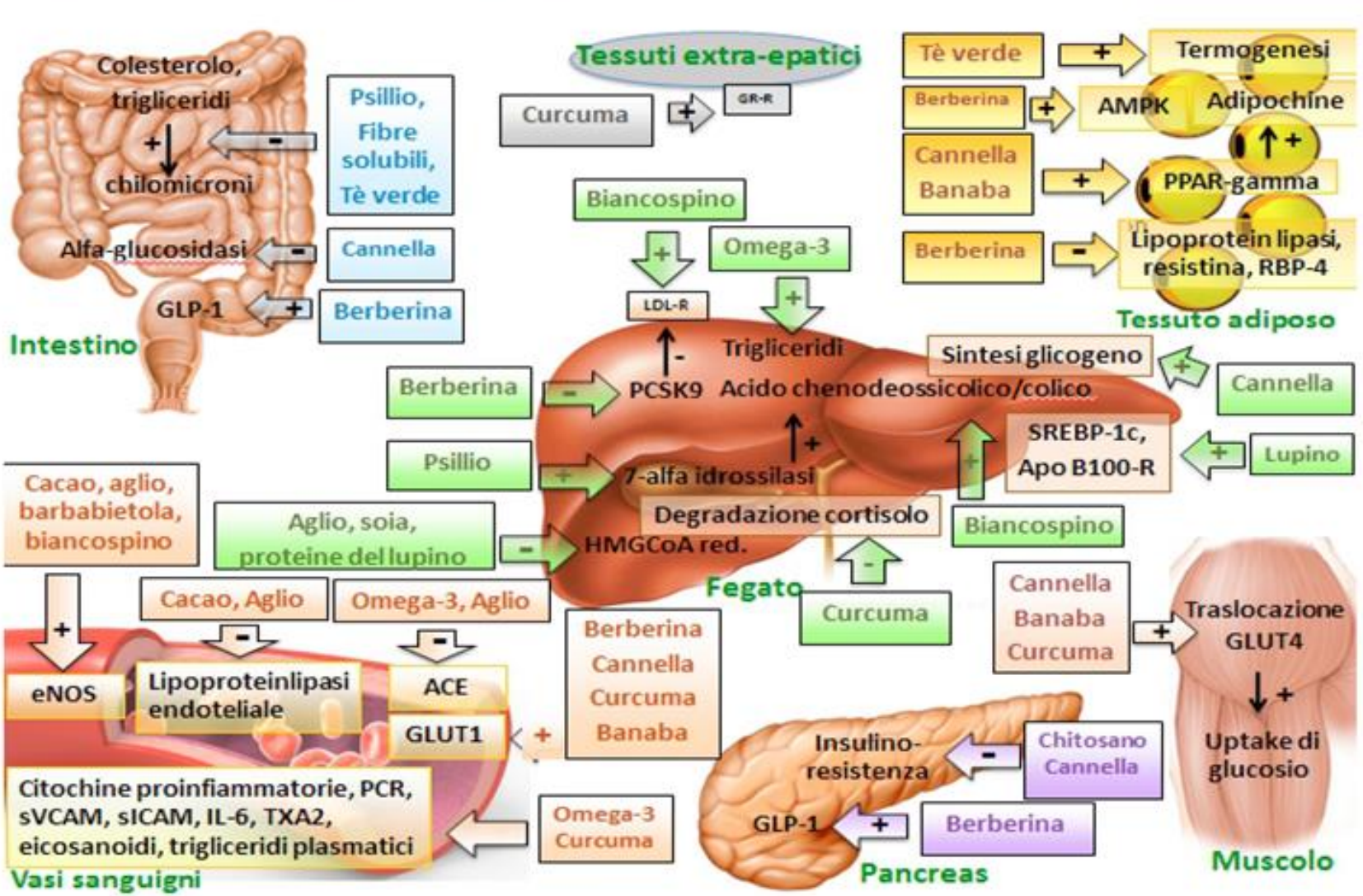
Sinergie e criticità nell'interazione fra farmaci ed integratori nella sindrome metabolica

Prof. Alberto Corsini
Università degli Studi di Milano

• FIG.1.

NUTRACEUTICI E SINDROME METABOLICA: MECCANISMI D'AZIONE



Cicero AFG e Colletti A Estratto da Role of phytochemicals in the management of metabolic syndrome" "Phytomedicine" 2015.

NUTRACEUTICI: AZIONI SULLA SINDROME METABOLICA.

Nutraceutici	Effetti sulla sindrome metabolica	Livello di evidenza
Fibre Psyllium	Ipocolesterolemizzante, anti-obesità, anti-diabetico, anti-ipertensivo	Meta-analisi di TCR nell'uomo
Gomma Guar	Ipocolesterolemizzante, insulino-sensibilizzante, anti-diabetico, anti-ipertensivo	TCR nell'uomo
Fibre del Fieno greco	Ipocolesterolemizzante, ipoglicemizzante	TCR nell'uomo
Chitosano	Ipocolesterolemizzante, anti-obesità, anti-diabetico, anti-ipertensivo	TCR nell'uomo
Glucomannano	Ipocolesterolemizzante, anti-obesità, anti-diabetico	Meta-analisi di TCR nell'uomo
Cannella	Ipocolesterolemizzante, anti-diabetico, anti-ipertensivo	Meta-analisi di TCR nell'uomo
Berberina	Ipocolesterolemizzante, insulino-sensibilizzante, anti-ipertensivo	Meta-analisi di TCR nell'uomo
Acido corosolico	Ipocolesterolemizzante, anti-diabetico, anti-obesità	TCR nell'uomo
Carantina	Insulino-sensibilizzante, ipoglicemizzante, anti-obesità	TCR nell'uomo
Catechine e flavonoli	Ipocolesterolemizzante, anti-obesità, anti-ipertensivo	Meta-analisi di TCR nell'uomo
Acidi grassi polinsaturi Omega-3	Ipocolesterolemizzante, anti-obesità, insulino-sensibilizzante, anti-ipertensivo	Meta-analisi di TCR nell'uomo
Alliina dell'aglio	Ipocolesterolemizzante, anti-obesità, anti-diabetico, insulino-sensibilizzante, anti-ipertensivo	Meta-analisi di TCR nell'uomo
Peptidi della soia	Ipocolesterolemizzante, anti-obesità, anti-diabetico, anti-ipertensivo	TCR nell'uomo
Curcumina della curcuma	Ipocolesterolemizzante, anti-obesità, ipoglicemizzante, insulino-sensibilizzante, anti-ipertensivo	TCR nell'uomo

TCR= trials clinici randomizzati

Cicero AFG e Colletti A Estratto da Role of phytochemicals in the management of metabolic syndrome" "Phytomedicine" 2015

ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano[1]* (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[1] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[1] (Finland), Lale Tokgozoglu[1] (Turkey), Olov Wiklund[1] (Sweden)

Document Reviewers: Christian Mueller (ESC Review Coordinator) (Switzerland), Heinz Drexel (EAS Review Coordinator) (Austria), Victor Aboyans (France), Alberto Corsini[1] (Italy), Wolfram Doehner (Germany), Michel Farnier (France), Bruna Gigante (Sweden), Meral Kayikcioglu[1] (Turkey), Goran Krstacic (Croatia), Ekaterini Lambrinou (Cyprus), Basil S. Lewis (Israel), Josep Masip (Spain), Philippe Moulin[1] (France), Steffen Petersen (United Kingdom), Anna Sonia Petronio (Italy), Massimo Francesco Piepoli (Italy), Xavier Pintó[1] (Spain), Lorenz Räber (Switzerland), Kausik K. Ray[1] (United Kingdom), Željko Reiner[1] (Croatia), Walter F. Riesen (Switzerland), Marco Roffi (Switzerland), Jean-Paul Schmid (Switzerland), Evgeny Shlyakhto (Russian Federation), Iain A. Simpson (United Kingdom), Erik Stroes[1] (Netherlands), Isabella Sudano (Switzerland), Alexandros D. Tselepis[1] (Greece), Margus Viigimaa[1] (Estonia), Cecile Vindis (France), Alexander Vonbank (Austria), Michal Vrablik[1] (Czech Republic), Mislav Vrsalovic (Croatia), José Luis Zamorano Gomez (Spain), Jean-Philippe Collet (ESC CPG Supervisor) (France)

Table 5 Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

	Total CV risk (SCORE) %	Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high-risk (see *Table 4*)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
	≥10, or at very-high risk due to a risk condition (see *Table 4*)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary prevention	Very-high-risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class[a]/Level[b]	IIa/A	I/A	I/A	I/A	I/A	I/A

CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Estimation.
[a]Class of recommendation.
[b]Level of evidence.

European Heart Journal (2019) 00, 178

Table 8 Impact of specific lifestyle changes on lipid levels

	Magnitude of the effect	Level	Reference
Lifestyle interventions to reduce TC and LDL-C levels			
Avoid dietary trans fats	++	A	129,138
Reduce dietary saturated fats	++	A	129,139
Increase dietary fibre	++	A	140,141
Use functional foods enriched with phytosterols	++	A	142,143
Use red yeast rice nutraceuticals	++	A	144–146
Reduce excessive body weight	++	A	147,148
Reduce dietary cholesterol	+	B	149,150
Increase habitual physical activity	+	B	151
Lifestyle interventions to reduce TG-rich lipoprotein levels			
Reduce excessive body weight	+	A	147,148
Reduce alcohol intake	+++	A	152,153
Increase habitual physical activity	++	A	151,154
Reduce total amount of dietary carbohydrates	++	A	147,155
Use supplements of n-3 polyunsaturated fats	++	A	156,157
Reduce intake of mono- and disaccharides	++	B	158,159
Replace saturated fats with mono- or polyunsaturated fats	+	B	129,137
Lifestyle interventions to increase HDL-C levels			
Avoid dietary trans fats	++	A	129,160
Increase habitual physical activity	+++	A	151,161
Reduce excessive body weight	++	A	147,148
Reduce dietary carbohydrates and replace them with unsaturated fats	++	A	147,162
Modest consumption in those who take alcohol may be continued	++	B	153
Quit smoking	+	B	163

The magnitude of the effect (+++ = >10%, ++ = 5–10%, + = <5%) and the level of evidence refer to the impact of each dietary modification on plasma levels of a specific lipoprotein class.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

European Heart Journal (2019) 00, 178

Pharmacological Research 134 (2018) 51–60

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Invited review

Nutraceuticals and functional foods for the control of plasma cholesterol levels. An intersociety position paper

Andrea Poli[a,*], Carlo M. Barbagallo[b], Arrigo F.G. Cicero[c], Alberto Corsini[d], Enzo Manzato[e], Bruno Trimarco[f], Franco Bernini[g], Francesco Visioli[h], Alfio Bianchi[i], Giuseppe Canzone[j], Claudio Crescini[k], Saula de Kreutzenberg[l], Nicola Ferrara[m], Marco Gambacciani[n], Andrea Ghiselli[o], Carla Lubrano[p], Giuseppe Marelli[q], Walter Marrocco[r], Vincenzo Montemurro[s], Damiano Parretti[t], Roberto Pedretti[u], Francesco Perticone[v], Roberto Stella[w], Franca Marangoni[a]

Table 1
Efficacy of some active ingredients on plasma LDL cholesterol.

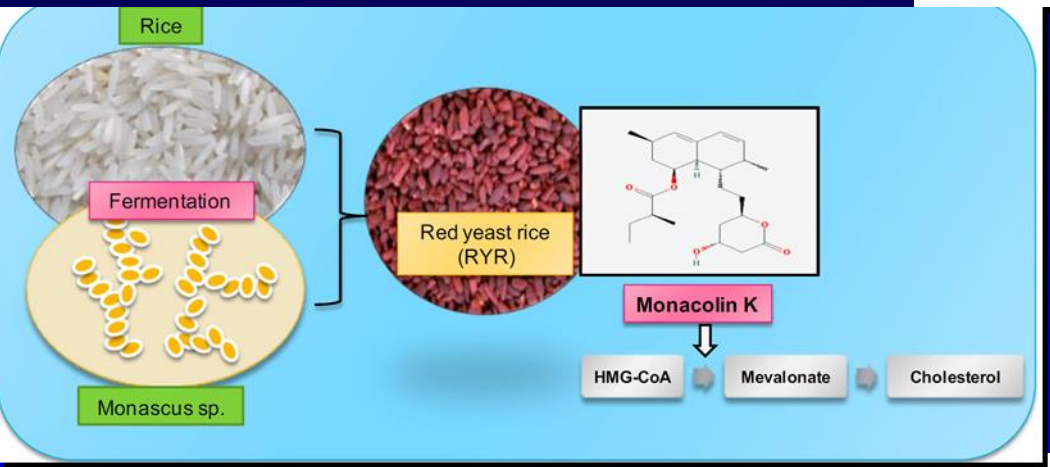
Active ingredient	Dose	Average effect on LDL-c
Sterols and plant stanols	1.5-3.0 g/day	13.8 mg/dL (-9.2-18.3) calculated from [19]
Red Yeast Rice	3-10 mg/day (titrated in Monacolin K)	33.4 mg/dL (-27.3-39.6) [25]
Beta glucan	3.4 g/day	7,3 mg/dL (-5.4-8.8) [34]
Policosanol	10-80 mg/day	0.0 mg/dL (-13.8 + 13.8) [48]
Berberine	500-1500 mg/day	25.0 mg/dL (-20.7-29.2) [35]
Soy	30 g/day	4.8 mg/dL (-2.3-7.3) [41]

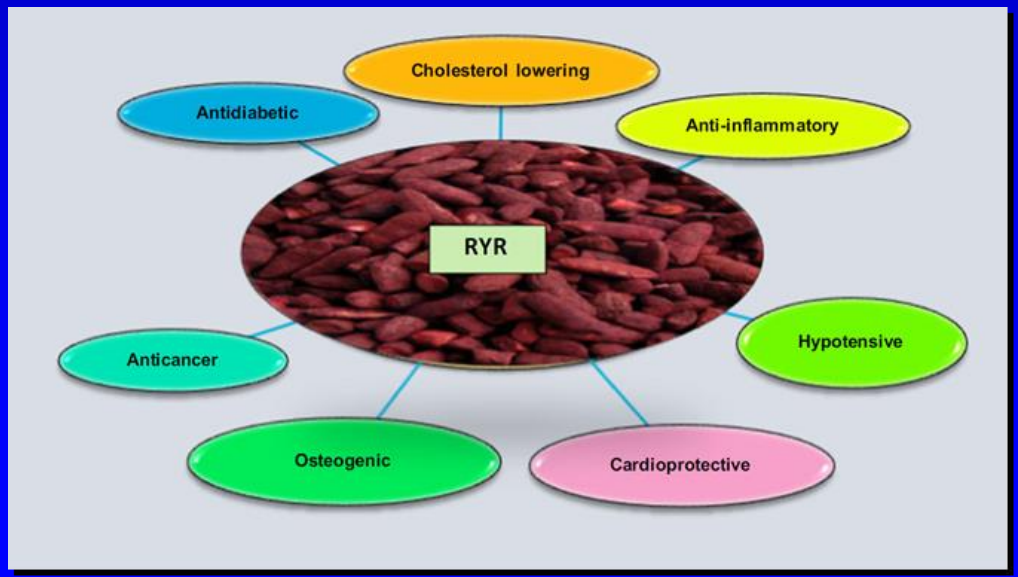
World J Microbiol Biotechnol (2016) 32:87
DOI 10.1007/s11274-016-2035-2

REVIEW

Functional food red yeast rice (RYR) for metabolic syndrome amelioration: a review on pros and cons

Seema Patel[1]





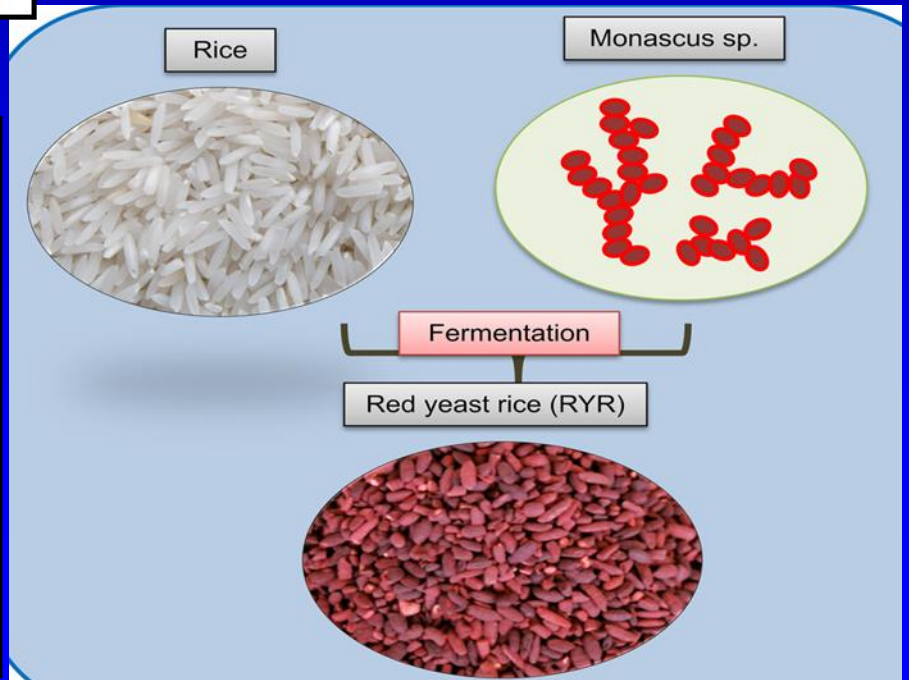


Table 7 Meta-analyses of randomized controlled trials in humans on the lipid-lowering effects of red yeast rice.

Type of study	Subjects (number, type)	Content of monacolin K	Mean duration (range)	Observed effect	Ref.
Meta-analysis of 93 RCT	n: 9625 Dyslipidemia	3–12.4 mg/day	8 weeks (4–24 weeks)	↓ LDL-C: −28 mg/dl ↓ TG: −36 mg/dl ↑ HDL-C: 5.8 mg/dl	[112]
Meta-analysis of 13 RCT	n: 804 Dyslipidemia	2–11.4 mg/day	12 weeks (4–24 weeks)	↓ LDL-C: −34 mg/dl ↓ TG: −20 mg/dl No effect on HDL-C	[113]
Meta-analysis of 20 RCT	n: 2811 Dyslipidemia Type 2 diabetes CHD, Hypertensive	4.8–24 mg/day	23 weeks 4–168 weeks	↓ LDL-C: −39 mg/dl ↓ TG: −23 mg/dl ↑ HDL-C: 2.7 mg/dl	[114]
Meta-analysis of 21 RCT	n: 4558 Hypertensive	(RYR 1200–1800 mg/day)	4–234 weeks	↓ LDL-C: −24 mg/dl No effect on TG and HDL-C	[115]

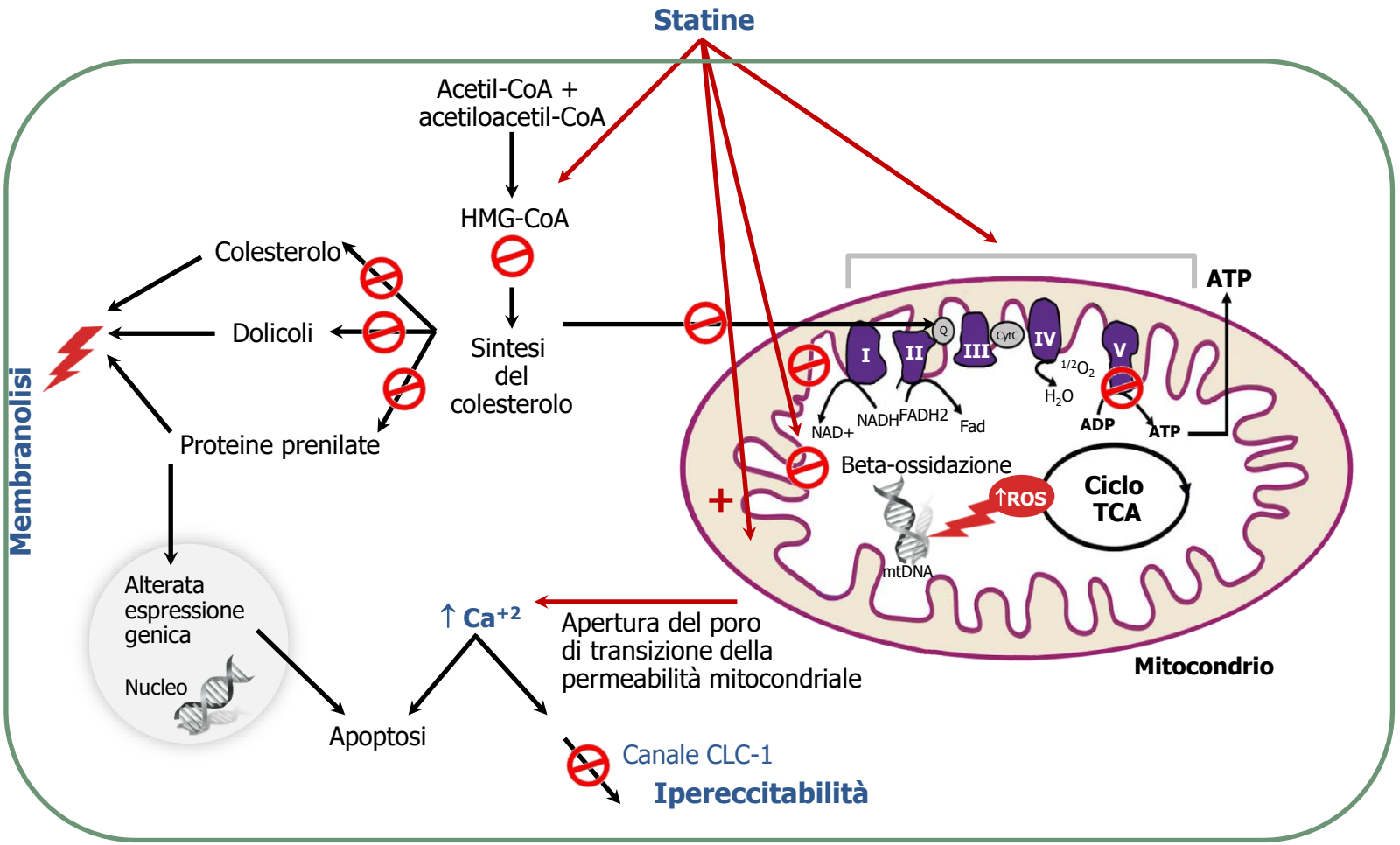
↑: increase, ↓: reduction, HDL-C: HDL cholesterol, LDL-C: LDL cholesterol, CHD: coronary heart disease, RYR: red yeast rice, TG: triglycerides, RCT: randomized controlled trials.

Pirro M et al Nutrition, Metabolism & Cardiovascular Diseases (2017) 27, 2e17

DOI: 10.1111/eci.12461
REVIEW

The role of mitochondria in statin-induced myopathy

Maria Apostolopoulou[*,†], Alberto Corsini[‡,§] and Michael Roden[*,†,¶]



Prof. Alberto Corsini

Apostolopoulou M et al. Eur J Clin Invest 2015;45(7):745-54

RHABDOMYOLYSIS DUE TO RED YEAST RICE *(Monascus purpureus)* IN A RENAL TRANSPLANT RECIPIENT

G. V. Ramesh Prasad,[1,3] Timothy Wong,[2] Galo Meliton,[1] and Salma Bhaloo[2]

Transplantation. 2002 Oct 27;74(8):1200-1

Symptomatic Myopathy due to Red Yeast Rice

19 September 2006 Annals of Internal Medicine Volume 145 • Number 6

The combination of red yeast with statins is not recommended.

Alberico L. Catapano et al. Eur Heart J 2016;eurheartj.ehw272

Effetti collaterali da RYR (Monascus) in Italia

- 52 reports (su 55 AR) relativi al RYR raccolti tra aprile 2002 e settembre 2015
- 13 ospedalizzazioni; tutti risolti positivamente
- **Una Rabdomiolisi***, 10 casi di danno epatico, 19 casi di mialgia e/o aumento CK

* In un paziente con pregressa rabdomiolisi da statina!

Mazzanti G et al, Brit J Clin Pharm, 2017

Il rischio di miopatia/rabdomiolisi potenziale o documentato è inoltre aumentato da:

- uso concomitante di lovastatina con potenti inibitori dell'enzima CYP3A4 (la lovastatina è un substrato del citocromo P450 isoforma 3A4 (CYP3A4)): amiodarone, cannabinoidi, claritromicina, ciclosporina, chinino, cimetidina, danazolo, delavirdina, diltiazem, eritromicina, fluconazolo, fluoxetina, fluvoxamina, inibitori delle HIV proteasi, indinavir, iperico, itraconazolo, ketoconazolo, omeprazolo, metronidazolo, miconazolo, nefazodone, nelfinavir, mibefradil, norfloxacina, propoxifene, ritonavir, saquinavir, sertralina, telitromicina, troleandomicina, verapamil, zafirlukast, discrete quantità di succo di pompelmo (0,20 l/die) e di camomilla.

Di conseguenza:
L'uso concomitante di lovastatina con itraconazolo, ketoconazolo, eritromicina, claritromicina, telitromicina, inibitori delle HIV proteasi, nefazodone, discrete quantità di succo di pompelmo (0,20 l/die) e camomilla dovrebbe essere evitato. Nei casi in cui il trattamento con questi farmaci fosse indispensabile, la somministrazione di lovastatina dovrebbe essere sospesa. L'uso concomitante di altri farmaci aventi un forte effetto inibitore del sistema CYP3A4 dovrebbe essere evitato salvo che i benefici attesi non prevalgano sul rischio possibile.

La dose di lovastatina non dovrebbe superare i 20 mg/die in pazienti che ricevano un trattamento concomitante con farmaci immunosoppressivi (esempio ciclosporina), gemfibrozil, altri fibrati, o alte dosi di niacina (acido nicotinico) (1 g/die o dosi maggiori).

Pharmacological Research 134 (2018) 51–60

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Current evidence shows that cholesterol management either reduces the likelihood of cardiovascular disease (CVD) or slows down its progression. Hence, it is important that all health professionals make appropriate use of all the available intervention strategies to control risk factors: from dietary improvement and positive lifestyle changes to the use of functional foods, food supplements, and drugs. This review examines the effect of the most frequently occurring cholesterol-lowering substances in functional foods or in supplements across Europe, namely plant sterols and stanols, monacolin K found in red yeast rice, berberine and beta-glucans. We conclude that currently available supplements and functional foods can effectively reduce plasma LDL cholesterol levels by about 5 to 25%, either alone or in combination. Suitable candidates for these products are mainly individuals at low absolute cardiovascular risk at a young age or according to classic algorithms. Of note, despite being freely available for purchase, these products should be used following shared agreement between the physician and the patient ("concordance").

Bundesinstitut für Risikobewertung

DOI 10.17590/20200205-121500

A questionable way to lower cholesterol: food supplements containing red yeast rice to be taken only on medical advice

BfR opinion No 003/2020 issued 15 January 2020

Red “yeast” rice (also known as red rice) has its traditional origin in China. Red yeast rice is made by fermenting boiled white rice with a type of mould of the *Monascus* genus. This produces substances that dye the rice bright red. In East Asia in particular, red yeast rice is therefore used as a food colouring. The fermentation process also leads to the production of compounds that can have pharmacological effects (like medicines) and that may also be harmful to health.

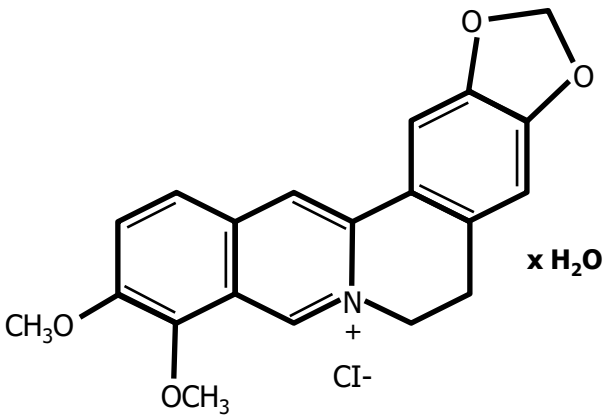
Important in this context are monacolins: these are chemical compounds that occur naturally in certain types of mould. Monacolins can also be found in red yeast rice and can inhibit an enzyme in the liver that the body requires in order to make cholesterol. **Monacolin K** is especially important, since red yeast rice contains considerable amounts of this compound. In terms of its structure and activity, monacolin K is identical to the drug substance **lovastatin**. This substance is used in medicinal products requiring authorisation, to lower cholesterol levels.

In an overview of ‘nutraceuticals’ in the context of dyslipidaemia, which also mentions red yeast rice products, Patti et al., 2017, also state that the consumption of these kinds of formulations cannot yet be recommended without more extensive data on the risk-benefit ratio, as well as further studies addressing the questions of tolerability and safety for long-term use (Patti et al., 2017). In a similar way, the position paper authored by Poli et al., 2018, also calls for the monitoring of red yeast rice product use by medical practitioners. The authors note in particular the need to monitor potential interactions between red yeast rice products containing monacolin K and certain kinds of medicines (Poli et al., 2018). In a subsequent publication, Poli and Visioli, 2019, underline the urgency of their recommendation for medical supervision during the consumption of red yeast rice products, referring once more to the potential for relevant interactions between certain kinds of medicines and for adverse events, which may occur at daily doses as low as 3 mg of monacolin K (Poli and Visioli, 2019). Other authors call for the systematic collection of more extensive clinical data on safety and efficacy before the placing on the market of formulations (some of which also referred to as ‘nutriceuticals’) such as red yeast rice products (Santini et al., 2018).

Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins

Weijia Kong[1,5], Jing Wei[2,5], Parveen Abidi[3,5], Meihong Lin[3], Satoru Inaba[3], Cong Li[3], Yanling Wang[4], Zizheng Wang[2], Shuyi Si[1], Huaining Pan[2], Shukui Wang[2], Jingdan Wu[2], Yue Wang[4], Zhuorong Li[1], Jingwen Liu[3] & Jian-Dong Jiang[1,4]

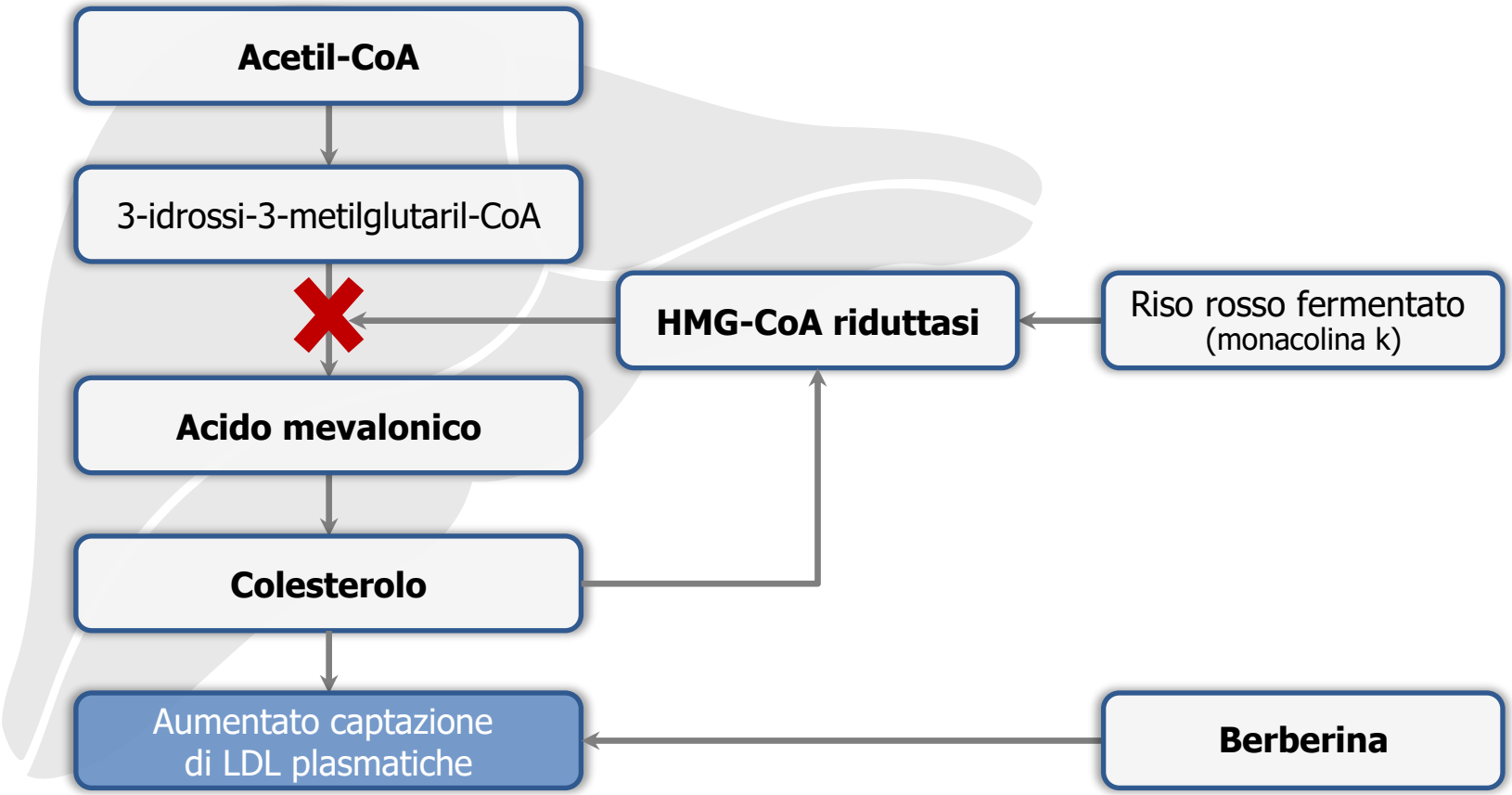
Effetti della berberina sui lipidi sierici in un sottogruppo di pazienti ipercolesterolemici non trattati con altri farmaci



Trattamento (3 mesi)		**Berberina**	**Placebo**
Colesterolo sierico >5,2 mmol/l		n=32	n=11
Colesterolo	Prima Dopo	5,9±0,7 4,2±0,9	6,1±0,6 6,0±2,8
Trigliceridi	Prima Dopo	2,3±1,8 1,5±0,9	2,2±0,8 2,1±0,9
C-HDL	Prima Dopo	1,1±0,3 1,1±0,3	1,2±0,5 1,2±0,4
C-LDL	Prima Dopo	3,2±0,7 2,4±0,6	3,7±0,7 3,7±0,8

Kong W et al. Nat Med 2004;10(12):1344-51

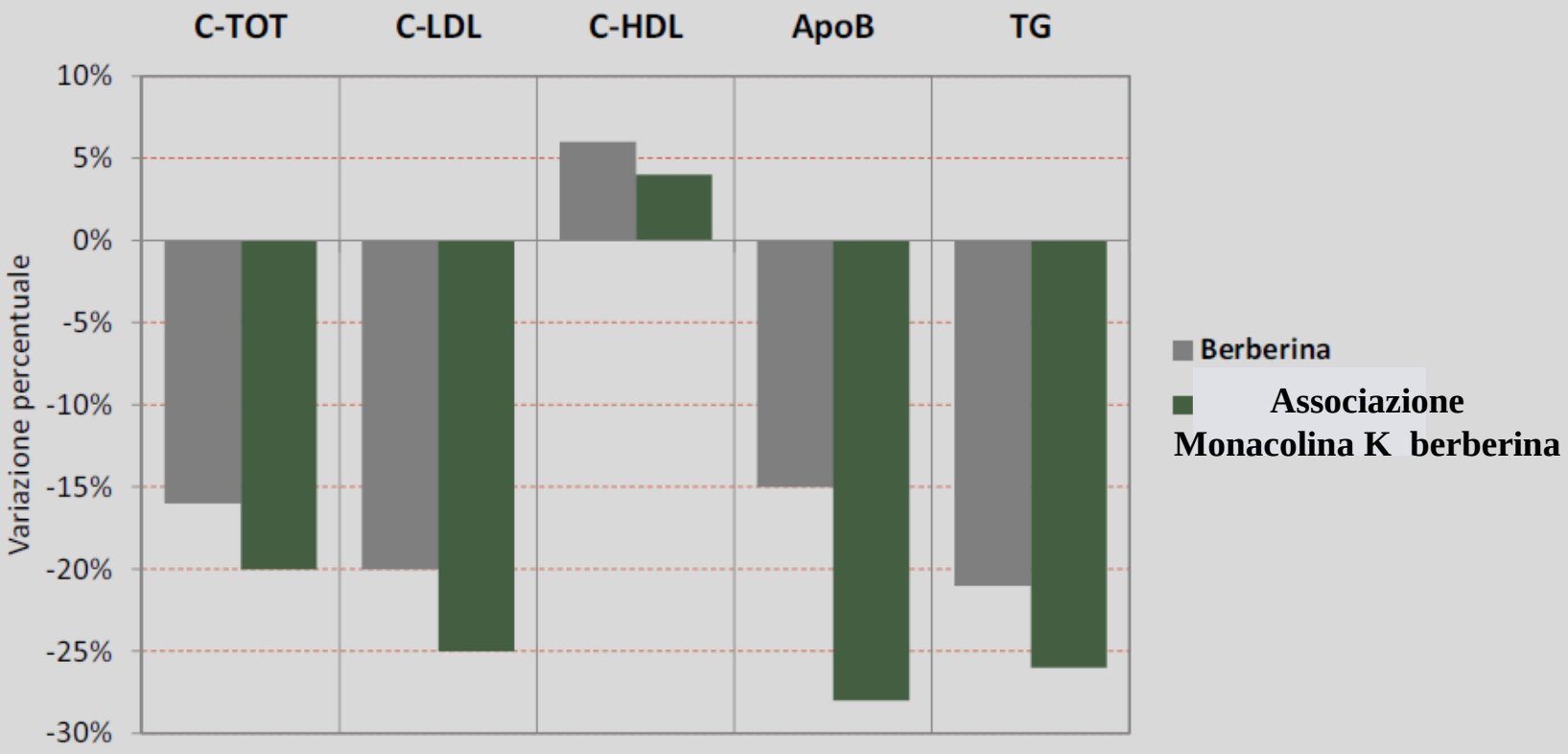
Meccanismi alla base della riduzione del colesterolo



- Mediante meccanismi che agiscono in modo complementare sulla regolazione dei **lipidi endogeni** si ottiene una riduzione del C-LDL circolante

Risultati

Variazione percentuale del profilo lipidico dopo 4 settimane di trattamento



AFG Cicero et al *Arzneimittel-Forschung (Drug Research)* **2007**; 57(1): 26–30

Risultati

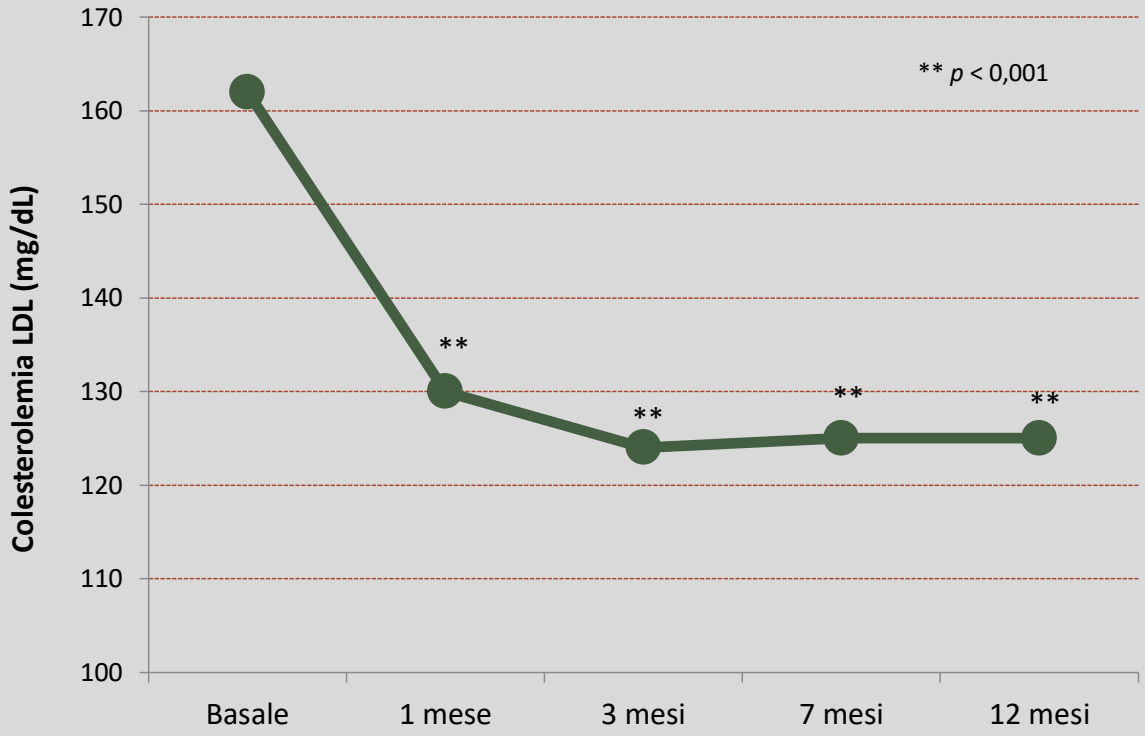
Variazione del profilo metabolico dopo 12 mesi di trattamento con monacolina k-berberina associato alla dieta o con la sola dieta

	N = 79 normopeso Associazione	N = 85 sovrappeso Associazione	N = 50 sovrappeso Dieta
Col TOTALE (mg/dL)	-38 ± 20	-42 ± 17	-23 ± 17
Col LDL (mg/dL)	-29 ± 26	-27 ± 21	-6 ± 22
Col HDL (mg/dL)	+5 ± 6	+5 ± 6	+2 ± 6
Trigliceridi (mg/dL)	-71 ± 56	-103 ± 54	-97 ± 51
BMI (kg/m^2)	-0.3 ± 0.1	-0.6 ± 0.8	-0.3 ± 0.1
Glicemia (mg/dL)	-	-21 ± 15	-11 ± 13
Insulinemia (mU/mL)	-	-4.3 ± 4.8	-3.5 ± 4.2
HOMA-IR	-0,2 ± 0,8	-1.6 ± 1.5	-1.2 ± 1.3
MMP-2 (ng/mL)	-279 ± 255	-419 ± 295	-257 ± 322
MMP-9 (ng/mL)	-69 ± 54	-85 ± 57	-43 ± 53
TIMP-1 (ng/mL)	-31 ± 74	-	-61 ± 41
TIMP-2 (ng/mL)	-1.9 ± 6.5	-1.5 ± 6.5	-6.6 ± 8.0

AFG Cicero et al *Nutrafoods* **2012**; 11; 55-61

Risultati

Variazione dei livelli di colesterolo LDL dopo 12 mesi di trattamento con associazione Monacolina K -Berberina in 40 pazienti dislipidemici in sovrappeso



MC Masoni et al *Il Giornale di AMD* **2014**, 58-60

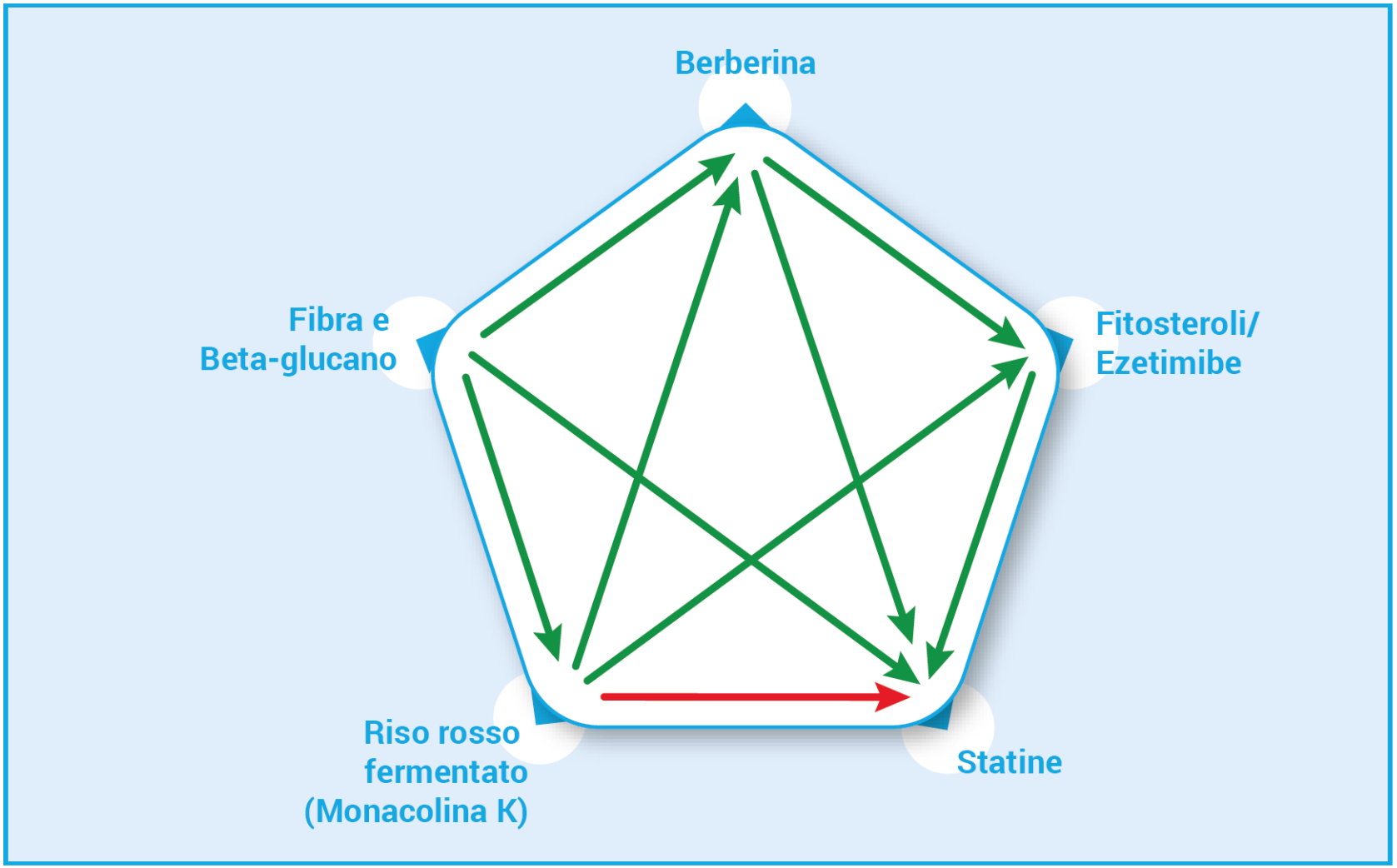


Figura 3

Possibili combinazioni di principi ad azione ipocolesterolemizzante.

Frecce verdi: combinazioni razionali. Frecce rosse: combinazioni non raccomandate

Poli A et al 2018 Documento Intersocietario

Gupta *et al. Diabetol Metab Syndr (2017) 9:59*
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Diabetology & Metabolic Syndrome

REVIEW

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Interactions between antidiabetic drugs and herbs: an overview of mechanisms of action and clinical implications

Ramesh C. Gupta[1,2], Dennis Chang[1,3*], Srinivas Nammi[1,3], Alan Bensoussan[1], Kellie Bilinski[1] and Basil D. Roufogalis[1,4]

Table 1 continued

Herb	Co-administered anti-diabetic drug	Experimental/ clinical study	Observation
St. John's wort	Metformin	Clinical	Decreased renal clearance of metformin but no other pharmacokinetic effects. However SJW decreased the area under glucose concentration-time curve. Improved glucose tolerance by enhancing insulin secretion independently of insulin sensitivity in male subjects taking metformin
	Repaglinide	Clinical	No effect on blood glucose lowering and insulin elevating effects of repaglinide. No significant effect on pharmacokinetics and pharmacodynamics of repaglinide
Radix astragali	Pioglitazone	Experimental	Co-administration did not affect pharmacokinetics of pioglitazone
Scutellaria	Metformin	Experimental	Significant elevations of plasma and pancreatic levels and reduction of plasma and hepatic levels of triglycerides an cholesterol
			Herb enhanced the antidiabetic action of metformin