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Nutraceutical alternatives to red yeast rice extract/monacolin K for moderate hypercholesterolaemia: Current evidence and knowledge gaps

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ABSTRACT

The nutraceutical approach to moderate hypercholesterolaemia is an interesting option in the context of appropriate conditions associated with low cardiovascular risk, and red yeast rice (RYR) extract is one of the most utilized products in this field. Monacolin K, the RYR main active component, reduces serum LDL-C levels via inhibition of β-Hydroxy β-methylglutaryl-CoA reductase, similarly to statins. In 2011, EFSA approved the claim regarding monacolin K from RYR extract and maintenance of normal cholesterol levels. However, in 2018, EFSA issued a warning about potential adverse effects of this nutraceutical and, in 2022, the European Commission published a Regulation with several limitations of its use. Therefore, current research and development efforts are aiming at assessing efficacy and safety of other known and novel nutraceutical products which may benefit patients with moderate hypercholesterolaemia. These active agents range from phytosterols, probiotics and berberine to bergamot, cabbage, artichoke extracts and soy protein. Moreover, plant extracts from traditional medicine, for example from African countries, are also a subject of study in this field. The full clinical exploitation of many of them, however, still requires robust clinical evidence, which should be the objective of future research.

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Keywords
Nutraceutical; hypercholesterolaemia; red yeast rice; monacolin K; LDL-cholesterol; phytosterol; berberine; probiotics

Introduction

Cardiovascular disease (CVD) is the first cause of death worldwide and is specifically linked to increased premature mortality and raised health care costs (1). CVD prevalence has gradually increased over the last decades, along with the number of associated deaths, largely due to modifiable risk factors (2). According to the comparative risk assessment analysis provided by the Global Burden of Diseases, Injuries, and Risk Factors Study (1), high systolic blood pressure has been identified as the leading CVD risk factor, followed by unhealthy diet related risks (3), high low-density lipoprotein cholesterol (LDL-C) and fasting glucose plasma levels, high body-mass index, smoking (4), alcohol abuse (5), and physical inactivity (6). Moreover, sleep quality (7), and psychological stress (8) contribute to increase the CVD risk (9). Therefore, the adjustment of these modifiable factors could help in limiting the development and in preventing of CVD (10, 11). Atherosclerosis is the dominant cause of CVD and results, when combined with thrombosis, in severe atherosclerotic CVD (ASCVD). Atherosclerosis is the result of several different pathophysiological events, including the deposition of cholesterol crystals at the level of the intima layer in the arteries, subsequently combined with a fibrous layer comprising smooth muscle cells, leukocytes, and connective tissue (12). As a direct consequence, lipid-lowering based therapy is indeed considered the first choice in patients with hypercholesterolaemia, combined or not with hyperlipidaemia (13-15). Lipid-lowering drugs include 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), Proprotein Convertase Subtilisin/Kexin type 9" (PCSK9) inhibitors, bempedoic acid,

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fibrates, bile acid sequestrants (anion exchange resins), niacin (nicotinic acid), and selective cholesterol absorption inhibitors (e.g., ezetimibe) (15-17). Moreover, there is evidence of reduction of CVD risk by lifestyle modifications (18, 19), mainly focused in the control of LDL-C levels (20), and that lifestyle modification is recommended as the first line of management for subjects with LDL-C level up to 116 mg/dL, if at low CVD risk (SCORE <1%), or with lower LDL-C level, if at greater CVD risk (13). It is well known that the long-term prescription of lipid-lowering drugs could be associated with side effects (21), such as hepatotoxicity (22) and myopathy (23, 24), in addition to the increased risk of type 2 diabetes mellitus (T2DM) (25, 26). To overcome this issue, it has been recently identified a "treatment gap" between lifestyle changes and the standard drug therapy. This gap could be filled up by nutraceuticals (27), which are defined as "a food or part of a food that provides benefits to health in addition to its nutritional content", and thereby could be used as an alternative or in addition to pharmacological therapy (28). More specifically, nutraceuticals have been thought to help in preventing illness onset of a variety of pathological conditions such as hypertension (29), T2DM (30), hypertriglyceridemia (31), or hypercholesterolaemia (32, 33). In this review we discuss the current nutraceutical approaches for mild or moderate hypercholesterolaemia, focusing our overview on red yeast rice (RYR) extract/monacolin K properties and critical issues and on the nutraceutical alternatives to this popular product for hypercholesterolemia.

Red yeast rice extract

Red yeast rice (RYR) extract is one of the most frequently used nutraceuticals for the management of mild/moderate hypercholesterolaemia. It is the product of *Monascus purpureus* yeast's fermentation of red rice (*Oryza sativa*). This fermentation process produces monacolins, about 2% in the commonly used RYR extract, and one of their subtypes is monacolin K. This is structurally identical to lovastatin, which was first isolated (under the name of mevinolin) at the end of the 1970s from the fungus *Aspergillus terreus* (34). The main mechanism of action of monacolin K is the inhibition of the β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase enzyme, a key player of the endogenous cholesterol synthesis pathway (**Figure 1**), making RYR a highly effective cholesterol-lowering nutraceutical on the market.

However, the pharmacokinetics and bioavailability of different RYR extract preparations may differ according to relative abundance of the several active components, which may affect the pharmacokinetic profile of monacolin K. On September 1987, the American Food and Drug Administration (FDA) approved lovastatin as a drug for clinical use under the name Mevacor. In 2011, the European Food Safety Authority (EFSA) and the European Commission (EC) declared the existence of a causal relationship between the daily intake of monacolin K from RYR and the maintenance of normal concentrations of LDL-C in the blood (https://www.efsa.europa.eu/it/efsajournal/pub/2304) (**Figure 2**). Both EFSA and the EC raised the warning that the RYR formulations could contain impurities, such as citrinin, which is a mycotoxin metabolite derived from *Monascus purpureus* fermentation (35). Several animal studies demonstrated that the chronic use of citrinin is nephrotoxic and gradually leads to hyperplasia of the renal tubular epithelium, renal adenomas, and sometimes to malignant renal tumors. Furthermore, citrinin may cause reproductive toxicity, malformations, or even embryo toxicity (36). In consideration of the presence of these impurities, in 2014 the EC established the maximum acceptable level of citrinin in food supplements based on rice fermented with *Monascus purpureus* as 2,000 pg of citrinin/1 kg of food supplement (EFSA Panel on Contaminants in the Food Chain (CONTAM)). Scientific opinion on the risk for public and animal health related to the presence of citrinin in food and feed. https://www.efsa.europa.eu/it/efsajournal/pub/2605). In 2018, EFSA approved the opinion that monacolin K in the form of lactone is identical to lovastatin, a drug used in the treatment of hypercholesterolaemia. EFSA stated that taking monacolin K from RYR in the form of dietary supplements can lead to monacolin K exposure equal to therapeutic doses of lovastatin and has therefore emphasized the possibility of adverse reactions similar to those occurring while using lovastatin. Furthermore, the information available to date on adverse reactions are sufficient to state that RYR monacolins used in food supplements at doses of 20 mg/day could cause serious health issues (37). Eventually, on October 2022, the EC reported that the label of nutraceuticals containing RYR extract must include the following warnings: "this food should not be consumed in a daily dose equal to or greater than 3 mg of monacolins; it must not be consumed by pregnant or in breastfeeding, by children below 18 years old and by adults of over 70 years old, by patients already taking statins and by people consuming other products containing RYR" (Commission Regulation (EU) 2022/860 - Publications Office. https://eur-lex.europa.eu › TXT › PDF › uri=-CEL...P). Nowadays, according to the above presented reasons the suggested dose of monacolins is below 3 mg. In consideration of these restrictions in the use of the RYR extracts, its future remains uncertain, although it seems that patients willing to pay for a natural alternative to statins are more compliant to therapy than those on conventional treatment (38).

In conclusion, the administration of RYR extract with low dose of monacolins (3 mg) could be considered a "relatively" safe nutraceutical with the aim of improving the CVD risk profile in those patients who have a mild or moderate hypercholesterolaemia. RYR should

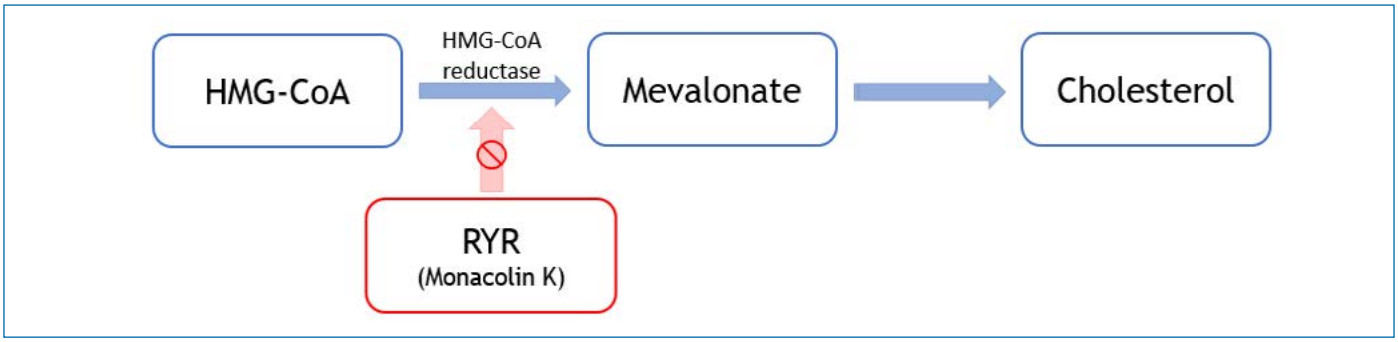

Figure 1 | Mechanism of action of monacolin k from red yeast rice (RYR) extract. HMG-CoA, β-Hydroxy β-methylglutaryl-CoA.

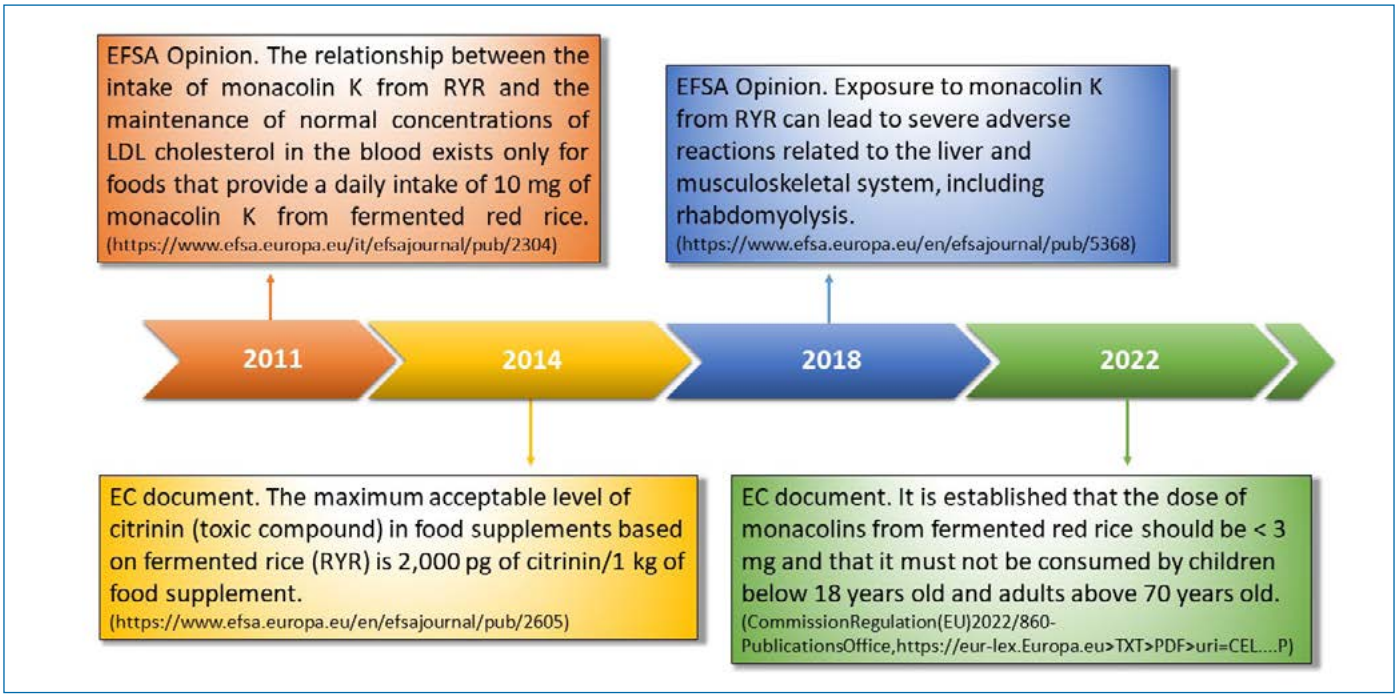

Figure 2 | Timeline of regulatory activities related to red yeast rice extract use. EFSA, European Food Safety Authority; EC, European Commission.

not be used, alone or in association with others hypocholesterolemic agents, when statins are not well-tolerated or when an evident nocebo effect is diagnosed (39). However, the available evidence supports that a large use of RYR should be still limited and RYR supplements should never replace statins or the other pharmacological approaches as first therapeutic option to effectively lower CVD risk (40).

Red yeast rice extract in combination with other active components

Similarly to canonical drug strategies, also in the case of RYR extract it has been demonstrated that treatment with a combination of active nutraceutical components with different mechanisms of action leads to an additive effect (32). A list of the main nutraceutical products for the treatment of moderate hypercolesterolaemia is shown in **Table 1**. For example, RYR extract has been used in combination with berberine, policosanol, astaxanthin, coenzyme Q10, and folic acid (41). Moreover, RYR extract has also been combined with the probiotic *Bifidobacterium Longum* BB536 (42, 43). Policosanols are a mixture of waxy alcohols derived from a variety of plants. They inhibit cholesterol synthesis by activation of AMP-kinase and modulating HMG-CoA reductase activity in hepatoma cells and cultured fibroblasts, respectively, showing different mechanisms of action (44, 45). Astaxanthin is a carotenoid providing a pink color characteristic of few species and it is one of the most powerful biological antioxidant compounds. This molecule is able to prevent the infiltration of peroxidized LDL-C into the arterial intima and the formation of atherosclerotic plaques, thanks to its free radical scavenging activity. Due to these characteristics, astaxanthin protects cell membranes, LDL-C, endothelium of blood vessels and tissues against lipid peroxidation and oxidative damage (46). RYR, astaxanthin and policosanols were tested alone and in combination, using a model of experimental atherosclerosis elicited in rabbits with a cholesterol-enriched feed. It was shown that this combination of compounds could lead to additive or synergistic health effects, thanks to the different mechanism of action of each compound (47). Berberine is an isoquinoline alkaloid plant extract that has historically been used in traditional Chinese medicine. Berberine has been associated with hypolipidemic, anti-inflammatory and hypotensive properties, resulting in antiatherosclerotic effects. Berberine is also associated with serum glucose level reduction, increased expression of LDL receptors and reduction of serum cholesterol concentration by inhibiting lipid synthesis (48, 49).

Treatments with nutraceutical combinations containing chitosan,

Table 1 | Summary of the features of the main nutraceutical product for the treatment of mild/moderate hypercholesterolaemia, features based on evidence.

Nutraceutical	LDL-C reduction (%)	Mechanism of action	Daily dose	Evidence level	Recommendation class	Reference
RYR extract	-15 to 25	LDL synthesis inhibition (HMG-CoA reductase inhibition)	3 mg (monacolin k)	A	IIa	51
Plant sterol/stanols	-12	Absorption inhibition	1500-3000 mg	B	IIb	54
Berberine	-15	LDL excretion Improvement (AMPK activation, other)	500-1500 mg	A	I	62
Soy protein	-5	LDL excretion Improvement (various mechanisms)	25-100 g	A	IIb	71
Artichoke	-10	HMG-CoA reductase inhibition, anti-inflammatory/anti-oxidant, othe	1-3 g	B	IIa	84
Probiotics	-5	Absorption inhibition (various mechanisms)	dependent on strain	B	IIb	91
Bergamot	-15	HMG-CoA reductase inhibition, anti-inflammatory/anti-oxidant, othe	500-1000 mg	B	IIa	84

RYR and berberine significantly reduced non-HDL-C and LDL-C in individuals with hypercholesterolaemia compared to placebo, without changes of PCSK9 plasma levels (50).

Moving beyond RYR extract: alternative nutraceutical products for the treatment of mild/moderate hypercholesterolaemia

In consideration of the above-mentioned critical issues and limitations in RYR extract use, a wide research effort has been devoted to the validation and development of well-established novel nutraceutical products with a good efficacy and safety profile. Some of them have already been mentioned above, in combination with RYR extract, while others are novel and have been proposed rightaway as alternative options (51).

Phytosterols. Phytosterols are triterpenes usually classified as sterols or stanols, according to the presence or absence of a double bond in position 5. A relevant structural difference is present between cholesterol and sitosterol, since the latter shows an additional ethyl group at position C-24, probably responsible for its relatively poor intestinal absorption (52, 53). The main mechanism responsible for phytosterol-induced reduction in circulating cholesterol levels resides in the competition with cholesterol for incorporation into mixed micelles in the intestinal tract (54). Phytosterols are more easily hydrolysable than cholesterol, and this leads to a lower solubilization of cholesterol into micelles, which decreases their absorption and increases fecal excretion of cholesterol and its metabolites. The cholesterol-lowering effect of phytosterols may be observed within a few weeks of treatment and remains stable upon supplementation (54). After interruption of phytosterol intake, circulating cholesterol concentrations return back to basal conditions (55). The reduction of cholesterol absorption in the intestine and reaching the liver through the chylomicron pathway promotes a greater endogenous synthesis of cholesterol as well as a greater uptake of plasma LDL-C by hepatocytes, in order to maintain cholesterol homeostasis. Such enhanced clearance of circulating LDL-C leads to a reduction of its plasma concentration, which is around 2–3% for a low (300-400 mg/day) dietary intake of phytosterols (56) and reaches an average of 9% for an intake of 1500-2000 mg per day (57). Greater dosages of phytosterols up to 3 g/day have been shown to promote a 12–12.5% reduction (53, 54). Recent meta-analyses of published trials (58) indicate that the effect of the intake of phytosterols on plasma LDL-C levels in humans is within the range indicated by EFSA in its 2008 Opinion (https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2008.781).

Berberine. Berberine is well known to be able to reduce intestinal cholesterol absorption by increasing the elimination of cholesterol through the faecal material and to stimulate the formation of bile acids. It also stimulates adenosine monophosphate activated protein kinase (AMPK), which can limit the synthesis of fatty acids (59). Berberine also increases glucose transporter-4 (GLUT-4) and glucagon like peptide-1 (GLP-1) levels (60). Several studies reported that three months of treatment with berberine (500 mg/day) results in reduction of plasma concentrations of total cholesterol, triglyceride and LDL-C and in increased concentration of HDL-C (61). Moreover, data obtained from a recent metanalysis of 19 clinical studies showed a significant reduction in total cholesterol and LDL-C. As regards HDL-C, a slight non-significant increase was observed (62). Moreover, *in vitro* studies on HepG2 human hepatocarcinoma cell line demonstrated that berberine inhibits the synthesis of cholesterol and triglycerides (63) and reduces the gene and protein expression of PCSK9 (64). Berberine has been shown to be safe in the majority of clinical trials. In a small percentage of patients, berberine has been reported to cause nausea, vomiting, constipation, hypertension, respiratory failure and paresthesia; however, clinical evidence of such adverse effects is not prominent in the literature. Rare adverse effects including headache, skin irritation, facial flushing, bradycardia have also been reported with the use of berberine (60).

Soy proteins. A large number of published studies has evaluated the hypocholesterolaemic potential of a regular consumption of soy protein. A health claim has been approved by the Food and Drug Administration stating that diets low in saturated fat and cholesterol that substitute 25-30 g/day protein from animal sources with an equal amount of soy protein, may reduce the risk of coronary heart disease (65). Some evidence show that the cholesterol-lowering effect of soy derivatives is due almost entirely to soy protein, while isoflavones have only a limited effect on blood lipids, but could play a key role in inflammation (66). In fact, the isoflavones are present as β-glucosides, after ingestion the glycosidic bond is hydrolyzed by the microbiota to release free aglycones, which can be absorbed or further metabolized. Isoflavones or their metabolized forms could enter in the blood circulation and act on endothelial function, in particular daidzein, dihydrodaidzein (DHD), equol, O-desmethylangolensin (O-DMA), genistein (67). Soy proteins are largely composed of storage proteins, and the two main components are known as β-conglycinin (7S globulin) and glycinin (11S globulin) (68, 66). The proposed cholesterol-lowering mechanisms of soy proteins are still unclear and may include down regulation of the expression of sterol regulatory element-binding protein (SREBP-1), modulation of the PI3K/Akt/GSK3b pathways, decrease of cholesterol synthesis, increase of ApoB receptor activity, modulation of the activity of bile acids (69). Most randomized controlled trials that evaluated the lipidemic profile after purified protein diet in adults with normal or moderate hypercholesterolaemia, resulted in a significant reduction in total cholesterol (at least - 4%) and LDL-C (about - 6%) (70). It should be noted that patients do not take soy protein in a purified form; therefore, a novel approach was used in a recent study in which patients were given whole soy foods (30 g of soy protein) possibly commercially available, on a low lipid diet for 12 weeks. Compared to a standard low-lipid diet with the same amount of animal protein, there was a reduction of total cholesterol (-4.8%), LDL-C (-5.2%), non-HDL-C (-7.1%) and apoB (-14.8%) levels in the circulation (71). Products containing soy could have beneficial effects because of their content of polyunsaturated fatty acids, fiber, vitamins and minerals and their low SFA content (72). The role of soy in the reduction of coronary artery disease remains controversial. As of today, EFSA has concluded that the hypocholesterolemic effect of isolated soy protein has not been established (73). In addition, the 2011 version of the ESC/EAS Guidelines suggested that soy can be used as a substitute for animal protein foods, despite the fact that LDL cholesterol lowering is modest and greater than subjects with hypercholesterolaemia (74). In contrast, the most recent 2019 version (75) downsized the role of this nutraceutical: "LDL-C-lowering effect was not confirmed when changes in other dietary components were taken into account" (76). In conclusion, the evidence currently available in the literature and the statements made by health agencies do not appear to reveal a clinical importance of soy protein in the management of hypercholesterolaemia.

Lupin proteins. Yellow lupin (*Lupinus luteus*) contains fiber (30%), protein (30-35%), carbohydrates, unsatured fat and also phosphorus, calcium, and magnesium. Lupin is different from other legumes, such as soy, because of the absence of phytoestrogens and low sodium content (77, 69). The observed activities of lupin

could be explained by the peptides deriving from the hydrolysis of lupin proteins. The mechanism of action of absorbed lupin peptides has been investigated in some molecular studies. They seem to interfere with HMG-CoA reductase activity, up-regulating LDL receptor and SREBP-2 (78), as already observed in the case of soy protein. Some works provided evidence that lupin peptides may also inhibit PCSK9 (79). The lipid–lowering effects of lupin may be also linked to the formation of short-chain fatty acids, specifically propionate and acetate (80). Clinical studies confirmed these experimental investigations (81), however others do not agree about the effects of lupin consumption. For example a study has shown that a 12-week treatment of individuals in low-lipid diet with a moderate dyslipidaemia with a lupin protein concentrate (30 g/day) leads to a non-significant reduction of total cholesterol, LDL-C, non-HDL-C, in comparison with those consumed a lactose-free skimmed milk powder (82). In conclusion, lupin protein intake represents a relatively weak adjuvant therapy in the treatment of hypercholesterolaemia, also according to most guidelines (76).

Artichoke. Artichoke (*Cynara scolymus* L.) is a plant native from the Mediterranean area (North Africa and Southern Europe). Receptacle of *C. scolymus* L., also known as "artichoke heart", is commonly consumed as a food. In addition, a traditional use of artichoke leaf extracts is reported, especially for its antioxidant, liver-protective, anti-microbial, choleretic, hepatoprotective, bile-enhancing and lipid-lowering effects. It is related to beneficial effects in atherosclerosis, biliary duct, digestive tract, and the treatment of scurvy and anemia (83). A recent review summarized beneficial effects of artichoke extracts on blood lipid concentrations after consumption of artichoke leaf extracts compared with placebo or reference pharmacological treatment (84). The active components of artichoke have been found to inhibit cholesterol synthesis and show relevant anti-inflammatory and antioxidant properties (85). Clinical trials showed a significant reduction of total cholesterol concentrations compared to placebo after 6 or 12 weeks of supplementation. Trials reports indicate mild, transient and infrequent adverse events. In addition, a recent meta-analysis analyzed data from 9 trials including 702 participants with mostly mild to moderate hypercholesterolemia. Consumption of artichoke extract, for 6 to 12 weeks, significantly decreased plasma concentrations of total cholesterol and LDL-C with no significant alteration in plasma HDL-C concentrations (86).

Probiotics. The gut microbiome has been shown to affect human health and disease, including hypercholesterolemia. A disbalance of the microbiota (*i.e.* dysbiosis), caused by different factors, can increase the intestinal permeability and eventually lead to higher levels of bacterial metabolites. This event together with other mechanisms promotes low-grade inflammation, which has been shown to be one of the main main contributor of atherosclerosis development (87, 88). Based on these observations, probiotics, prebiotics and their combinations have gained interest as a new promising approach for dyslipidemia treatment. The World Health Organization defines probiotics as: "live microorganisms that, when administered in adequate quantities, confer health benefits to the host" (89). Probiotics insinuate additional microorganisms in the host, prebiotics stimulate their growth in the intestinal tract, while synbiotics combine these applications to improve the viability. The hypocholesterolaemic effect of probiotics may result from several mechanisms, including:

1) bile salt hydrolase activity regulation, thus reducing the bile salts enterohepatic circulation;
2) cholesterol incorporation into cellular membranes of bacteria;
3) cholesterol conversion into prostanol, hence reducing its absorption and facilitating the excretion via the feces;
4) cholesterol transport modulation by NPC1L1, ABCA1, CD36, and SR-B1 down-regulating gene expression;
5) cholesterol synthesis modulation through short-chain fatty acids production;
6) exopolysaccharides production, which then bind to free bile acids and increase their elimination through the feces (90, 91).

Previous clinical studies described controversial results regarding probiotics effect on dyslipidemia. Several meta-analyses of human trials suggest that, in most cases, probiotic treatment significantly reduced total cholesterol and LDL-C, with little effect on triglycerides and HDL-C (92). Differently from others, a significant TG level reduction has also been reported (93). There are difficulties since the effects on lipid profile depended on intervention times and probiotic strains, which are different in each study. Hence, many of these mechanisms still need to be clarified in humans.

Bergamot. Bergamot (*C. bergamia*) belongs to the Citrus fruits and differs from others Citrus fruits for its high-content of flavonoids and statin-like compounds (94). Bergamot-derived molecules have been shown to ameliorate plasma lipid profile and visceral fat in clinical trials (84, 95). Specifically, among bergamot constituents, naringin, neoeriocitrin, and rutin were found to inhibit the oxidation of LDL particles (96). Moreover, the scientific literature of the last decade has provided evidence about the potential anti-inflammatory and antioxidant effects of bergamot extracts (97). Interestingly, clinical studies have also shown lipid-lowering effects of bergamot-derived compounds such as the reduction of LDL-C, triglycerides, non-HDL-C, and malonyl dialdehyde (98).

Cabbage. *Brassicaceae* (crucifers) is one of the most extensive angiosperm families, composed of 360 genera and approximately 3709 species distributed worldwide. One important *species* is cabbage, that is an essential part of the human diet thanks to its high nutritional value, mainly due to its content in fiber, minerals and vitamins (99). Cabbage exhibits anti-aging, anticancer and antioxidant properties, and presents multiple health benefits (100). Cabbage's dietary fiber (DF) can be classified into insoluble DF (IDF) and soluble DF (SDF). Pectin and oligosaccharides, the main components of SDF, can decrease blood glucose and cholesterol, prevent cardiovascular diseases, and serve as important probiotic sources. Soluble DF also generates short-chain fatty acids, which can regulate immunity and promote the growth of probiotics in the digestive system to prevent inflammatory bowel diseases (101). Moreover, several studies suggest that cabbage has a functional potential to regulate glucose homeostasis and improves health in people with T2DM (102). Plant food groups such as berries, green leaves, and crucifers (including cabbage) would play a significant role in reducing the risk of T2DM (103). A prospective study in Japan analyzed the relationship between the intake of different plant food groups and the incidence of T2DM. The results showed a significant higher risk reduction among the male population and consumption of vegetables, including cabbage (104). Moreover, the effects of cabbage on serum lipid levels in hypercholesterolaemic patients were investigated. Their serum total cholesterol levels significantly decreased from 6.7 ± 0.8 to 6.1 ± 0.6 mmol/L, and, more strikingly, the level of LDL-C significantly decreased from 4.4 ± 0.8 to 3.8 ± 0.7 mmol/L. At 9 weeks after the cessation of administration, these levels returned to the preadministration levels (105).

Goji (*Lycium barbarum* L.). *Lycium barbarum* is a well-known traditional Chinese herbal medicine. Supplemental *L. barbarum* is beneficial to nourish the liver and kidney and brighten the eyes. In support of these traditional properties, scientific evidence has shown that *L. barbarum* fruit possesses a variety of biological activities, such as anti-aging, neuroprotection, anti-fatigue/endurance, increased me-

tabolism, glucose control in diabetics, glaucoma, antioxidant properties, immunomodulation, anti-tumor activity and cytoprotection (106). *L. barbarum* includes polysaccharides, carotenoids, flavonoids, betaine, cerebroside, beta-sitosterol, p-coumaric acid, vitamins and other phytochemicals. Among them, *L. barbarum* polysaccharides (LBP) have various physiological effects, such as antioxidant effects (107), anti-diabetes (108) and cardiovascular benefits (109). The effect of *L. barbarum* on the cardiometabolic risk factors was investigated in a meta-analysis (106), combining seven randomized controlled trials with a total of 548 participants. Authors concluded that *L. barbarum* significantly reduced total cholesterol and triglycerides concentrations in participants aged ≥60 years or intervention period duration of ≥3 months (106). In another clinical trial, 50 participants with a metabolic syndrome were randomly divided into two groups, control and supplemented with 14 g/day of goji berry in the diet. Both LDL-C and VLDL-C were significantly reduced in the supplemented group (110).

Olea europaea. The olive tree leaves (*Olea europaea* L.), native from the Mediterranean area, have been used in traditional herbal medicine with the aim of preventing or treating several conditions like hypertension, diabetes and inflammation. Potential effects could be related to the rich content of polyphenols oleuropein and hydroxytyrosol that benefits human health (111). Current studies show great potential in these effects: in a recent meta-analysis, olive leaf extract shows improvement of lipid profile in normal-weight subjects (trigliceride (– 9.21 mg/dL), total cholesterol (– 6.69 mg/dL), systolic blood pressure (– 7.05 mmHg), as well as in patients with hypertension (triglyceride (– 14.42 mg/dl), total cholesterol (– 9.14 mg/dL), LDL-C (– 4.6 mg/dL) (112). In a randomized, double-blind, controlled crossover trial, olive leaf extract (providing 136.2 mg oleuropein and 6.4 mg hydroxytyrosol per day) significantly reduced plasma LDL-C, total cholesterol and triglyceride concentrations in 60 men with slightly elevated blood pressure (113). Furthermore, in another randomized placebo-controlled clinical trial, there was a significant improvement in the triglyceride-to-HDL-cholesterol ratio and a significant decrease in triglyceride levels (114). Olmez et al. (115) described a lipid-lowering effect in rats supplemented with olive leaf extract (50 or 100 mg/kg/day) for 8 weeks. LDL-C and total cholesterol were significantly lower than in rats fed with a high cholesterol diet only. Overall results from literature seem to be promising, although there is a need for further studies to fully understand the related mechanisms.

Ethnic medicine and cardiometabolic disease: experimental evidence

In many countries, herbs and spices have been traditionally used as remedies for a wide range of pathological conditions, including cardiovascular and metabolic diseases, and some of them, like berberine, have been discussed above. Recently, experimental studies have been focused on additional extracts, especially from plants of African origin, which appear to have been less exploited by appropriate research. Indeed, before human use as potential nutraceuticals, it is crucial to better understand the active components and the potentially toxic compounds of such botanical preparations, highlighting their activity in modulating specific molecular pathways linked to cardiometabolic diseases, including hypercholesterolaemia. In this field, extracts from *Adansonia digitata* L. (also known as baobab) and from a series of Cameroonian spices have been studied for their potential usefulness in cardiometabolic disease using cell-based and in vivo models. In particular, the fruit pulp and leaf extracts of *Adansonia digitata* L. have been shown a good inhibitory activity against relevant enzymes such as HMG-CoA reductase, in addition to alpha-amylase, alpha-glucosidase, angiotensin-converting enzyme, and pancreatic lipase (116). Moreover, *Adansonia digitata* leaf extracts were found to reduce hyperglycaemia and hyperlipidaemia (including LDL-C reduction) of diabetic rats (117). A series of spice extracts from Cameroon has also been extensively studied in different experimental settings, showing that some of them may positively modulate enzymes relevant to arbohydrate/lipid metabolism and cardiometabolic disorders (118), oxidative stress, inflammation and metabolic pathways related to lipid biosynthesis in hepatic and adipose human cell models (119, 120) and in animal models of diet-induced obesity (121). Taken together, well-characterized extracts from plants used in African traditional medicine have been shown to positively modulate molecular pathways associated with hypercholesterolaemia and other events promoting atherosclerosis, suggesting their use in cardiometabolic conditions of moderate severity. These promising data should prompt further research, especially in the context of clinical trials.

Concluding remarks

The use of nutraceutical products represents a feasible option for the management of mild to moderate hypercholesterolaemia in subjects with low cardiovascular risk, and RYR extract is one of the most effective and used products in this field. The current warnings for potential adverse effects and the limitations of use of RYR extract/monacolin K highlight the need to identify and validate additional active compounds for the management of this condition. The use of these nutraceuticals as add-on therapy on top of current drug treatments for hypercholesterolaemia is also an area deserving to be studied. Moreover, important socio-economical aspects, like their global sustainability and the potential exploitation of agro-food waste in terms of human health benefit, should also be taken into consideration in the context of such nutraceutical development.

Conflict of interest

All authors have no conflict of interest to disclose.

Authors' contribution

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Permission Information

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