the supplement Armolipid plus® for 2 years. An increase of liver enzymes (AST = 87; ALT = 168) was discovered during a routine blood test, and an additional laboratory test reported total bilirubin 0.5, γ-GT 53, ALP 109. Creatine kinase was normal, thus suggesting that the increase in transaminases did not have a muscular aetiology. The ultrasound scan did not show clinically important signs of hepato-biliary damage, except for moderate steatosis and lithiasis (previously documented). Major infective hepatitis was excluded, no recent flu-like episodes or gastro-intestinal symptoms were documented, no history of pre-existing liver or biliary disease, blood transfusion or alcohol abuse was documented. Concomitant drugs included levothyroxine (for 7 years) and chenodeoxycholic acid (for 5 years). The product was suggested by healthcare professionals because of the patient's complaints about symptomatic myopathy, probably related to the administration of statins. Notably, no elevation of CPK or hepatic transaminases was previously documented when the woman was treated with statins. The supplement was suspended. Laboratory blood test, performed after less than 4 weeks, gave normal values for AST, ALT, γ-GT and ALP. Based on transaminases values, the liver injury was classified as hepatocellular and the application of the CIOMS/RUCAM scale resulted in a score of 5 (*possible*).

In cases *21*, *22*, *23*, *24*, *25* and *16*, the causality assessment performed by the WHO method, resulted as *probable*; case *28* was *unassessable*, due to lack of information about time to onset of the reaction, duration of treatment, outcome and dechallenge, while case *29* was judged *unlikely* because, despite the positive dechallenge, the reaction recurred without rechallenge; moreover, information about time to onset and treatment duration were lacking.

Skin and subcutaneous disorders. Nine cutaneous reactions associated with RYR products were collected**.** Most of them (*42*, *44–47*) occurred with a 1–4-day latency, the others occurred after 10 days (*48*), 3 weeks (*5*) or about 2 months (*48*) of treatment. Four cases (*41*, *43*, *45* and *48*) were serious and required hospitalization. In case *41*, which involved a 57-year-old woman, the reaction consisted in *Pemphigus vulgaris*, diagnosed by titration of anti-desmoglein 1 and 3 antibodies and by biopsy. The reaction occurred 2 weeks after discontinuation of the supplement and needed a pharmacological therapy. The patient was not taking other drugs, but as she had experienced a previous episode of *Pemphygus* eight years before, then the reaction could be considered a relapse and the causality was judged as *unlikely*. Patient *43* (a 75-year-old woman) was admitted to hospital with severe urticaria, rash and oedema of the lips. The reaction improved after discontinuation of the RYR supplement but recurred after 6 days, without rechallenge. It is to be underlined that this patient, even without predisposing conditions, was taking various medications (cardioaspirin, amiloride plus hydrochlorothiazide, triazolam, metoprolol, lansoprazole, risedronate), but, most importantly, received flu vaccine 5 days before the onset of the reaction, so, also in this case, the causality was judged as *unlikely*. In cases *5*, *45* and *47*, the causality was judged as *possible* despite a positive outcome and dechallenge, because patients were taking other drugs, some of which (amiloride plus hydrochlorothiazide, lansoprazole) have been reported to induce cutaneous adverse reactions [42, 43]. Patient *48* was hospitalized for DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, a severe drug-induced reaction [44]. Laboratory tests suggested that the patient had a *Herpes simples* virus infection, a condition associated with DRESS [45]. Cases of DRESS are described also for atorvastatine [46], a lipid-lowering drug belonging to the statins class (as monacolin contained in RYR), as well as for omeprazole [47], a proton pump inhibitor similar to pantoprazole that the patient was consuming. Based on these considerations, the causality between DRESS and RYR preparation was judged as *possible*. In the other cutaneous reactions (*42*, *44* and *46*) the causality was considered as *probable* on the basis of the positive dechallenge, outcome and absence of alternative causes.

Others miscellaneous reactions. Case *49* involved a 78-year-old woman who was taking warfarin and showed an increase of INR (international normalized ratio) after consumption of the RYR supplement Armolipid plus®. The dose of warfarin was reduced and the INR value returned to normal. In this case a pharmacodynamic interaction between the anticoagulant drug and RYR supplement can be hypothesized, even if the dechallenge was not done. Furthermore, three patients showed nausea, vertigo and hazy vision (*50*), tingling of extremities (*51*) and tachycardia (*52*); the latter required hospitalization. Dechallenge was always positive and other causes were excluded, so the causality was judged as *probable* in all of them. Nevertheless, it has to be pointed out that in case *52* the supplement consumed (Fisiostatin®) contained, besides RYR, green tea [*Camellia sinensis* (L.) O. Kuntze], a source of caffeine that could be responsible for the adverse reaction.

Discussion

From April 2002 to September 2015, a total of 1261 spontaneous reports of suspected ARs to natural health products (mainly dietary supplements, 65%) were collected within the Italian Surveillance System of Natural Health Products. In this article, we describe 55 suspected ARs to RYR food supplements collected within the system in the same period. Because clinical trials are not requested by food supplements legislation and no risk–benefit profile is known before marketing, spontaneous reports are the only tool available to evaluate their safety.

Overall, our findings raise the hypothesis that the safety profile of RYR is similar to synthetic statins: myopathies (myalgia, CK and transaminases elevation [48–51]), cutaneous reactions, gastrointestinal and liver reactions emerged as a potential safety signals of RYR and have been reported as not uncommon adverse reactions associated with statins [52–55]. These data are also in line with cases collected from WHO-Vigibase and reports received by the ANSES French Agency, where muscle- and liver-related ARs were largely reported with RYR [30]. In 14 cases (27%), the reactions were

serious and mostly required hospitalization, especially those related to hepatic injury. Most of the reactions involved women, probably because they use more dietary supplements than men [56, 57]. Notably, some patients who showed muscular adverse reactions associated with statin switched to RYR supplements as an alternative and experienced similar adverse effects. The time to onset of muscle- and liver-related ARs was relatively rapid: one third of cases occurred during the first month of treatment, and two-thirds within 60 days.

Therefore, clinicians should be informed that monacolin K contained in RYR is identical to lovastatin, and consider early monitoring of liver function and signs of muscle injury. In parallel, consumers should be discouraged from using RYR preparations as self-medication, particularly if they have experienced previous adverse reactions to statins. When self-prescribed, without medical advice and monitoring and possibly for the long term, patients should be aware they are consuming an active substance, with both therapeutic and toxic effects. In fact, even serious adverse reactions, such as hepatitis or rhabdomyolysis, can remain asymptomatic for long periods with the risk of organ failure progression. In contrast, when statins are taken under medical control, blood tests to check CK and organ function are performed periodically so that statin use can be stopped as soon as abnormal results are shown.

We acknowledged limitations, especially underreporting, which is likely to affect the so-called 'natural' products to a larger extent, by both patients and physicians, who may not correlate suspected ARs to dietary supplements [58, 59]. Furthermore, sales data of food supplements are not available, given that the regulatory status of RYR (not reimbursed) does not allow their capture by administrative databases. Future studies should explore the extent of RYR use through *ad hoc* created strategies (e.g., questionnaire-based surveillance), in order to gain information on the pattern of use of RYR and to make cross-national comparisons.

All supplements involved, except one, contained other natural components besides RYR. For this reason, as already stated, the assessment causality refers to the supplement in its whole composition. Nevertheless, we can assume that the reactions here described, mainly myopathy and liver injury, can reasonably be ascribed to RYR, which has been reported to induce such reactions [10, 23, 24, 26, 27, 29, 60, 61].

Causality assessment presents some limitations due to the fact that spontaneous reporting systems involve general practitioners, specialists, hospital doctors, pharmacists, but also herbalists and consumers. As a consequence, forms were sometimes incomplete (i.e. lack of information about latency of the reaction, treatment duration, concomitant drugs or predisposing conditions). The application of the CIOMS/RUSCAM score to hepatic reactions requires knowledge of the complete serology of the patient, and the course of the disease, with regard to liver enzyme values, is needed. This kind of information was rarely available in most of our reports, so the score was applied only to two cases (*26, 27*) with an available detailed medical history. However, to the extent of our knowledge, these are the first two reports where the CIOMS/RUCAM score was applied to assess hepatic safety of RYR. All these limitations made the causality assessment quite difficult. Notwithstanding, for 56% of reactions, an at least probable causal association emerged.

From a regulatory standpoint, in Italy, the Ministry of Health in 2003 (note 600.12/AG21/2839 of January 1, 2003 and following memorandum 600.12/AG21/3178 of November 11, 2003) allowed a maximum dose of 3 mg per day of monacolin K in dietary supplements to ensure the safety of the product. Moreover, a recommendation not to assume RYR products together with statins was added on the package. However, in 2011, the European Food Safety Authority (EFSA) sustained that the health claim for RYR in maintaining normal blood LDL cholesterol concentrations was supported for a daily dose of 10 mg of monacolin [62]. Therefore, in 2012, the European Union increased the maximum dose allowed to 10 mg per day (Official Gazette of European Union, L136, May 25, 2012), which prompted some manufacturers to increase the monacolin content in RYR preparations. This may theoretically expose subjects to an increased risk of ARs. Based on our data, in only four out of 23 cases did the preparation contain 10 mg of monacolin, thus making it is difficult to establish the real consequences of the increase in monacolin dose on the number and severity of ARs.

A further problem with efficacy and safety of RYR commercial preparations is the variability in monacolin K content. Analysing 12 RYR products, Gordon *et al*. [63] labelled '600 mg/capsule' of active product, found: monacolins 0.31–11.15 mg/capsule; monacolin K (lovastatin) 0.10–10.09 mg/capsule, and monacolin K acid 0.00–2.30 mg/capsule. More recently, Avula *et al*. [64] analysed three authentic samples of RYR, 31 RYR commercial raw materials and 14 dietary supplements. In the authenticated RYR samples, the monacolin K content ranged from 1.9 to 2.3 mg/g (w/w). Ten of 31 commercial RYR raw material samples did not show the presence of any monacolin; in the remaining 21 the amount of monacolin K was in the range 0.7–24.3 mg/g (w/w). Amounts of monacolin K in dietary supplements labelled as containing 600 mg of RYR ranged from 0.03 mg to 2.18 mg. From these data it appears that a problem of standardization with RYR commercial products does exist.

Conclusions

Our assessment of suspected ARs reported with RYR highlights two potential safety issues, namely muscle and hepatic injuries, in line with data obtained from accessing the public web-based version of the WHO-Vigibase and a similar analysis recently carried out by the ANSES French Agency. These findings raise the hypothesis that the safety profile of RYR is highly similar to that of synthetic statins and warrants further investigation to finally characterize the safety profile of RYR. The proportion of serious reports (27%), the relatively rapid time to onset and the lack of concomitant drugs and/or predisposing medications in several cases warrant regulatory consideration and call for: (1) continuous monitoring of the safety of 'natural' dietary supplements through spontaneous reports; and (2) appropriate information being provided to clinicians and consumers, who should timely submit suspect reports to regulatory agencies.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). They declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Contributors

G.M. and F.M.I. conceived and designed the study, analysed data and drafted the first version of the manuscript; P.A.M., E.R. and R.D.C. provided substantial contribution to the study design and data analysis. All authors provided substantial contribution to data interpretation and their discussion; they critically revised the content and approved the final version of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13171/suppinfo

Supplementary material 1 Reporting Form for suspected adverse reactions to natural health products

Supplementary material 2 Adverse events recorded in the WHO-Vigibase using the term 'red yeast rice' (www.vigiaccess.org; access date: 13/09/2016). Individual Case Safety Reports are presented in decreasing order of frequency (≥5 reports), and coded according to the WHO Adverse Reaction Terminology (WHO-ART). Please note that the number of adverse events may exceed the number of individual case safety reports, depending on the different types of events reported