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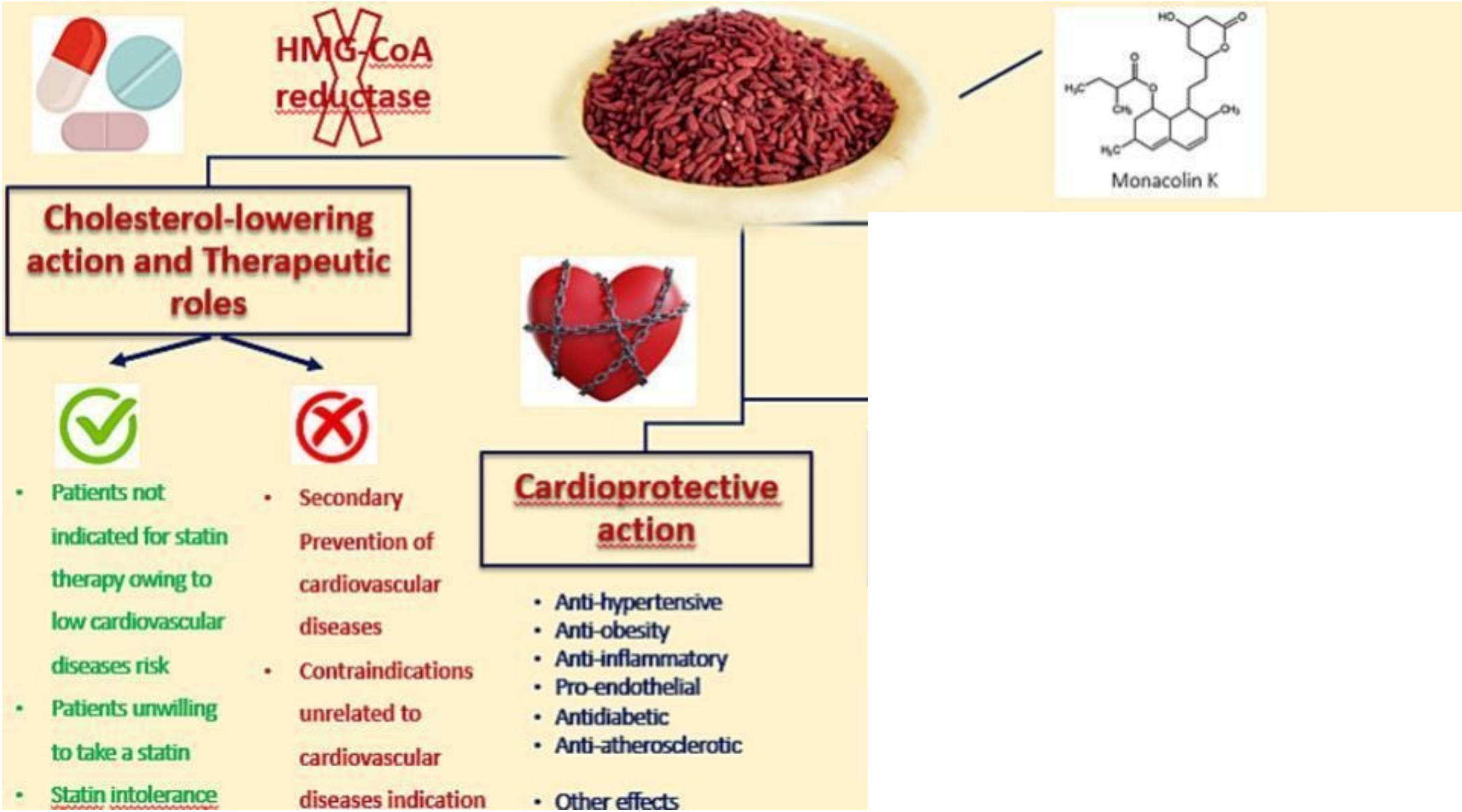
Società Italiana di Nutraceutica

NUTRACEUTICA E SICUREZZA: TAUTOLOGIA O OSSIMORO?

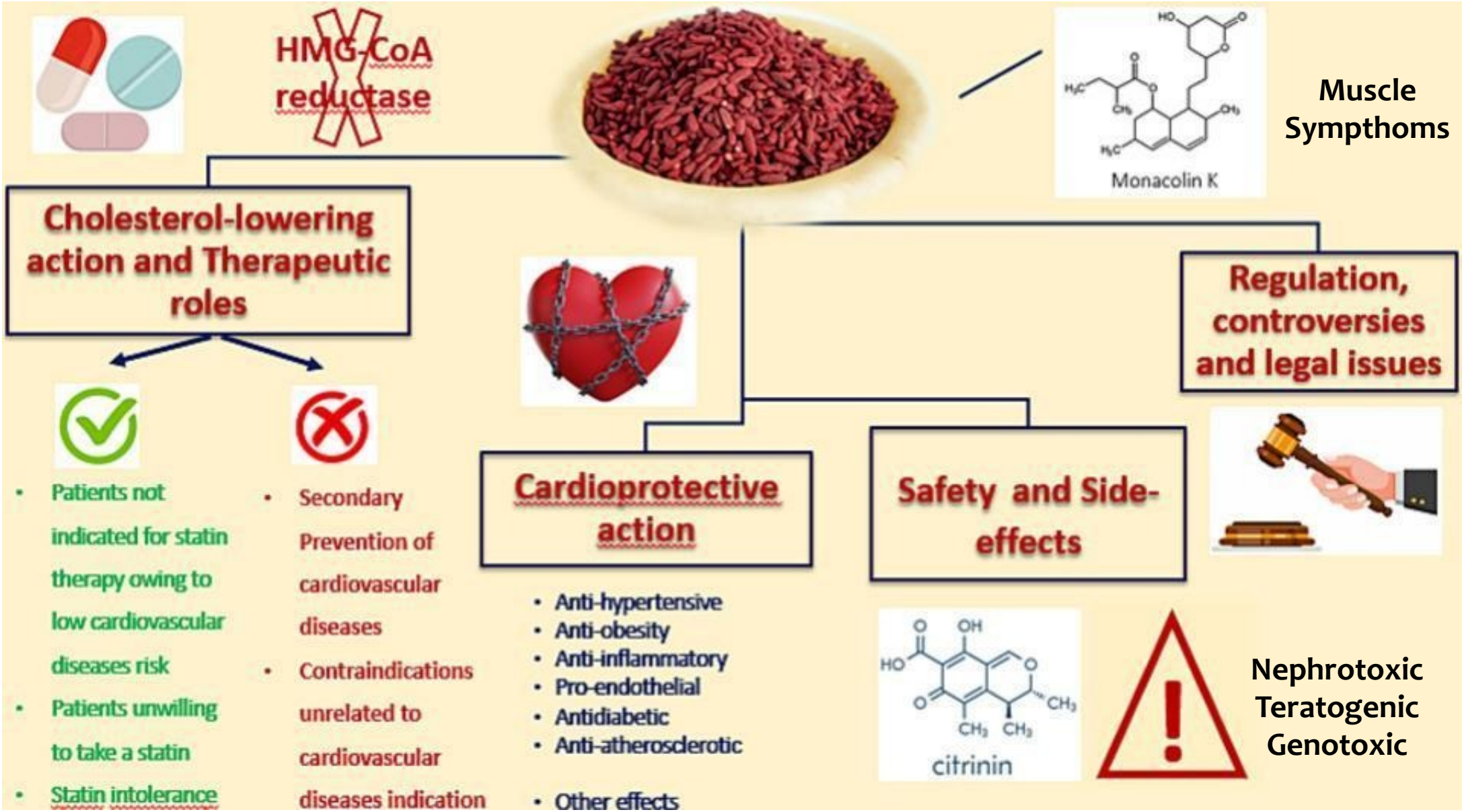
Case history 3: Riso rosso fermentato

Giuseppe Danilo Norata
University of Milan, Italy

Fermented Red Yeast Rice



Fermented Red Yeast Rice



European Food Safety Authority

<u>2018: Scientific Opinion</u>

Monacolin K in the lactone form is identical to lovastatin and that, based on the available information, the intake of monacolins from red yeast rice via food supplements could result in an estimated exposure to monacolin K in the therapeutic dose range of lovastatin (10mg/day) with side effects observed >3mg/ day.

<u>2022: Regulatory decision</u>

based on evidence of adverse health effects associated with the use of monacolins from RYR at levels of 10 mg/day and isolated cases of severe adverse health effects at levels as low as 3 mg/day, the European Commission issued a regulation that RYR products must contain less than 3 mg of monacolins for daily consumption.

Contents lists available at ScienceDirect

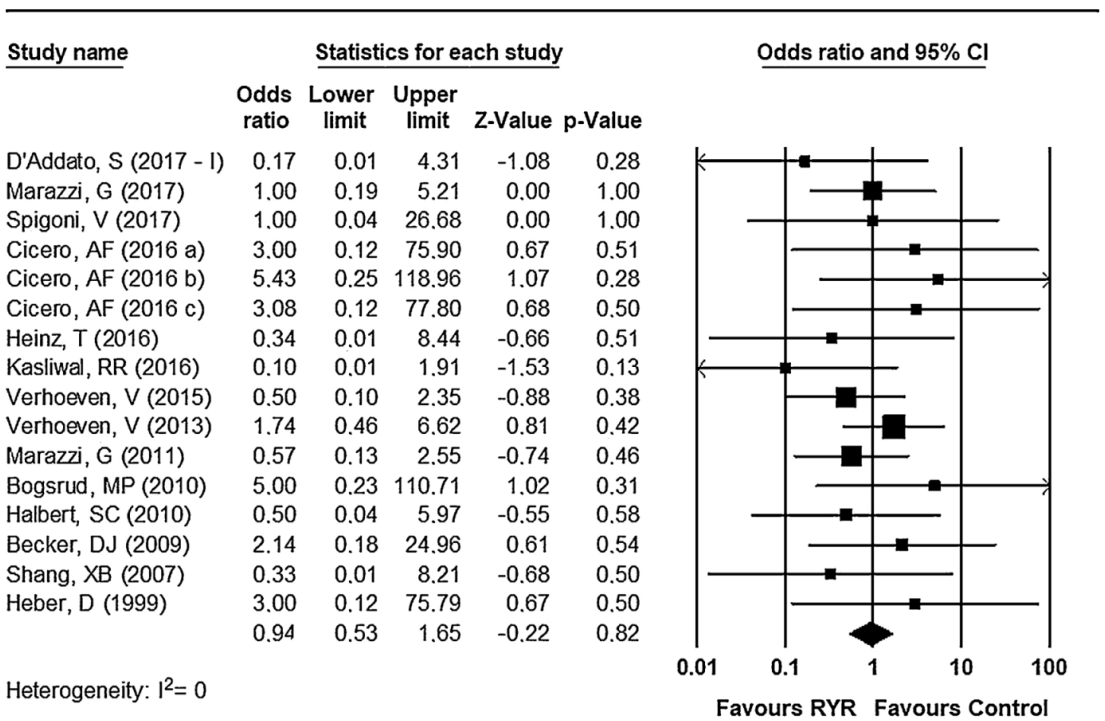
Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Safety of red yeast rice supplementation: A systematic review and meta-analysis of randomized controlled trials

Federica Fogacci[a,1], Maciej Banach[b,c,d,**,1], Dimitri P. Mikhailidis[e], Eric Bruckert[f], Peter P. Toth[g,h], Gerald F. Watts[i], Željko Reiner[j], John Mancini[k], Manfredi Rizzo[l], Olena Mitchenko[m], Daniel Pella[n], Zlatko Fras[o], Amirhossein Sahebkar[p,q], Michal Vrablik[r], Arrigo F.G. Cicero[a,*], on behalf of the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group, the International Lipid Expert Panel (ILEP)



Meta Analysis

Clinical research

Lipid disorders

Postmarketing nutrivigilance safety profile: a line of dietary food supplements containing red yeast rice for dyslipidemia

Maciej Banach[1,2,3], Niki Katsiki[4], Gustavs Latkovskis[5,6], Manfredi Rizzo[7], Daniel Pella[8], Peter E. Penson[9,10], Zeljko Reiner[11], Arrigo F.G. Cicero[12,13]

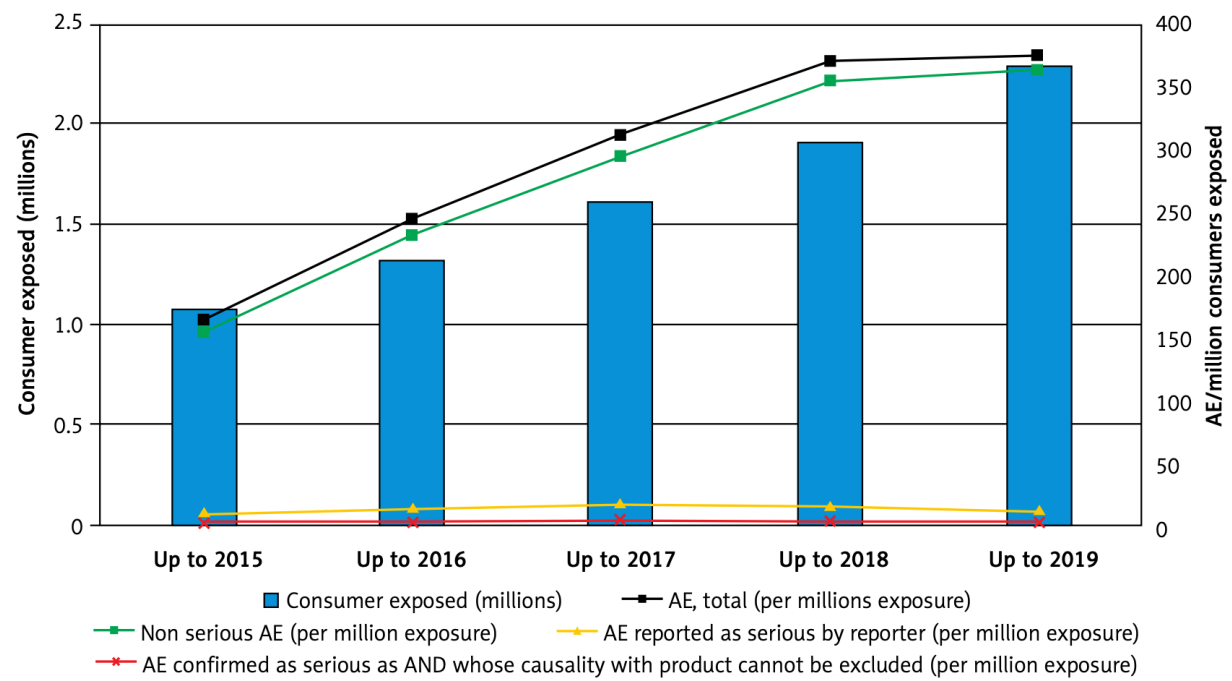


Figure 1. Adverse events on millions of exposed consumers

Current Atherosclerosis Reports (2023) 25:879–888
https://doi.org/10.1007/s11883-023-01157-4

REVIEW

Rhabdomyolysis or Severe Acute Hepatitis Associated with the Use of Red Yeast Rice Extracts: an Update from the Adverse Event Reporting Systems

Maciej Banach[1] · Giuseppe Danilo Norata[2]

The FDA Adverse Event Reporting System (FAERS) Public Dashboard is a highly interactive, web-based tool that enables the retrieval of FAERS data in a user-friendly manner to obtain information on human adverse events reported to the FDA by the pharmaceutical industry, health care providers and consumers (https://open.fda.gov/data/faers/).

The CFSAN Adverse Event Reporting System (CAERS) is a database that contains information on adverse events and product complaints submitted to the FDA for foods, dietary supplements and cosmetics (https://open.fda.gov/data/caers/). The database contains data reported by consumers and health care practitioners, data voluntarily reported by industry and data from mandatory reports from dietary supplement industry as of January 2004. The reports in CAERS are evaluated by clinical reviewers in the Centre for Food Safety and Applied Nutrition (CFSAN) to monitor the safety of consumer products. If a potential safety risk is identified in CAERS, further evaluation is conducted.

Rhamdomyolysis cases associated with the use of RYR products

In FAERS, out of 44833 case of Rhabdomyolysis reported (4655 fatal), 4 cases (non fatal) were reported in women taking RYR. 14591 cases related to statins (238 lovastatin).

In CAERS, 3 cases for RYR.

Table 1 Rhabdomyolysis cases associated with the use of RYR products

FDA reporting systems						
FAERS	Initial FDA received date	Product	Patient age	Sex	Reactions	Case outcome
	27-Sep-2018	*Monascus purpureus*	74 y	Female	Myopathy; rhabdomyolysis	n.a.
	21-Aug-2018	*Monascus purpureus*	77 y	Female	Rhabdomyolysis; myopathy	n.a.
	10-Oct-2018 (event date 12-May-2012)	*Monascus purpureus*	78 y	Female	Myopathy; rhabdomyolysis	n.a.
	07-Sep-2018	*Monascus purpureus*; Sertraline	70 y	Female	Myopathy; food interaction; drug interaction; rhabdomyolysis	n.a.
CAERS	Event date	Product	Patient age	Sex	Reactions	Case outcome
	16-Sep-2005	Red yeast rice 600 mg/d	-	Female	Confusional state; dizziness; fatigue; influenza-like illness; muscular weakness; rhabdomyolysis; tremor	Other outcomes
	23-Feb-2015	Red yeast rice 600 mg/d	78 y	Male	Abasia; arrhythmia; bradycardia; rhabdomyolysis; swelling	Hospitalisation, visited emergency room
	21-Apr-2018	Red yeast rice	61 y	Male	Amnesia; anaemia; ↑blood potassium; bradykinesia; catatonia; claustrophobia; fall; ↑heart rate; mydriasis; ↑platelet count; rhabdomyolysis; ↑weight; ↑white blood cell count	Life-threatening, hospitalisation, other serious or important medical event, visited emergency room
Published case reports						
	Year of publication	Product	Patient age	Sex	Reactions	Case outcome
	2002	Red yeast rice	28 y	Female	Rhabdomyolysis; drug interaction with cyclosporine	n.a.
	2019	Red yeast rice 315 mg/d	65 y	Male	Acute renal deficiency; rhabdomyolysis;	Hospitalisation
	2023	Red yeast rice	50 y	Female	Chest discomfort; myalgia; rhabdomyolysis	Hospitalisation

n.a. not available

Banach M et al. Curr Ather Reports 2023; Norata GD et al Nutrients 2024

Severe hepatic adverse events associated with the use of RYR products

In FAERS, RYR out of 23339 case of severe hepatitis/Liver injury, 3 cases (non fatal) were reported in subjects taking. (257 cases with statins).

In CAERS, 2 cases.

Table 2 Severe hepatic adverse event cases associated with the use of RYR products

FDA reporting systems						
FAERS	Initial FDA received date	Product	Patient age	Sex	Reactions	Case outcome
	14-Aug-2019	*Monascus purpureus*	56 y	Male	Drug Interaction; hepatic cytolysis	n.a.
	26-Mar-2019	*Monascus purpureus*	56 y	Male	Hepatic cytolysis; drug interaction	n.a.
	29-May-2013	*Monascus purpureus*	45 y	Male	Urticaria; hepatic cytolysis	n.a.
CAERS	Event date	Product	Patient age	Sex	Reactions	Case outcome
	04-Apr-2011	Red yeast rice	69	Female	Chromaturia; faeces discoloured; hypercholesterolaemia; jaundice; liver injury	Other serious or important medical event, visited a health care provider
	07-Jan-2017	Red yeast rice	46	Male	Hepatic failure	Life threatening, hospitalisation, disability
Published case reports						
	Year of publication	Product	Patient age	Sex	Reactions	Case outcome
	2008	Red yeast rice 600 mg	62 y	Female	Flu-like symptoms; nausea; vomiting; diarrhoea; chills; daily fever; hepatitis	Hospitalisation
	2009	Red yeast rice (monacolin K 10 mg)	71 y	Female	Fulminant hepatitis with cytolysis	Death
	2019	Red yeast rice 1200 mg	50 y	Female	Acute hepatitis	Hospitalisation
	2019	Red yeast rice 315 mg	65 y	Male	Acute renal deficiency; hepatitis rhabdomyolysis	Hospitalisation

n.a. not available

Banach M et al. Curr Ather Reports 2023; Norata GD et al Nutrients 2024

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	2019	Red yeast rice 1200 mg	50 y	Female	Acute hepatitis	Hospitalisation
	2019	Red yeast rice 315 mg	65 y	Male	Acute renal deficiency; hepatitis rhabdomyolysis	Hospitalisation

n.a. not available

In summary, the available data suggest that the occurrence of rhabdomyolysis or severe acute hepatitis that could be associated with RYR use is very to extremely rare compared to cases reported to be associated with statins, which are rare to common.

Banach M et al. Curr Ather Reports 2023; Norata GD et al Nutrients 2024

nutrients

MDPI

Brief Report

The Impact of Red Yeast Rice Extract Use on the Occurrence of Muscle Symptoms and Liver Dysfunction: An Update from the Adverse Event Reporting Systems and Available Meta-Analyses

Giuseppe Danilo Norata [1,2] and Maciej Banach [3,*]

	In People Taking RYR	Total in FAERS	% of RYR-Associated Adverse Events
Musculoskeletal and connective tissue disorders	**8**	**402,758**	**0.002%**
Myopathy	5	4823	0.1%
Rhabdomyolysis	4	21,605	0.019%
Pain in extremity	1	199,374	0.0005%
Muscular weakness	1	71,270	0.0014%
Myalgia	1	104,736	0.001%
Sacral pain	1	950	0.105%
Hepatobiliary disorders	**4**	**28,133**	**0.014%**
Hepatic cytolysis	3	15,215	0.02%
Liver injury	1	12,918	0.008%

Table 2. Number of cases of muscular adverse events in people taking red yeast rice versus total cases in the CAERS database.

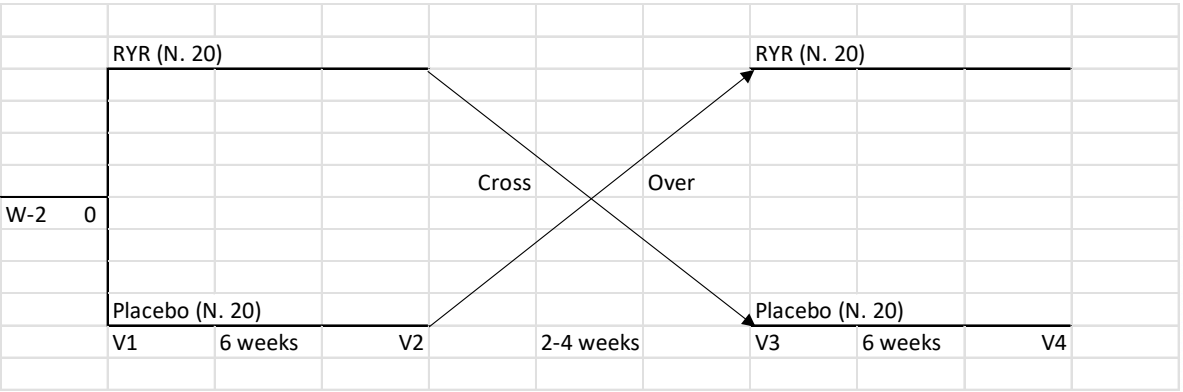
Adverse Event	In People Taking RYR	Total in CAERS	% of RYR-Associated Adverse Events
Musculoskeletal disorders	**53**		
Muscle disorders	3	24	12.5%
Muscle fatigue	1	34	2.94%
Muscle spasms	29	1107	2.62%
Muscle tightness	1	45	2.22%
Muscular weakness	6	295	2.03%
Musculoskeletal chest pain	1	48	2.08%
Musculoskeletal discomfort	1	22	4.55%
Musculoskeletal pain	1	104	0.96%
Musculoskeletal stiffness	2	181	1.10%
Myalgia	29	753	3.85%
Myopathy	2	5	40.0%
Pain in extremity	3	395	0.76%
Rhabdomyolysis	3	242	1.24%

Table 3. Number of cases of hepatic adverse events in people taking red yeast rice versus total cases in the CAERS database.

Adverse Event	In People Taking RYR	Total in CAERS	% of RYR-Associated Adverse Events
Alanine aminotransferase increased	3	474	0.63%
Aspartate aminotransferase increased	2	459	0.44%
Hepatic enzyme increased	4	716	0.56%
Hepatic failure	1	231	0.43%
Hepatic pain	1	57	1.75%
Hepatomegaly	1	91	1.10%
Liver function test abnormal	21	536	3.92%
Liver injury	1	398	0.25%

Banach M et al. Curr Ather Reports 2023; Norata GD et al Nutrients 2024

Effects of low-dose monacolin K (<3mg/day) on the circulating proteome in individuals with suboptimal cholesterolaemia: A randomised clinical trial



	NUT	PLACEBO	p
Age (years)	57,5 (12,7)	63,1 (16,2)	ns
TC (mg/dL)	217,47 (20,8)	215,24 (27,7)	ns
TG (mg/dL)	121,9 (50,2)	111,29 (27,7)	ns
HDL-C (mg/dL)	49,4 (10,1)	50,2 (13,6)	ns
LDL-C (mg/dL)	143,6 (19,4)	142,7 (22.0)	ns
ApoB (mg/dL)	102,2 (21,5)	101,6 (31,1)	ns
ApoAI (mg/dL)	146,7 (26,9)	150,2 (31,2)	ns
FPG (mg/dL)	90,1 (7,4)	92,6 (12.0)	ns
AST (U/L)	22,5 (5,6)	22,9 (4,2)	ns
ALT (U/L)	20,2 (9,6)	21,8 (8,4)	ns
CPK (U/l)	137,9 (69,3)	106,2 (58,6)	ns

Participants with LDL-C levels between 115 and 190 mg/dL were randomised to receive either a dietary supplement (referred to as NUT) containing RYR (total monacolin <3 mg) or a placebo, both in combination with a standard Mediterranean diet (rich in vegetables, whole grain carbohydrates, extra-virgin olive oil, and low in salts, processed foods and animal fats) with low cholesterol content (Standard of Care - SOC), (<200 mg/day, as indicated by the European Atherosclerosis Society guidelines).

All patients received an information document describing the study and signed a consent form to participate in the study. The study was approved by the Ethics Committee of the University of Bologna and registered on www.clinicatrial.gov (ID: **NCT06368258**).

Cicero A et al. MedRx 2024;

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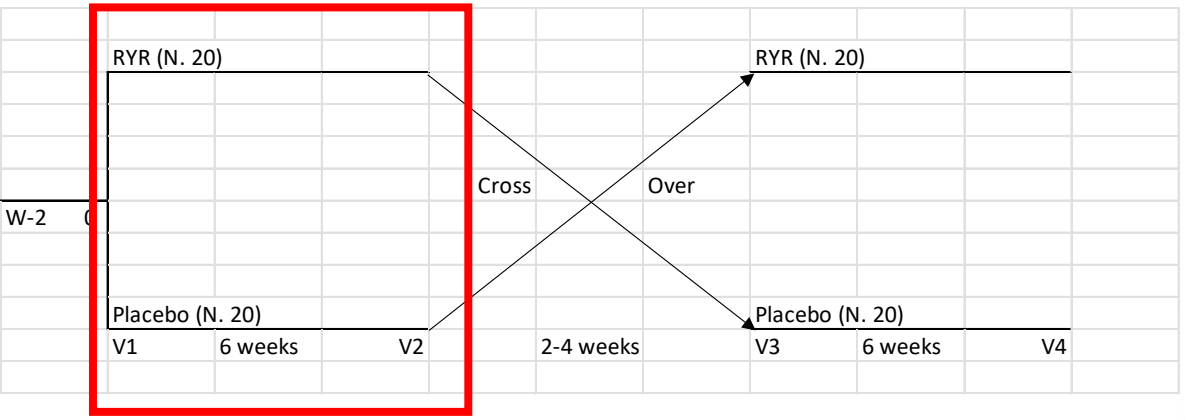

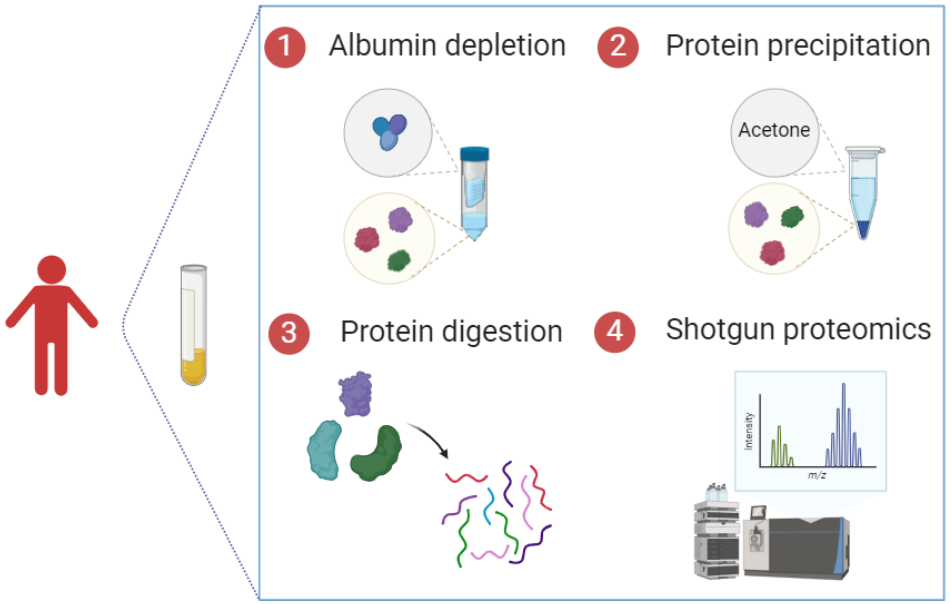

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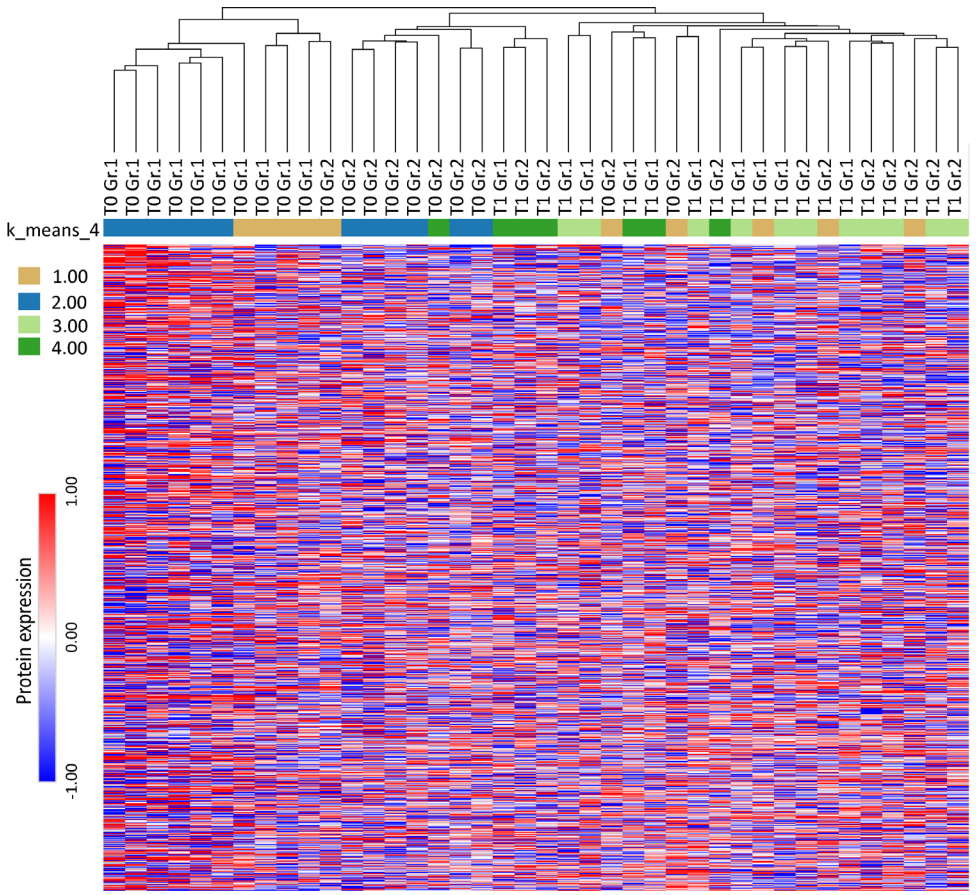

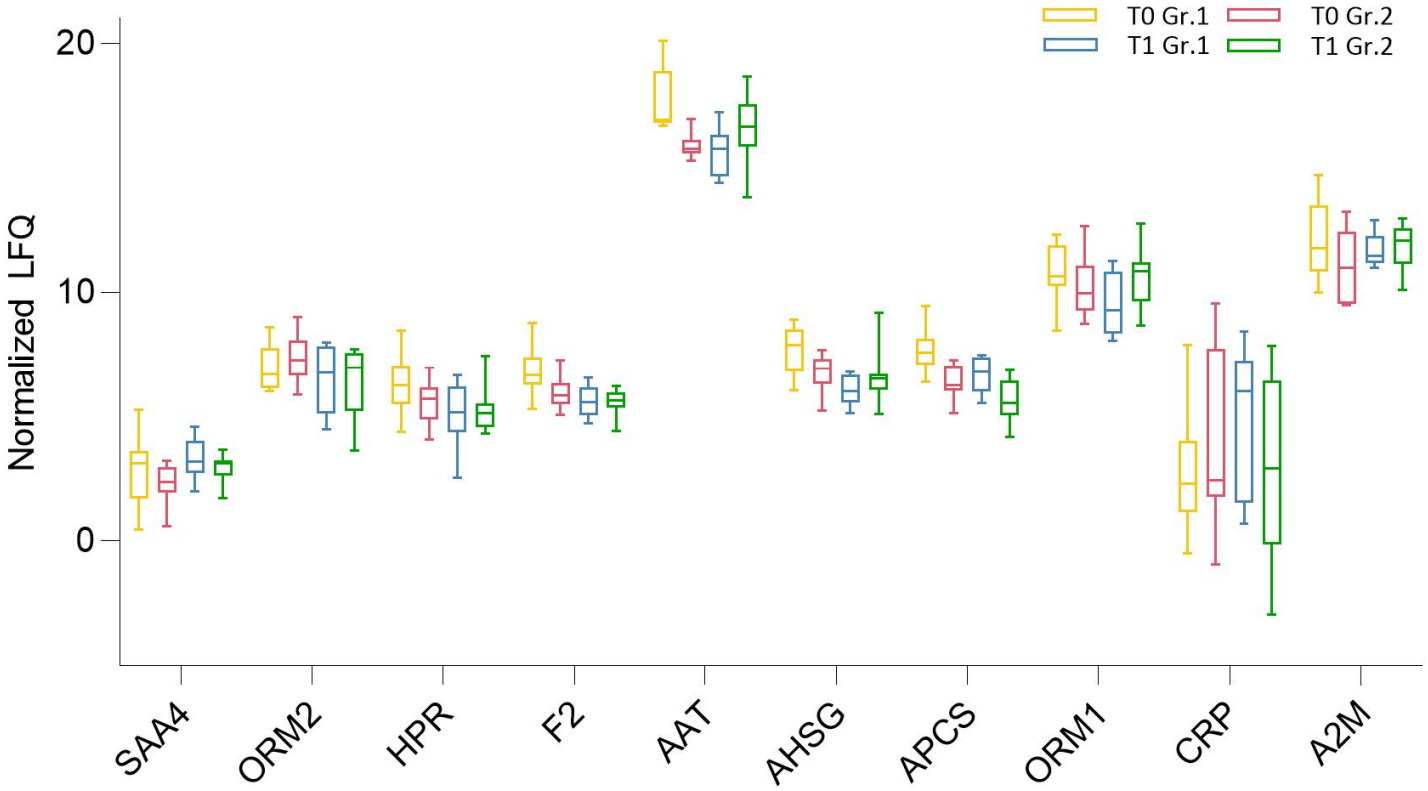

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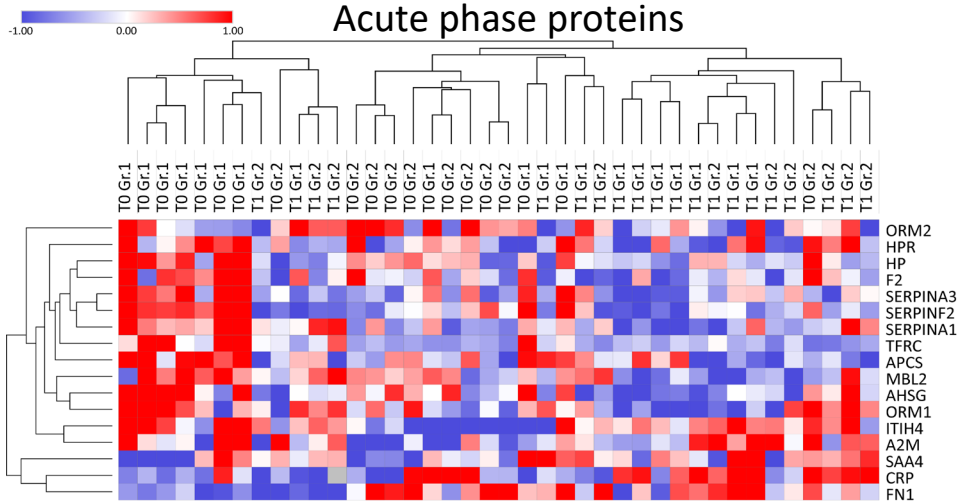
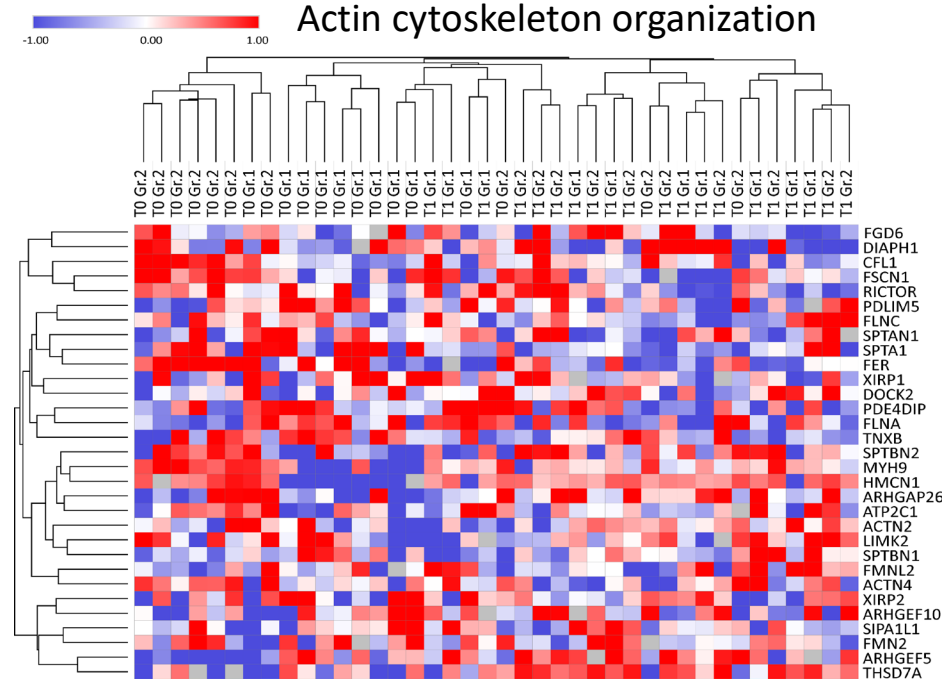
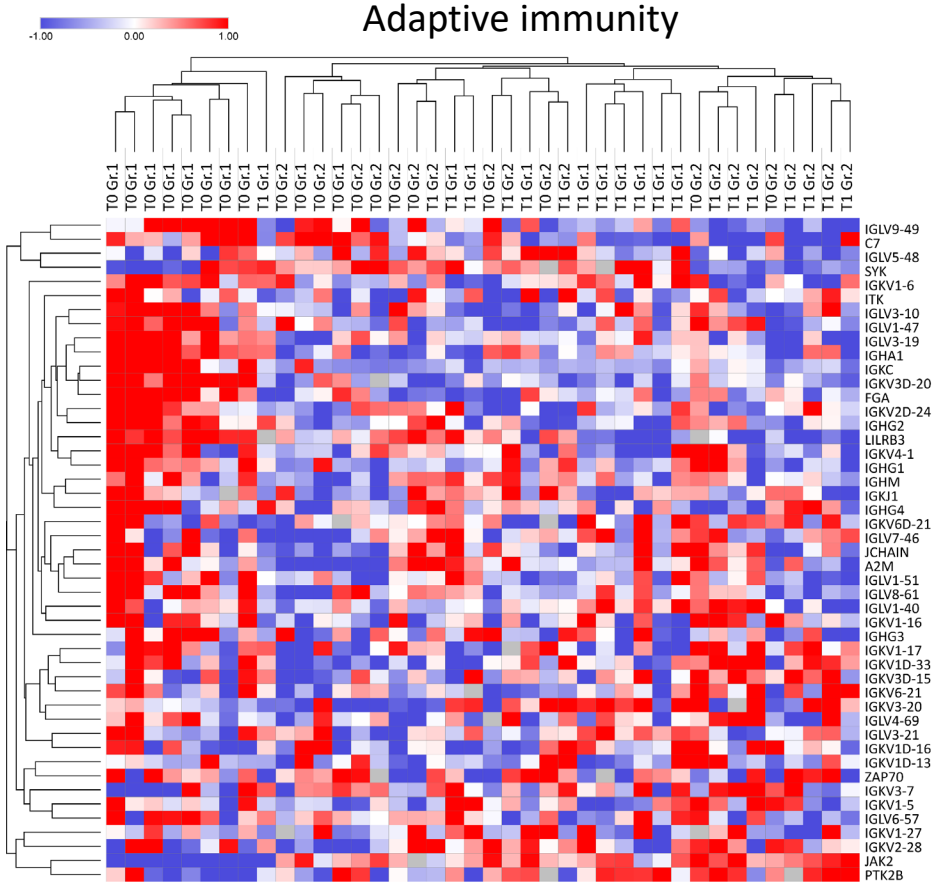
Acute phase proteins



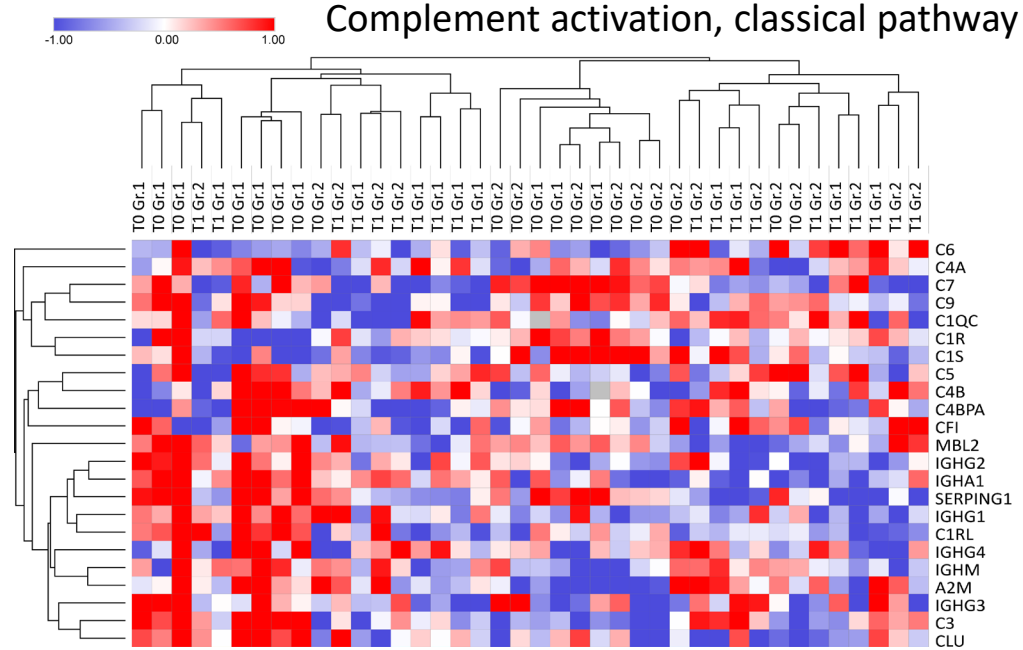
Actin cytoskeleton organization



Adaptive immunity



Complement activation, classical pathway



Cicero A et al. MedRx 2024;

Effects of low-dose monacolin K (<3mg/day) on the circulating proteome in individuals with suboptimal cholesterolaemia: A randomised clinical trial

No changes in classical markers of liver (AST, ALT) or muscle (CPK) function were detected in the plasma samples of patients treated with the supplement compared to placebo. Interestingly, the analysis of circulating proteins marking an early acute response in the liver, such as serum amyloid A4, orosomucoid 2, haptoglobin-related protein, prothrombin, α-1-antitrypsin, α-2-HS-glycoprotein, serum amyloid P (APCS), orosomucoid 1, c-reactive protein (CRP) and α-2-macroglobulin confirmed an overlapping profile in the two groups. Similarly, the analysis of ryanodine receptor 1, titin, dystrophin and myosin 7 again showed a similar profile in the two groups. These data indicate that a low dose of monacolin K (<3 mg/day) in subjects with suboptimal cholesterolaemia does not increase levels of markers of liver and skeletal muscle function in plasma, excluding a deleterious effect of monacolin K on these tissues.

Cicero A et al. MedRx 2024;

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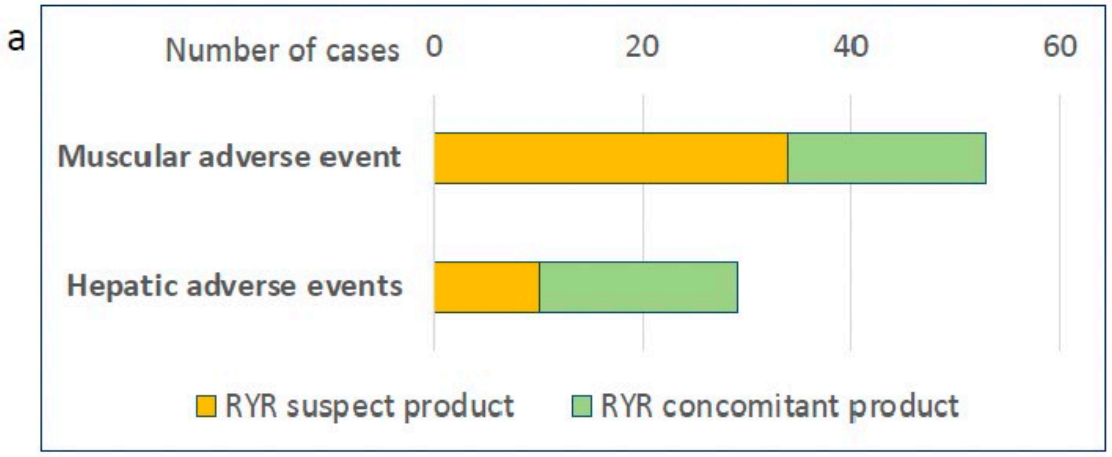
NUTRACEUTICA E SICUREZZA: TAUTOLOGIA O OSSIMORO?

RYR

- The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) analysed four sources of case reports (WHO, ANSES, Italian Surveillance System, FDA).

- 54 RCT (8535 subjects)
- Post marketing nutrivigilance
- Database FAERS e CAERS
- Proteome profiling in a RCT

Conclusion



ciated with the adverse events. However, from the names of the RYR-containing products entered into the CAERS system, one could infer that most cases are well above the recommended dose of monacolin of 3 mg/day. This would also suggest that the number of cases attributable to RYR products with a monacolin limit within the current EFSA regulation will definitely be lower. In addition, for some RYR-containing products in the CAERS database, it was later determined by the FDA that other impurities may have been responsible for the reported adverse events (https://www.safemedicines.org/2013/07/fda-alert-healthy-life-chemistry-by-purity-first-b-50-fda-health-risk-warning-undeclared-ingredients.html, accessed on 3 November 2023), although these cases are still included in the CAERS database.

FDA Alert: Healthy Life Chemistry By Purity First B-50: FDA Health Risk Warning – Undeclared Ingredients

July 26, 2013

This is a reprint of an FDA Alert

[Posted 07/26/2013]

AUDIENCE: Consumer, Health Professional

ISSUE: FDA is warning consumers that they should not use or purchase Healthy Life Chemistry By Purity First B-50, marketed as a vitamin B dietary supplement. A preliminary FDA laboratory analysis indicated that the product contains two potentially harmful anabolic steroids—methasterone, a controlled substance, and dimethazine. These ingredients are not listed in the label and should not be in a dietary supplement.

BACKGROUND: The FDA has received reports of 29 adverse incidents associated with the use of Healthy Life Chemistry By Purity First B-50. These reports include fatigue, muscle cramping, and myalgia (muscle pain), as well as abnormal laboratory findings for liver and thyroid function, and cholesterol levels. Females who used this product reported unusual hair growth and missed menstruation, and males who used the product reported impotence and findings of low testosterone.