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Integratori contenenti riso rosso fermentato: aspetti di sicurezza alla luce del nuovo regolamento europeo

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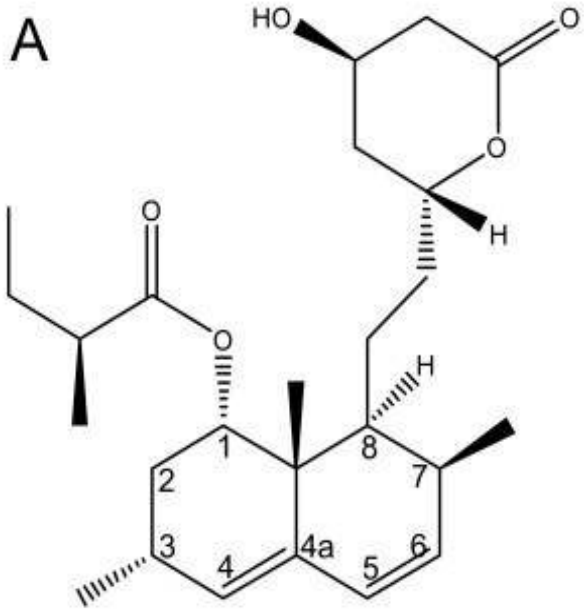
Il riso rosso fermentato (RYR)

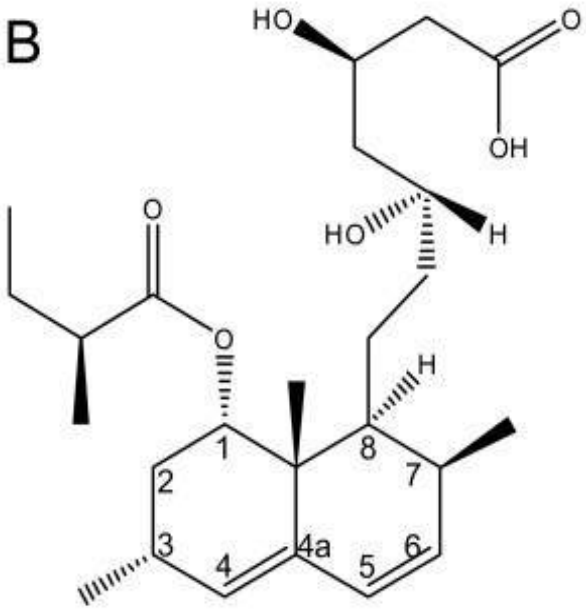
- Utilizzato in integratori alimentari per coadiuvare la riduzione della colesterolemia
- Tra i prodotti del metabolismo dei lieviti utilizzati per la fermentazione si trovano le monacoline, tra cui la principale è la monacolina K

La produzione di RYR secondo il tradizionale processo Zen OTTENUTO IN UN CONTENITORE di legno (Chen et al., 2015)

Molecole attive del riso rosso fermentato



Monacolina K



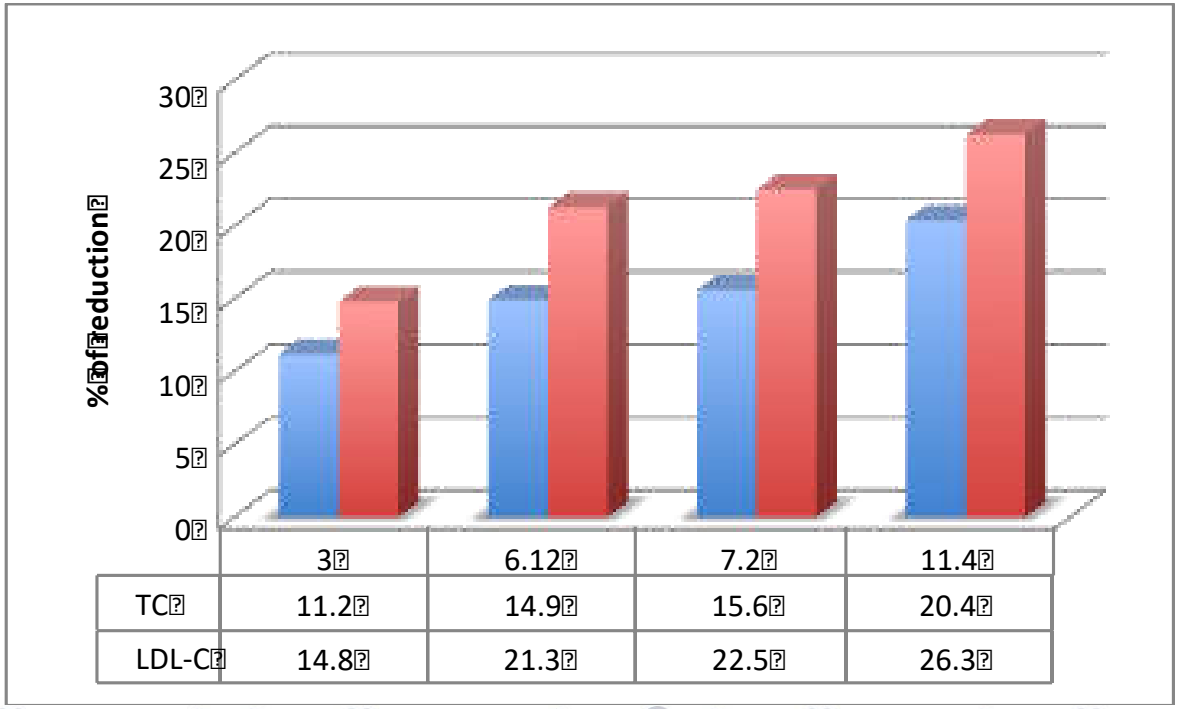
Monacolina Ka (forma acida)

Cambiamenti dei livelli di colesterolo totale e colesterolo LDL riportati in studi controllati in cui RYR era l'unico trattamento per ridurre l'ipercolesterolemia

Reference	Type of study (Period)	Number of patients	Sex age	Daily dose of RYR (monacolin K)	Total cholesterol in RYR group		LDL-Cholesterol in RYR group	
					Change (%)	Statistical significance vs placebo	Change (%)	Statistical significance vs placebo
Bogsrud et al., 2010	R, DB, PC (16 wks)	C=22 T=20	M/F 18-75 yrs	1200 mg (7.2 mg)	- 15.0	p<0.001	- 23.0	p<0.001
Becker et al., 2009	R, PC (24 wks)	C=31 T=31	M/F 21-80 yrs	3600 mg (6.12 mg)	- 14.9	p<0.016	- 21.3	p<0.011
Huang et al., 2007	R, DB, PC (8 wks)	C=40 T=39	M/F 18-65 yrs	1200 mg (11.4 mg)	- 20.4	p<0.001	- 26.3	p<0.001
Heber et al., 1999^	R, DB, PC (12 wks)	C=41 T=42	M/F 34-78 yrs	2400 mg (7.2 mg)	- 16.1	p<0.05	- 21.9	p<0.05
Heinz et al., 2016*	R, DB, PC (12 wks)	C=72 T=70	M/F 18-70 yrs	200 mg (3 mg)	- 11.2	p<0.001	- 14.8	p<0.001
Lin et al., 2005**	R, DB, PC (8 wks)	C=38 T=37	M/F 23-65 yrs	1200 mg (11.4 mg)	- 20.4	P<0.001	-26.3	p<0.001

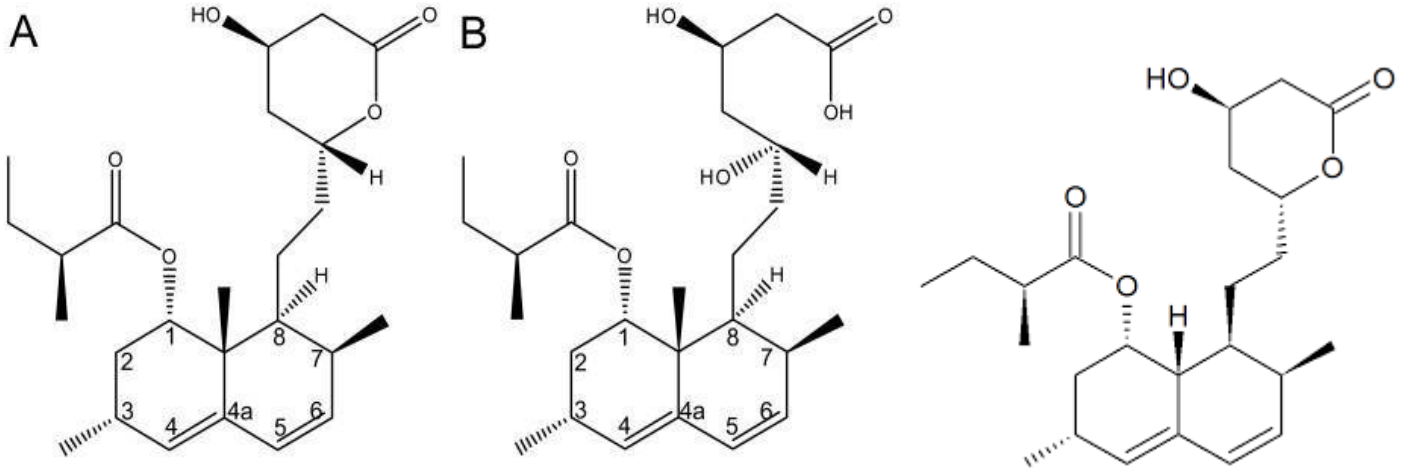
R= Randomizzato **DB= Doppio Cieco** **PC= Controllato con placebo**
C= Gruppo Controllo **T= Gruppo trattato**

Correlazione tra dose di monacolina K e riduzione della colesterolemia



	3	6.12	7.2	11.4
TC	11.2	14.9	15.6	20.4
LDL-C	14.8	21.3	22.5	26.3

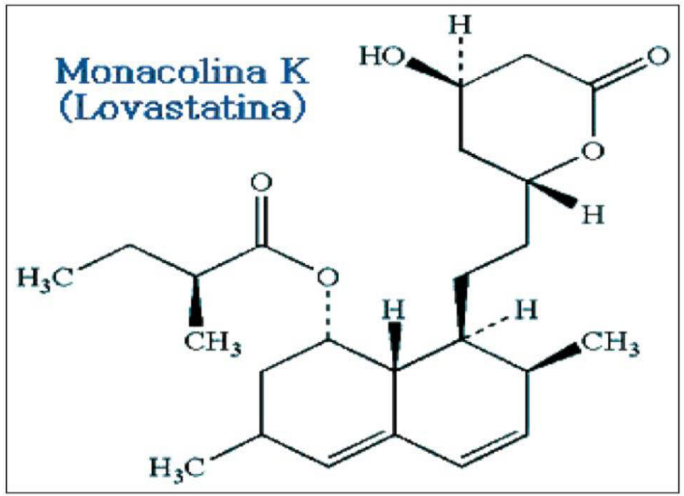
C'è una correlazione tra statine e RYR?

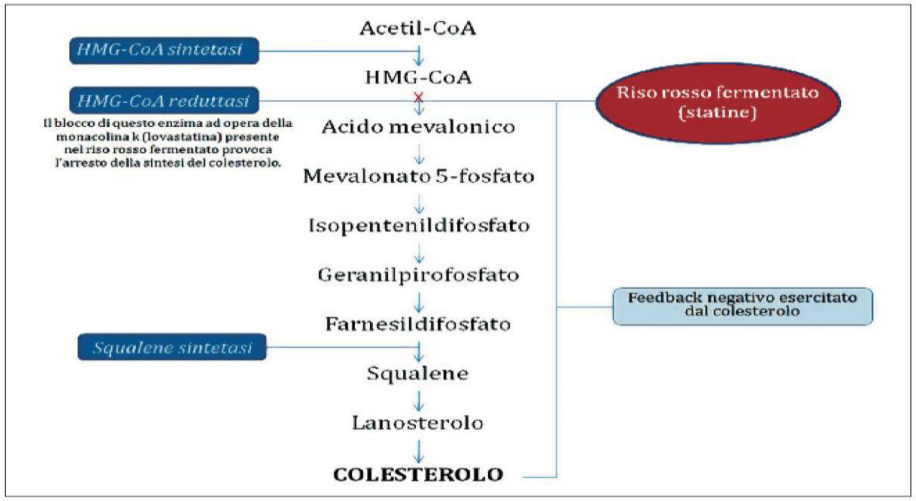


Monacolin K Monacolin Ka (acid form) **Lovastatin**

La Lovastatina è la forma lattamica della Monacolina K!

Monacolina K e statine





- Fino al giugno 2022, per utilizzare negli integratori alimentari il claim salutistico stabilito da EFSA era necessario apportare con la dose giornaliera 10 mg di monacolina K (Regolamento Europeo 432/2012)
- Problematiche di sicurezza per effetti collaterali (apparato muscoloscheletrico ed epatico), standardizzazione degli estratti e per la biodisponibilità della monacolina K che può essere variabile

Eventi avversi DOVUTI A RYR RACCOLTI DA WHO, ANSES, FDA and EU phytovigilance

- Globalmente sono stati segnalati circa **320 eventi avversi** da RYR, sebbene non tutti supportati da un controllo di causalità
- Gli organi/sistemi coinvolti negli effetti avversi segnalati dalle 4 fonti nazionali/internazionali CONSULTATE, sono:
  - I più frequenti sono associati al **tessuto muscoloscheletrico e connettivo (circa il 30% dei casi)**, con pochi eventi di rabdomiolisi;
  - **Il sistema gastrointestinale** è stato coinvolto in circa **il 15% dei casi**;
  - Gli **eventi cutanei** e sottocutanei sono stati registrati in circa il **12% dei casi**;
  - Il **sistema epatobiliare** era l'obiettivo di una percentuale significativa di casi: dal **9% dei casi WHO** al **32% di quelli ANSES**.
  - I sintomi sono identici a quelli riscontrati con l'uso di lovastatina

Appendix B – Case collected by FDA and European phytovigilance Units with assessment of level of causality[a]

Organ/system involved	ANSES (2009–May 2013)			Italian surveillance system (Apr 2002–Sep 2015)			FDA (CAERS)		
	Number cases for symptom[b]	% Total cases	Causality	Number cases for symptom[b]	% total cases	Causality	Number cases for symptom[b]	% Total cases	Causality
Musculoskeletal and connective tissue	8	32.0	VL = 1 L = 7	19	36.5	L = 11 P = 8	47	28.7	SP = 31 CM = 16
Rhabdomyolysis	1	4.0	L = 1	1	1.9	C = 1	2	1.2	SP = 2
Nervous system (including psychiatric disorders)	0	0		0	0		21	12.8	SP = 9 CM = 12
Gastrointestinal system	3	12.0	L = 2 UN = 1	12	23.1	L = 6 P = 5 UN = 1	31	18.9	SP = 21 CM = 10
Skin and subcutaneous tissue	2	8.0	VL = 1 P = 1	9	17.3	L = 3 P = 4 UN = 2	20	12.2	SP = 10 CM = 10
Hepatobiliary system	8	32.0	L = 3 P = 4 UN = 1	10	19.2	L = 7 P = 1 UN = 2	25	15.2	SP = 8 CM = 17
Other	7	28.0	P = 3 UN = 3 EX = 1	4	7.7	L = 4	56	34.1	SP = 41 CM = 15
TOTAL CASES	**25**	–		**52**			**164**		

NR: Not Reported; C: Certain; VL: Very Likely; L: Likely; P: Possible; UN: unassessable, unlikely; EX: Excluded; SP: Suspected; CM: concomitant.
(a): www.vigiaccess.org, https://www.fda.gov; ANSES; 2014; Mazzanti et al., 2017.
(b): Symptoms for each subject can be more than one.

Scientific opinion on the safety of monacolins in red yeast rice

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS),
Maged Younes, Peter Aggett, Fernando Aguilar, Riccardo Crebelli, Birgit Dusemund,
Metka Filipič, Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy,
Gunter Georg Kuhnle, Claude Lambré, Jean-Charles Leblanc, Inger Therese Lillegaard,
Peter Moldeus, Alicja Mortensen, Agneta Oskarsson, Ivan Stankovic, Ine Waalkens-Berendsen,
Rudolf Antonius Woutersen, Raul J. Andrade, Cristina Fortes, Pasquale Mosesso,
Patrizia Restani, Fabiola Pizzo, Camilla Smeraldi and Matthew Wright

2018

Abstract

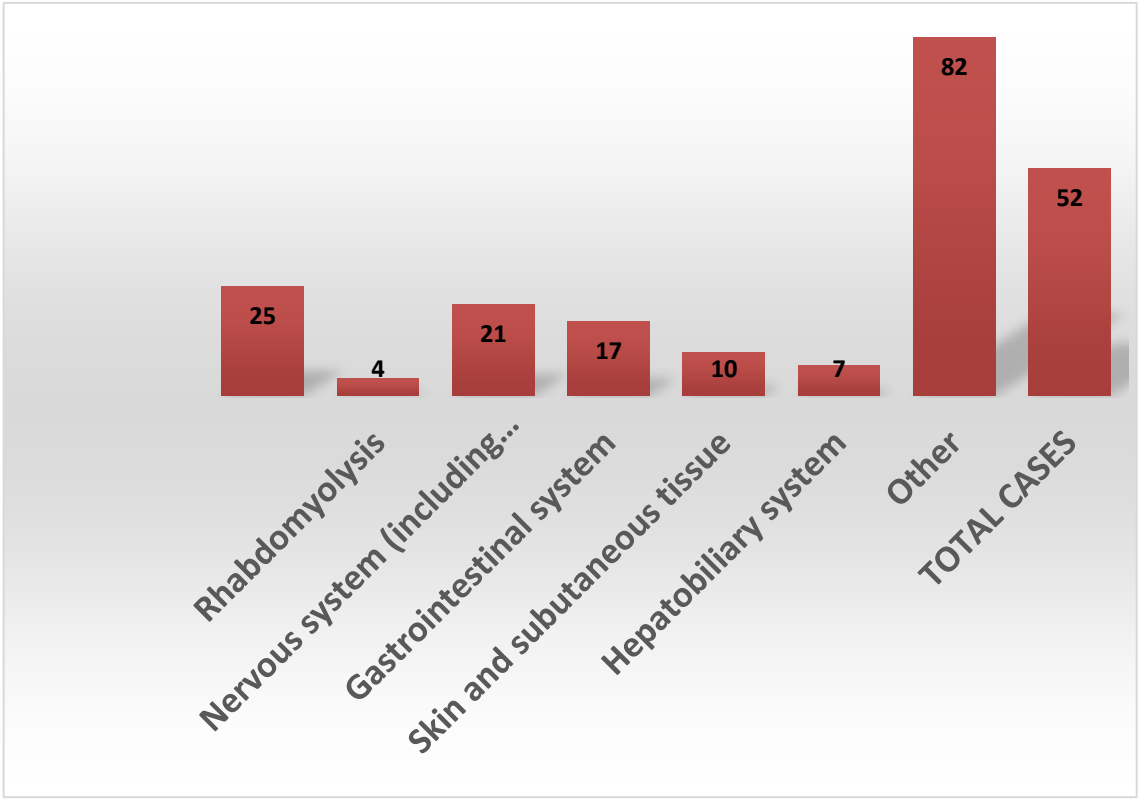
The Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to deliver a scientific opinion on the safety of monacolins in red yeast rice (RYR) and to provide advice on a dietary intake of monacolins that does not give rise to concerns about harmful effects to health. The Panel reviewed the scientific evidences available as well as the information provided by interested parties in response of a public 'Call for data' launched by EFSA. The Panel considered that monacolin K in lactone form is identical to lovastatin, the active ingredient of several medicinal products authorised for the treatment of hypercholesterolaemia in the EU. On the basis of the information available, the Panel concluded that intake of monacolins from RYR via food supplements, could lead to estimated exposure to monacolin K within the range of the therapeutic doses of lovastatin. The Panel considered that the available information on the adverse effects reported in humans were judged to be sufficient to conclude that monacolins from RYR when used as food supplements were of significant safety concern at the use level of 10 mg/day. The Panel further considered that individual cases of severe adverse reactions have been reported for monacolins from RYR at intake levels as low as 3 mg/day. The Panel concluded that exposure to monacolin K from RYR could lead to severe adverse effects on musculoskeletal system, including rhabdomyolysis, and on the liver. In the reported cases, the product contained other ingredients in addition to RYR. However, these reported effects in particular musculoskeletal effects, have both occurred after ingestion of monacolin K and lovastatin independently. On the basis of the information available and several uncertainties highlighted in this opinion, the Panel was unable to identify a dietary intake of monacolins from RYR that does not give rise to concerns about harmful effects to health, for the general population, and as appropriate, for vulnerable subgroups of the population.

Table 9: Case reports of myopathy and rhabdomyolysis associated with intake of food supplements containing monacolin K from RYR preparations, published in the scientific literature

Patient data	Daily intake of monacolin K	Period of intake	Adverse effects	Reference
Female, 52 years old	2.6 mg	90 days	Increase level of serum CK; Myalgia	Philibert et al. (2016)
Female, 53 years old	3 mg	60 days	Increased level of serum CK	Lapi et al. (2008)
Sex unknown, 48 years old	3 mg	60 days	Rhabdomyolysis (hospitalisation)	Mazzanti et al. (2017)
Female, 45 years old	3 mg	24 days	Nocturnal leg muscle cramps	Mazzanti et al. (2017)
Female, 45 years old	3 mg	54 days	Myalgia in the leg	Mazzanti et al. (2017)
Female, 53 years old	3 mg	97 days	Generalised muscle aches	Mazzanti et al. (2017)
Female, 57 years old	3 mg	60 days	Increased level of serum CK (10 times).	Mazzanti et al. (2017)
Female, 65 years old	3 mg	31 days	Cramps and myalgia of lower extremities	Mazzanti et al. (2017)
Female, 67 years old	3 mg	31 days	Increased level of serum CK, myopathy, asthenia. Previous myopathy by statins	Mazzanti et al. (2017)
Female, 68 years old	3 mg	62 days	Localised muscle pain; increased level of serum CK	Mazzanti et al. (2017)
Female, 69 years old	3 mg	25 days	Myalgia of lower extremities	Mazzanti et al. (2017)
Female, 70 years old	3 mg	90 days	Myalgia, increased level of serum CK, Previous statin intolerance	Mazzanti et al. (2017)
Female, age unknown	3 mg	> 365 days	Increased level of serum CK, previously observed with statins	Mazzanti et al. (2017)
Male, 60 years old	3 mg	165 days	Increased level of serum CK	Mazzanti et al. (2017)
Female,	4–8 mg	4 months	Myalgia	Venhuis et al. (2016)
Male, 49 years old	5 mg	60 days	Increased level of serum CK	Lapi et al. (2008)
Female, 64 years old	10.2 mg	30 days	Increase level of serum CK	Philibert et al. (2016)
Female, 51 years old	19.8 mg	30 days	Myalgia	Philibert et al. (2016)
Male, 37 years old	19.2 mg	48 days	Rhabdomyolysis, increased level of serum CK	Philibert et al. (2016)
Female, 51 years old	19.8 mg	30 days	Myalgia	Philibert et al. (2016)

CK: creatine kinase.

Casi in Italia dal 2002 al 2015 (3 mg of monacolina k) (Mazzanti et al. 2017)



HAS ADOPTED THIS REGULATION:

Article 1

Annex III to Regulation (EC) No 1925/2006 is amended as follows:

1. The following entry is added in the table in Part B 'Restricted substances' in alphabetical order:

Restricted substance	Conditions of use	Additional requirements
'Monacolins from red yeast rice	Individual portion of the product for daily consumption shall provide less than 3 mg of monacolins from red yeast rice.	The label shall provide the number of individual portions of the product for maximum daily consumption and a warning not to consume a daily amount of 3 mg of monacolins from red yeast rice or more. The label shall indicate the content of monacolins per portion of the product. The label shall include the following warnings: "Should not be consumed by pregnant or lactating women, children below 18 years old and adults above 70 years old". "Seek advice from a doctor on consumption of this product if you experience any health problems"; "Should not be consumed if you are taking cholesterol-lowering medication"; "Should not be consumed if you are already consuming other products containing red yeast rice".'

Conclusioni

- La monacolina K presente nel riso fermentato presenta lo stesso profilo farmacologico e gli stessi effetti collaterali della lovastatina
- Con il regolamento EU 2022/860, l'apporto giornaliero di monacolina non deve superare i 3 mg

Conclusioni

- Nell'opinion del 2018, EFSA ha evidenziato alcuni aspetti critici:

❖ Variabilità compositiva delle formulazioni
❖ Formulazioni multicomponenti e possibili interazioni
❖ Variabilità del rapporto della forma lattonica/acida della monacolina
❖ Mancanza di dati relativi all'effetto di altri componenti del riso rosso

- Il Panel ha concluso che non è possibile identificare un dose giornaliera di monacolina K che possa essere ritenuta sicura, poiché molti eventi avversi si sono verificati anche alla dose di 3 mg/die

GRAZIE DELL'ATTENZIONE

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