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REVIEW

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Efficacy, side effects, adherence, affordability, and procurement of dietary supplements for treating hypercholesterolemia: a narrative review

Isabel von Känel-Cordoba[1], Katharina Wirnitzer[2,3,4,5], Katja Weiss[1], Pantelis T. Nikolaidis[6], Asli Devrim-Lanpir[7,8], Lee Hill[9], Thomas Rosemann[1] and Beat Knechtle[1,10*]

Abstract

Introduction : Statins are effective in reducing high cholesterol levels; however, due to associated side effects, many patients actively seek alternative medications. This review evaluates the efficacy, side effects, patient adherence, cost-effectiveness, and accessibility of dietary supplements (DS) as a treatment option for hypercholesterolemia.

Methods This narrative review compares red yeast rice (RYR), flaxseed, artichokes, bergamot, Ayurvedic mixtures (with garlic as a prominent ingredient), and statins for treating hypercholesterolemia. We searched PubMed, Scopus, and Cochrane databases for studies published between 2012 and 2024 using "hypercholesterolemia" in combination with a dietary supplement (red yeast rice, flaxseed, artichokes, garlic, or bergamot). The selected articles were published until 28th January 2024 with no language restrictions.

Results Study results suggest that alternative treatments using dietary supplements such as flaxseed, bergamot, or red yeast rice may effectively reduce cholesterol levels, with the specific value varying based on the study.

Conclusion The following natural ingredients - red yeast rice, artichoke extract, bergamot, garlic, and flaxseed - have been specifically selected for their cholesterol-lowering properties. Based on consistent usage, except for aged garlic extract, these ingredients appear to have a beneficial impact on cholesterol levels. (1) It is advisable to conduct a comprehensive cohort study to assess the efficacy of relevant dietary supplements, particularly red yeast rice, bergamot, and flaxseed, in treating hypercholesterolemia. This is important due to the varying effectiveness of alternative treatments. However, there are lingering concerns regarding the lack of supervision and quality control that require attention. (2) Further research into the specific molecular composition and the underlying mechanisms by which it reduces cholesterol levels is warranted.

Keywords Hypercholesterolemia, LDL, Dietary supplements, Statins [Supplementary Concept], Red yeast rice

*Correspondence:
Beat Knechtle
beat.knechtle@hispeed.ch

Full list of author information is available at the end of the article

Introduction

Chronic diseases represent a significant global health challenge. Approximately one-third of adults worldwide are affected by multiple chronic conditions, including cardiovascular diseases, diabetes, depression, and cancer [1, 2]. Annually, non-communicable diseases such as cardiovascular diseases, cancer, respiratory disorders, and diabetes cause approximately 41 million deaths, which constitutes 71% of global mortality. These chronic conditions predominantly affect low- and middle-income countries, where 85% of premature deaths occur among individuals aged 30 to 69 [3]. From 1990 to 2019, the global prevalence of hypertensive heart disease increased by 137.91%, from 7.82 million to 19.60 million [4]. Based on these facts, it is not surprising that the desire for dietary supplements is also increasing. Nutraceuticals, dietary supplements, and functional foods offer medical or health benefits beyond basic nutrition. The FDA regulates dietary supplements and dietary ingredients, while the European Commission uses EFSA for nutraceutical regulation, allowing health claims based on scientific evidence [5]. Many of the most common diseases are manifested by increased inflammation levels. So, the same dietary supplements can counteract different diseases due to the reduction of C-reactive protein over MDA (Malondialdehyde) [6, 7]. Propolis supplementation containing prenylated flavonoids shows an improvement in inflammation levels in both primary pneumosepsis and rheumatoid arthritis, due to the reduction of cytokines, which also promote atherosclerosis [6, 7]. Pycnogenol (Maritime pine bark extract, Pinus pinaster) containing polyphenols like bergamot highlights its therapeutic potential in reducing inflammation and oxidative stress through the modulation of insulin receptor signaling pathways and protects against lipid peroxidation [8, 9]. A study has found that traditional Iranian medicine has demonstrated efficacy in enhancing the conditions of COVID-19 patients and reducing the levels of C-reactive protein. This traditional medicine encompasses a blend of Ficus carica, Vitis vinifera, Cicer arietinum, Descurainia sophia seeds, safflower, Ziziphus jujuba, as well as chicken and barley soup, complemented by rose water, saffron, and cinnamon spices [10]. The compound of Ficus carica includes polyphenols and flavonoids [11]. There is evidence indicating that conjugated linoleic acid, particularly the c9 and t11 isomers, exhibits anti-inflammatory properties. Nonetheless, it is important to note that no uniform recommendation can be provided [12]. In the meta-analysis by Xu et al. in 2020, green tea appeared to have a lowering effect on the LDL profile [13]. The four main catechins (flavonoids) in green tea, particularly epigallocatechin gallate (EGCG), exhibit anti-inflammatory and anti-obesity properties. They function as antioxidants that prevent LDL oxidation, thereby inhibiting receptor binding activity in HepG2 cells [14]. Licorice (Glycyrrhiza glabra) contains glabridin, a flavonoid that activates PPARγ (Peroxisome Proliferator-Activated Receptor Gamma) and shows a lowering effect on cholesterol levels [15]. Considering the anti-inflammatory and LDL-lowering properties of flavonoids in propolis, green tea and Licorice [6, 7, 12, 15], as well as the benefits of conjugated linoleic acid from Ficus carica [11] and the therapeutic potential of Pycnogenol in reducing inflammation and oxidative stress [8, 9], it is important to understand their possible effects of one of the major factors oft morbidity, the atherosclerotic cardiovascular diseases (ASCVD). It is related to low-density lipoprotein cholesterol (LDL-C) [16] circulating levels, which can result from several factors, including hypercholesterolemia and dyslipidemia [17]. Defining hypercholesterolemia presents challenges due to the variability of blood cholesterol levels based on sex and age [18], as well as its susceptibility to environmental and genetic factors [19]. It can be characterized as a plasma concentration of LDL-C ≥ 130 mg/dL (≥ 3.4 mmol/L) and/or non-HDL-C ≥ 160 mg/dL (≥ 4.1 mmol/L) [20]. The outcomes of a recent longitudinal study of 279,221 patients living in the UK have revealed a two-fold increase in the prevalence of primary hypercholesterolemia/mixed dyslipidemia [21]. The proportion of the population with non-HDL-C levels below 100 mg/dL in the USA increased from 7.3 to 30.3% between 1999 and 2018 [22]. Considering the extensive impact of ASCVD outcomes on a global scale, it is imperative to devise strategies to address atherosclerosis and heart diseases by reducing blood cholesterol concentrations.

Hypercholesterolemia is asymptomatic; however, if left untreated for long periods, elevated serum cholesterol may contribute to atherosclerotic plaques and ASCVD formation [23]. Since ASCVD has long been one of the leading causes of death worldwide, various strategies, including pharmacotherapy and dietary therapies, have been developed to prevent its development and possible adverse health effects [24]. The negative impact of antihypertensive medications' adverse effects, coupled with high costs, particularly in regions with lower socioeconomic indices, contributes to reduced treatment adherence, consequently resulting in poorer medical outcomes [25]. HMG-CoA reductase inhibitors or statins are a class of hypolipemic agents that are the most prescribed medications for decreasing LDL-C levels [26]. However, as statins may sometimes cause undesirable side effects or are not well tolerated [27], several alternative dietary supplements have been developed to help reduce high serum cholesterol levels. However, despite their potential to lower cholesterol levels, no conclusive studies show that plant-based supplements reduce the risk of coronary heart disease. The purpose of this review is to provide

an overview and evaluation of the most recent alternative treatments for hypercholesterolemia. Our objectives included assessing the effectiveness, side effects, patient adherence, affordability, and availability of these treatments. Additionally, we aimed to explore the use of dietary supplements (DS) for treating hypercholesterolemia, as well as their potential economic impact given the prevalence of this condition. Numerous relevant articles have demonstrated that the use of dietary supplements in cholesterol management has been extensively researched over the past decade. As a result, we also emphasize the need for further systematic studies in this area. We opted for a narrative review due to the considerable methodological diversity among the studies included. This review specifically focuses on research conducted from 2013 to 2024 on the use of dietary supplements for lowering cholesterol levels.

Materials and methods

Literature search strategy

In this narrative review, research results on the topic of alternative DS to statins were qualitatively assessed and summarized. The narrative review utilized a systematic search of keyword combinations in the three most relevant medical databases: PubMed, Scopus, and Cochrane. The search was conducted three times by both researchers (IK and BK). The list of relevant articles was reviewed by all authors for additional potentially relevant articles. The literature review was conducted according to the guidelines for evaluating studies, including their validity, size, and reproducibility [28]. The selected articles were related to the topic and were published until 28th January 2024 with no language restrictions. Keyword combinations were used to search term combinations, and results are presented in Table 1 [29]. Articles were screened by title, abstract, and full text. The search on PubMed yielded 210 results comprising reviews, meta-analyses, or single studies addressing treating hypercholesterolemia with statin alternatives. Articles were selected for analysis if they investigated alternative medicine in the context of hypercholesterolemia. The focus was on individual studies and meta-analyses examining the administration, effect, and procurement of statins and statin alternatives. For more accurate descriptions, we also used cited and referenced studies. When reviewing the relevant articles, RYR, artichoke, bergamot, flaxseeds, garlic, Coenzyme Q10 and omega-3 fatty acids were noted as potentially useful DS. Coenzyme Q10 was excluded due to exclusive combination preparations and omega-3 fatty acids were also not included due they have been linked to arrhythmias [30]. We also excluded animal models, individual case studies and studies dealing with familial hypercholesterolemia. Regarding Scopus, the search was conducted for sources of high-quality scientific information [31]. Free-text words were employed in the search [32]. Additionally, we referenced the Cochrane Central Register of Controlled Trials (CENTRAL).

Results

Hypercholesterolemia – the role of the statins

Statins are extensively studied pharmaceuticals designed to reduce both LDL-C and total cholesterol levels. They have been shown to produce a 15% relative risk reduction in individuals with coronary heart disease undergoing intensive lipid-lowering therapy [33]. They are known to improve endothelial function and cardiovascular outcomes, reducing plaque vulnerability and inflammatory processes in the body [34]. Morbidity and mortality from cardiovascular disease can be decreased via statin administration [35]. When statins are used as a control in DS efficacy trials, they are generally more effective [36]. However, the statin regimens may cause side effects, including liver toxicity [37], elevated levels of liver and muscle enzymes, and increased incidence of diabetes [16, 38]. A recent review on statins and their potential side effects showed that the most common cause to stop statin medication is statin-induced myopathy [38]. These myopathies occur as mild muscle pain or life-threatening rhabdomyolysis. Pharmacists describe the approach of dose modification to avoid muscle discomfort and switching statin types to achieve optimal treatment for patients [39]. In addition, as the adherence to statin

Table 1 Search terms in PubMed, number of journal articles in 2012–2024, number of articles selected

Search term hypercholesterolemia AND ryr NOT familial hypercholesterolemia, hypercholesterolemia AND bergamot NOT familial hypercholesterolemia, hypercholesterolemia AND artichokes NOT familial hypercholesterolemia, hypercholesterolemia AND flaxseeds NOT familial hypercholesterolemia, hypercholesterolemia AND garlic NOT familial hypercholesterolemia'	**RYR**	**Bergamot**	**Artichokes**	**Flaxseeds**	**Garlic**	**Article total**
Found articles (*n*)	89	13	22	23	35	182
Adjusted for articles on animal models, without DOI or otherwise not retrievable; Duplicates removed: shortlist item(s) (*n*)	40	8	10	5	9	72
Articles screened in depth for review (*n*)	36	6	5	8	8	62
Articles included in review (*n*)	**6**	**5**	**5**	**8**	**5**	**29**

intake regimens is found to be suboptimal [40], physicians should monitor patients closely to improve adherence and manage potential side effects.

Dietary supplements – alternatives for statins?

Treatment of hypercholesterolemia with alternative substances lowers blood cholesterol levels without the known side effects of statin administration. The literature search on dietary supplements and hypercholesterolemia has revealed the RYR, artichoke, bergamot, garlic, and flaxseeds.

The power of red yeast rice

RYR, also known as Xuezhikang, Cholestin, Hypocol, or Zhitai, has been used in traditional Chinese medicine to regulate blood lipids and circulation [41]. It has been widely used for its potential efficiency on inflammation, blood pressure, blood glucose, cancer, and osteoporosis [42]. RYR is recognized as a food supplement in Europe, in addition to being consumed in Asian countries. It is important to note that RYR does not have approval as a food supplement in Switzerland [43, 44].

For the publication period of 2012–2024, the literature search retrieved 89 articles in the PubMed database. A total of 6 papers included RYR only to treat hypercholesterolemia. We identified 10 articles in SCOPUS (title/abstract search). In the end, 4 articles were considered. In Cochrane, we found a total of 12 articles with no limitations. However, none of the articles were ultimately considered.

Three papers on RYR supplementation compared to placebo revealed that 200 to 2400 mg/day had a significant efficacy on lowering blood LDL-C concentrations in patients with dyslipidemia. Consistent with these results, two research papers administering a dose of 1200 mg/day RYR compared to statin treatment showed similar outcomes on blood lipids in patients with dyslipidemia and unstable angina pectoris. On the contrary, another study administering RYR supplementation (2400 mg/day) for 28 days showed that statin (rosuvastatin) supplementation caused more significant reductions in LDL-C levels compared to RYR group in adults with no history of atherosclerotic cardiovascular disease.

Using RYR supplements along with other herbal extracts also shows promising results. Together with bergamot and artichoke, a synergistic effect is suspected in treating hypercholesterolemia [46]. Cicero et al. reported in 2017 an 18.2% improvement in LDL-C levels when RYR, artichoke extract, and banaba extract were administered to patients over a 6-week period [45]. However, Gerards et al. emphasized in 2015 the importance of heterogeneity in studies and state that better or comparable results can be achieved with RYR against an ineffective control, as in studies with regular statin therapy [47]. Peng et al. considered in 2017 RYR an effective cholesterol-lowering agent, especially when patients exhibit statin intolerance [50]. Iskandar et al. reported in 2020 on the RYR product NutraforChol® in their double-blind, randomized, placebo-controlled study. Compared to the placebo, a 15% reduction in total cholesterol and up to 20% reduction in LDL-C was observed [51]. Adherence to dosing regimens appears to be ensured in the studies conducted. The efficacy of RYR as a cholesterol-lowering agent seems to be undisputed, but the composition of the active ingredients varies from product to product. The costs of RYR treatment are like those of classical statin therapy.

Artichoke & bergamot–- Mediterranean food concentrated in pills

Artichoke is used in traditional medicine to lower cholesterol and blood lipids. The active ingredients of the artichoke are caffeoylquinic acid derivative, glycosides of the flavone luteolin, and bitter substances (sesquiterpene lactones) [52]. It is believed to have cholesterol-lowering, hepatoprotective, and antioxidant effects.

After conducting our search, we identified a total of 22 articles in PubMed. Ultimately, 5 articles met our criteria and were considered for further review. In SCOPUS, we discovered a total of 7 articles through a title/abstract search. Ultimately, 2 articles were deemed relevant. In Cochrane, we found 1 article without any restrictions; however, the article was ultimately considered.

Three research articles by the same researchers applying artichoke extract were identified. Two studies showed that a dose of 500 mg/day of artichoke extract for eight weeks decreased the LDL-C levels or total-C/HDL-C ratio levels compared to the placebo group in patients with mild hypercholesterolemia [54]. Consistent with these studies, a meta-analysis of 9 research papers on artichoke [55] and network analysis of artichoke [56] also underlined a meaningful benefit of artichoke extract administration in patients with mild to moderate hypercholesterolemia. The reduction in blood LDL-C ranged from 6.1 to 9.9%.

Recent research has raised an interesting question about the beneficial impact of artichoke, which could be related to the Taq IB polymorphism in the cholesteryl ester transfer protein (CETP) gene. The findings showed that a high dose of artichoke extract supplementation (1800 mg/day) for 12 weeks caused a decrease in LDL-C concentrations in men carriers of Taq IB—B1B1. More studies are required to elucidate these outcomes [57].

The cholesterol-lowering effect of bergamot is attributed to the polyphenol fraction of bergamot, which functions as an HMG-CoA reductase. Bergamot fruits also contain flavonoids [58, 59]. For bergamot, we found a total of 13 articles in PubMed, out of which 5 were

considered. In SCOPUS, we initially found 4 articles. After careful consideration, we narrowed down the selection to 2 articles. In Cochrane, we found a total of 14 articles without any limitations. However, none of the articles were considered in the end.

Three research studies on bergamot and hypercholesterolemia presented positive outcomes regarding blood cholesterol modification in patients with moderate hypercholesterolemia and mixed hyperlipidemia. Two of these studies showed that both bergamot flavonoids (1300 gr/day) and bergamot polyphenol fraction (500 or 1000 mg/day) for 30 days regulated blood cholesterol concentrations. In addition, one of these studies highlighted that the application of bergamot polyphenol fraction and statins (rosuvastatin (10 mg)) provided better outcomes regarding blood cholesterol regulation.

In line with these studies, one study showed promising results of long-term bergamot extract supplementation (150 mg/day for six months) regulated blood LDL-C fractions. It decreased carotid intima-media thickness in patients with hypercholesterolemia. In addition, a meta-analysis of food supplements and their impact on lipid regulation identified Bergamot supplementation as the most efficacious dietary supplement in reducing LDL-C by 18.2%. It is important to note that the overall number of participants in the studies was relatively small [56].

Flaxseeds - an everyday ingredient

Flaxseeds are well-known as a dietary ingredient and are increasingly used as a natural or plant source of linolenic acid [62]. We discovered in PubMed a total of 23 articles. Ultimately, 8 articles were considered. In SCOPUS, we found an overall number of 3 articles (title/abstract search). In the end, no article was considered. In Cochrane, we found 1 article with no limitations. However, in the end, no article was considered.

Seven research studies applying flaxseed. They differ in study duration ranging from 40 days to 10 weeks and in forms including powder, raw, cooked (in biscuits), or oil, presented positive results regarding blood lipid regulation in patients with hypercholesterolemia or dyslipidemia. All three long-term (49 days to 10 weeks) placebo-controlled studies showed that flaxseed administration in either oil (25 g/day) [63] or cooked in biscuits (28 g/d) [64] forms resulted in a decrease in total cholesterol and LDL-C concentrations in patients at high cardiovascular risk. In the study comparing the effects of a weight loss diet al.one versus the diet combined with the supplement, no discernible variance was noted between the flaxseed group and the sunflower oil group. Two studies included control groups (no supplementation) against the flaxseed supplementation [65]. The outcomes showed that long-term (40 days to 3 months) flaxseed supplementation, either raw or roasted flaxseed powder (30 g/day), significantly reduced total cholesterol and LDL-C concentrations in patients with dyslipidemia compared to the control group. In addition to these studies, one study included two phases for the same group 10 weeks of flaxseed supplementation (28 g/day in the biscuits) after 10 weeks of ordinary diet application [66]. The study findings indicated that although supplementation reduced total cholesterol concentration, no alteration was observed in blood LDL-C levels in the supplementation period compared to the ordinary diet period. Another study applying lipid loss diet vs. flaxseed supplementation (15 ml flaxseed oil/day) showed that blood LDL-C concentrations were reduced in the flaxseed group compared to the diet group [67]. In addition to these research papers, a meta-analysis on flaxseed and hypercholesterolemia indicated that flaxseed supplementation for 12 weeks caused a reduction in blood LDL-C concentrations in patients with high LDL-C levels and with dyslipidaemia [68]. To summarise these studies, flaxseed supplementation positively impacts lipid modification regardless of its supplementation form. The studies do not provide specific details on side effects or adverse reactions. A free text search yielded no hits when used as intended. However, it is important to consider potential side effects when evaluation the study results.

Garlic and herbal mixtures – are ayurvedic and Asian treatments efficient?

Garlic, also known as Allium sativum, is a well-known vegetable known for its organosulfur compounds, particularly allicin [94]. Garlic is recommended in Ayurvedic teachings to cleanse the blood, but is not recommended as part of a normal diet. We found in PubMed a total of 35 articles. Ultimately, 5 articles were considered. In Scopus, we found a total of 10 articles through a title/abstract search, but ultimately none of the articles were deemed relevant. We found in Cochrane a total of 1 article with no limitations. Ultimately, none of the articles were considered.

Four research articles investigated garlic (extract or whole form), and its effect on blood lipid levels was identified [69–72]. Although previous research mainly administered normal garlic extracts (fresh garlic gloves), three of the four papers applied black garlic (produced through fermentation) supplementation [69–71].

Two of the studies [69, 71] administering long-term aged garlic supplementation showed no meaningful alteration in blood cholesterol levels in patients with hypercholesterolemia. The only study using normal garlic supplements showed that statin supplementation presented better results than garlic supplementation in adults with cardiovascular disease [36]. However, a recent meta-analysis on garlic supplementation and its ayurvedic impact on hypercholesterolemia revealed

positive outcomes of garlic supplementation, indicating that garlic extract supplementation attenuated blood LDL-C concentrations by 10.37 mg/dL [19]. The meta-studies by Sun, Wang, and Qin showed in 2018 beneficial effects of garlic supplementation on LDL-C level [73]. Ried, Toben, and Fakler also showed in 2013 a reduction in the LDL-C level by up to 10% [74].

It is in the mix: dietary supplements are more than just pure ingredients

Numerous studies have used combinations of active ingredients, such as RYR, to treat hypercholesterolemia. Potential therapeutics include [76–78], CoQ10 [79, 80], olive extract [81], antioxidants [82–84], and polyphenols [46, 85, 86], bergamot [87], chromium picolinate [53], and artichoke extract [88]. The same is true for garlic, which is commonly applied with Guggulu [75]. A study by Cicero et al. in 2017 determined a significant reduction in cholesterol levels with a product consisting of RYR, artichoke extract, and banaba extract [45]. Another study by the same research group in 2015 showed a 22% reduction in LDL-C levels with the drug combination of RYR and polyunsaturated fatty acids [89]. Therefore, it appears that DSs may synergistically match in combination and produce better results in reducing blood lipid levels than single agents. However, when administering together, it is also important to clarify its potential side effects on health.

Discussion

In considering the efficacy and potential side effects of dietary supplements, it is essential to recognize that the diverse preparations available may vary in their chemical composition. Notably, red yeast rice stands out as the sole source of Monacolin K, a statin compound [90]. While due consideration is given to possible side effects, the confirmed efficacy of these supplements is noteworthy. Additionally, artichoke contains luteolin, which may influence the expression of HNF4α in the liver and potentially contribute to favorable blood lipid homeostasis [91]. Bergamot may lower blood LDL-C levels and may be especially effective in combination with artichoke [92]. Flaxseed seems to be one of the most effective diet supplements against atherosclerosis and may decrease cholesterol levels based on its fiber, linoleic acid, and phenolic contents [93]. The studies on garlic are contradictory, a distinction must be made between the different dosage forms. The latest studies have shown that garlic does not have significant effects on lowering cholesterol [94], The compound contains allicin, a well-known inhibitor of HMGCR, sterol 4a-methyl oxidase, and acetyl-CoA-synthetase enzymes. Consequently, this compound may inhibit cholesterol synthesis effectively [94]. However, further studies are needed to clarify this biochemical interaction. In addition to questionable quality control of dietary supplements, patients themselves may be endangered by using over-the-counter dietary supplements. Statins and other drugs used to lower cholesterol are prescribed by specialist doctors, considering the patient's entire clinical picture. In the long term, with close follow-up of patients, their health conditions and possible side effects of statins are controlled. However, the increased use of dietary supplements and their easy access without requiring supervision may lead to uncontrolled and/or incorrect treatment, and this lack of standardization may pose a risk for patients [42]. It is advised that individuals remain aware of the potential adverse effects associated with using dietary supplements and take the precaution of seeking guidance from a medical professional before proceeding.

Since 2011, the guidelines of the European Cardiology Society and the European Atherosclerosis Society have suggested using red yeast rice extract to treat mild hypercholesterolemia [95]. In addition to red yeast rice, other promising candidates are available on the dietary supplements market that could potentially replace statins or be used as an adjunct therapy. Table 2 summarises the potential advantages and disadvantages of alternative cholesterol treatments.

The findings on RYR showed that RYR supplementation could be beneficial in lowering blood lipid levels in LDL-C levels compared to placebo and statins in patients with dyslipidemia [50]. These effects are attributable to its chemical component, Monacolin K, which is chemically identical to lovastatin, a statin derivative. The potential metabolism of Monacolin K is thought to be acting as a rate-limiting step for the enzyme hydroxymethylglutaryl coenzyme A reductase, thereby reducing cholesterol production in the body [34, 96, 97]. In terms of its safety, a recent systematic review and meta-analysis on RYR safety showed that RYR is considered a safe and well-tolerated supplement in patients with moderate hypercholesterolemia [98]. However, despite these positive outcomes on RYR safety, authorities, including the European Food Safety Authority (EFSA), Federal Drug Administration (FDA), and Swiss Agency for Therapeutic Products (Swissmedic), have several concerns about RYR supplementation. In 2018, the EFSA panel was unable to determine the safe and tolerable level for RYR supplementation, highlighting that RYR can cause various side effects on muscle and liver [99]. Additionally, it is important to note that both the FDA and Swissmedic have categorized RYR supplements as unsafe for administration [100, 101]. While the existing studies on RYR and its impact on hypercholesterolemia/dyslipidemia are promising and indicate good tolerance, further high-quality research is imperative to comprehend its effects on cardiovascular metabolism as well as potential side effects.

Table 2 Advantages and disadvantages of administering dietary supplements treating hypercholesterolemia

Advantages	Disadvantages
Food could possibly be considered more as a remedy or supporter of healing processes.	The field of DSs is rather confusing; the concentration and quality of active ingredients are subject to a wide range of variation.
DSs have been well studied and if taken regularly, they positively influence patients' cholesterol levels.	Possible lack of medical supervision regarding the necessity of intake, adherence to intake, and the consequences of possible self-therapy.
No need for doctors	Lack of quality control, the large number of manufacturers, and possible impurities in the DSs also have a negative effect.
No control	Many of the researched and selected studies deal with combinations of active ingredients. Single preparations already contain more than the pure active ingredient.
No regulations	The validity of the studies could be strengthened by increasing the number of subjects and dividing the subjects into smaller groups.
The DSs are freely marketable and available in the nearest health food store or online.	The data situation is currently not sufficient to consider the administration of nutritional supplements to be sensible in the case of cholesterol levels in the range of medium hypercholesterolemia.
There is documentation and studies regarding the administration of DSs to lower cholesterol, especially LDL cholesterol.	
Dietary supplements (DSs), synergistically matched in combination, produce better results in reducing blood lipid levels than single agents.	
Side effects are not known; rarely, digestive, or upper abdominal discomfort occurs	

RYR contains monacolin K, equivalent to lovastatin, so its efficacy is proportional to the amount of monacolin K. Monacolin K can cause the side effects known from statins [39, 45]. According to studies, there is evidence to suggest that the side effects are not prevalent. Furthermore, patients who experienced difficulties with statins were able to tolerate RYR preparations effectively [45]. RYR products have a high tolerability profile but vary in monacolin K concentration [48]. Known side effects of RYR products include headache, dizziness, visual and digestive disturbances, skin rashes, muscle cramps, or pain [49].

A meta-analysis of RYR and blood lipid concentrations found that RYR has a lipid-lowering effect like low-dose pravastatin, simvastatin, or lovastatin when studied for 2–20 months [49]. Notwithstanding, the discerned outcomes of the conducted studies exhibit a degree of ambiguity, indicating that the empirical evidence is not uniformly decisive. This nuanced perspective underscores the intricate nature of the subject matter, where variables and contextual nuances contribute to the complexity of interpretation. The number of patients participating in the studies is between 30 and 1000; the studies are usually randomized and double-blinded. However, the quality of the administered DS or their composition is insufficiently clarified. Many questions about the toxicology and drug interactions of RYR extracts have now been clarified [102], but the composition of a fermented 'natural product' is more diverse than a purely chemically produced active ingredient.

Artichoke has been classified as a potential lipid-reducing agent in the literature due to its phenolic content, particularly luteolin, caffeic acid, cynarine, and chlorogenic acid [103]. While there is a need for more research papers on the relationship between artichoke and hypercholesterolemia, the results pertaining to blood lipid regulation show promise. The biochemical pathways of artichoke seem to be two- the luteolin impact on HNF4α expression in the liver, thereby inhibiting two important regulator proteins of sterol synthesis, sterol regulatory element-binding proteins (SREBPs), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) and Acyl-coenzyme A Cholesterol acyltransferase (ACAT) [104]. This interaction results in attenuating cholesterol synthesis [105]. The second possible mechanism could be its higher fiber content and inulin-type fructans; however, this mechanism has only been well-validated in animal studies [106]. Its side effects are generally unknown; however, it is reported to cause digestive or upper abdominal discomfort rarely [53].

Future research in artichokes is crucial to enhance our understanding and uncover potential benefits or drawbacks, contributing to a more comprehensive knowledge base.

Bergamot, also recognized as Citrus Bergamia, is a well-known plant with high flavonoid contents, including naringenin [107] and shows a beneficial effect on LDL-C. Its possible benefits on cholesterol regulation seem to be these flavonoids inhibiting HMGCR, thereby repressing cholesterol synthesis [108]. It is widely accepted that flavonoids significantly enhance the intracellular synthesis of antioxidant enzymes, potentially doubling their production [8]. Human studies on bergamot and hypercholesterolemia have shown that supplemental bergamot ingestion for 30 days may provide benefits in reducing blood LDL-C levels in patients with mild to moderate hypercholesterolemia [109]. Furthermore, the use of Bergamot extract in combination with rosuvastatin has been recommended to enhance the impact of rosuvastatin therapy [110]. Bergamot oil or bergamot products are included in the common dietary supplements and are approved for use by Swissmedic in Switzerland. Often, the products are found in combination with artichoke as capsules on the market. The combination product of 600 mg bergamot oil and 10 mg artichoke extract showed very good results without the side effects of statins [111].

No side effects were reported in the studies. A free text search revealed certain concerns, particularly regarding bergamottin, a furanocoumarin found in various citrus plants. Furanocoumarins inhibit the metabolizing enzyme cytochrome P450 3A4 (CYP3A4). Inhibition of this enzyme may increase the bioavailability and plasma concentration of certain medications, leading to potential drug interactions [60]. Grapefruit juice is currently not recommended in combination with medication, unlike bergamot, due to the unclear amount of this furanocoumarin [61]. Although the results show the benefits of bergamot extract supplementation [112], more research is needed, including a high sample size.

Flaxseed (linseed), also known as *Linum usitatissimum*, shows in all research studies a positive effect on LDL-C, is classified as one of the greatest anti-atherogenic herbs with its fiber [113] and biochemical components including a-linoleic acid, linoleic acid, and phenolic contents [114]. The benefits of flaxseed lignans have been indicated with their cholesterol-lowering effects and could regress atherosclerotic processes [113–115]. Husna Dharma Putera et al. mentioned in 2023 that the benefits of conjugated linoleic acid are caused by its two main isomers, c9, t11-CLA and trans-10, cis-12 (t10, c12) [12]. All research studies, including this review, have shown flaxseed's beneficial effects on blood lipid regulation regardless of application form. In line with these findings, Sadat Masjedi et al. found in 2022 a markedly significant decrease in LDL-C concentration after flaxseed consumption in subjects with a BMI>25 kg/m^2 [115]. Prasad, Khan, and Shoker recommend in 2020 flaxseed as an additional agent in cholesterol-lowering therapy. It is recommended as an additional agent in the context of cholesterol-lowering therapy at a daily dose of 10–60 g for flaxseeds or their products [116]. Thus, flaxseed supplementation could be an effective strategy in regulating blood lipid levels; however, more studies on this supplement are needed due to the limited number of studies.

Garlic is known for its organosulfur compounds, particularly Allicin [87] and shows different effects on LDL-C. When garlic is processed, alliinase converts alliin into allicin. Raw garlic and garlic powder dried below 60 °C retain enzyme activity. However, heat-treated garlic mainly contains alliin due to enzyme inactivation by heat [119]. N-alpha-(1-deoxy-D-fructos-1-yl)-L-arginine (Fru-Arg) has been identified as an antioxidant compound in aged garlic [120]. Allicin is classified as a powerful anti-inflammatory, anti-arteriosclerotic and anti-oxidant agent and is known for its inhibitory role in cholesterol synthesis by inhibiting HMGCR, sterol 4a-methyl oxidase, and acetyl-CoA synthetase enzymes [116]. Studies show a cholesterol synthesis inhibitory effect via water-soluble organosulfur compounds, particularly S-allyl-cysteine from aged garlic extract, and diallyl disulfide contained in garlic oil [118]. In terms of garlic administration side effects, they may include gastrointestinal disturbances, skin rashes, nausea, bad breath, and body odor [75]. However, these side effects are more pronounced when using whole garlic. The dosage form and the containing of different sulfur components of garlic appears to have a difference in the effect [121]. While recent studies on the efficacy of aged garlic supplementation did not reveal significant benefits for hypercholesterolemia, further research is warranted, specifically investigating normal garlic, whether in extract form or as a whole food. This is crucial to understanding potential distinctions between past and current findings.

Since the active substances used in dietary supplements form the basis of the low-cholesterol Mediterranean diet, further studies are needed in which the food can be evaluated as a healing agent or at least an accelerator of healing processes [117]. The validity of research studies can be strengthened by increasing the number of subjects and considering various personal characteristics such as weight, BMI, and sex. In patients with mild to moderate hypercholesterolemia, administering dietary supplements may be beneficial regarding cholesterol values to postpone statin treatment to a later time. Nonetheless, an experienced healthcare provider might recommend alternative medications to lower cholesterol levels, balancing the associated risks for the patient. This recommendation hinges on acquiring a comprehensive medical history and ensuring regular monitoring of blood values.

Limitations

Our narrative review had few limitations. We identified a diverse kind of literature on the topic of hypercholesterolemia and dietary supplements, but several methodological limitations were evident. While most studies had a correct design, they varied in terms of population, study design, sample size, and the types of processing and quantities of DS evaluated. These limitations complicate efforts to compare and synthesize the findings without introducing bias. To account for these constraints and still capture recent developments, side effects and limitations, we opted for a narrative review instead of a systematic review. Additionally, many studies addressed hypercholesterolemia only indirectly, which was a further limitation. Some relevant studies focusing primarily on cardiovascular and inflammatory diseases may have been excluded. Future research should address these limitations by adopting more standardized methodologies in DS research and by examining the molecular mechanisms involved. This would allow for broader generalizations regarding the physical compartments affected.

Conclusion

Cardiovascular diseases stand as the foremost cause of death in Switzerland. Faced with concerns about potential side effects and media uncertainty surrounding statins, many patients seek alternative treatment options. This review explores various approaches to managing hypercholesterolemia through a comprehensive literature review. Red yeast rice, artichoke extract, bergamot, garlic, and flaxseed were chosen as supplements for lowering cholesterol. Except for aged garlic extract, these supplements appear to positively influence cholesterol levels when consumed regularly. However, the administration of these dietary supplements is complicated by variable concentrations and the quality of active ingredients. Enhancing the validity of individual studies could be achieved by increasing the sample size and incorporating previously determined values. Competent specialists can prescribe alternative cholesterol-lowering agents with acceptable risk, while closely monitoring the patient's blood values. The lack of medical oversight, quality assurance, and potential contamination associated with dietary supplements pose challenges in their effectiveness in modifying cholesterol levels.

Abbreviations

ALS	Alpha linolenic acid
BMI	Body-Mass-Index
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
HMG-CoA	3-Hydroxy-3-Methylglutaryl-Coenzyme-A
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
DS	Dietary Supplements
PCSK9	Proprotein-Convertase Subtilisin/Kexin Type 9
RYR	Red-Yeast-Rice
SRF	Swiss Radio and Television (Schweizer Radio und Fernsehen)
TG	Triglycerides

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Data availability

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Declarations

Ethics approval and consent to participate

This is a narrative review. Only literature whose ethical procedure had already been approved was used.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Note

The combination 'hypercholesterolemia AND XXX NOT familial hypercholesterolemia' was always chosen as the search term. The dietary supplement XXX is listed in the table.

Author details

[1]Institute of Primary Care, University of Zurich, Zurich, Switzerland
[2]Department of Pediatric Oncology and Hematology, Otto-Heubner Centre for Paediatric and Adolescent Medicine (OHC), Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
[3]Department of Sport Science, Leopold-Franzens University of Innsbruck, Fürstenweg 185, Innsbruck 6020, Austria
[4]Research Center Medical Humanities, Leopold-Franzens University of Innsbruck, Innrain 52, Innsbruck 6020, Austria
[5]Department of Research and Development in Teacher Education, University College of Teacher Education Tyrol, Pastorstraße 7, Innsbruck 6010, Austria
[6]School of Health and Caring Sciences, University of West Attica, Athens, Greece
[7]School of Health and Human Performance, Dublin City University, Dublin, Ireland
[8]Department of Nutrition and Dietetics, Istanbul Medeniyet University, Istanbul, Turkey
[9]Dept. of Pediatrics, Research Institute, McGill University Health Centre, Montreal, Canada
[10]Medbase St. Gallen Am Vadianplatz, St. Gallen, Switzerland

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References

1. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet [Internet]. 2012;380(9859):2197–223. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)61689-4/fulltext
2. Hajat C, Stein E. The Global Burden of Multiple Chronic conditions: a Narrative Review. Preventive Medicine Reports [Internet]. 2018;12(1):284–93. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6214883/
3. Bhattacharya S, Heidler P, Varshney S. Incorporating neglected non-communicable diseases into the national health program—A review. Front Public Health. 2023;10.
4. Lu Y, Lan T. Global, regional, and national burden of hypertensive heart disease during 1990–2019: an analysis of the global burden of disease study 2019. BMC Public Health. 2022;22(1).
5. Mannarino MR, Ministrini S, Pirro M. Nutraceuticals for the treatment of hypercholesterolemia. European Journal of Internal Medicine [Internet]. 2014;25(7):592–9. https://pubmed.ncbi.nlm.nih.gov/24997485/
6. Does propolis have any effect on rheumatoid arthritis? A review study. ProQuest [Internet]. 2022;1003–20. https://www.proquest.com/scholarly-journals/does-propolis-have-any-effect-on-rheumatoid/docview/2649700990/se-2
7. Naseh Pahlavani M, Malekahmadi, Sedaghat A, Rostami A, Kamal O, Taifi A et al. Effects of Melatonin and Propolis supplementation on inflammation, oxidative stress, and clinical outcomes in patients with primary pneumosepsis: a Randomized Controlled Clinical Trial. 2022;29(4):275–85.
8. Nattagh-Eshtivani E, Gheflati A, Barghchi H, Rahbarinejad P, Hachem K, Shalaby MN et al. The role of Pycnogenol in the control of inflammation and oxidative stress in chronic diseases: Molecular aspects. Phytotherapy research: PTR [Internet]. 2022;36(6):2352–74. https://pubmed.ncbi.nlm.nih.gov/35583807/
9. Malekahmadi M, Shadnoush M, Islam SMS, Shirvani A, Pahlavani N, Gholizadeh Navashenaq J, et al. The effect of French maritime pine bark extract supplementation on inflammation, nutritional and clinical status in critically ill patients with traumatic brain injury: a randomized controlled trial. Phytother Res. 2021;35(9):5178–88.
10. Hajibeygi R, Mirghazanfari SM, Pahlavani N, Jalil AT, Alshahrani SH, Rizaev JA et al. Effect of a diet based on Iranian traditional medicine on inflammatory markers and clinical outcomes in COVID-19 patients: A double-blind, randomized, controlled trial. European Journal of Integrative Medicine [Internet].

2022 Oct 1 [cited 2023 Jan 30];55:102179. https://www.sciencedirect.com/science/article/pii/S1876382022000804
11. Mopuri R, Ganjayi M, Meriga B, Koorbanally NA, Islam MS. The effects of Ficus carica on the activity of enzymes related to metabolic syndrome. J Food Drug Anal. 2018;26(1):201–10.
12. Putera HD, Doewes RI, Shalaby MN et al. Andrés Alexis Ramírez-Coronel, Clayton ZS, Walid Kamal Abdelbasset,. The effect of conjugated linoleic acids on inflammation, oxidative stress, body composition and physical performance: a comprehensive review of putative molecular mechanisms. Nutrition & Metabolism. 2023;20(1).
13. Xu R, Yang K, Li S, Dai M, Chen G. Effect of green tea consumption on blood lipids: a systematic review and meta-analysis of randomized controlled trials. Nutr J. 2020;19(1).
14. Bursill CA, Roach PD. Modulation of cholesterol metabolism by the Green Tea Polyphenol (–)-Epigallocatechin gallate in cultured human liver (HepG2) cells. J Agricultural Food Chem [Internet]. 2006;54(5).
15. Wahab S, Annadurai S, Abullais SS, Das G, Ahmad W, Ahmad MF, et al. Glycyrrhiza glabra (licorice): a Comprehensive Review on its Phytochemistry, Biological activities, clinical evidence and toxicology. Plants. 2021;10(12):2751.
16. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The Forgotten Lipids: Triglycerides, Remnant Cholesterol, and Atherosclerotic Cardiovascular Disease Risk. Endocrine Reviews [Internet]. 2018;40(2):537–57. https://academic.oup.com/edrv/article/40/2/537/5126386
17. Wang A, Richhariya A, Gandra SR, Calimlim B, Kim L, Quek RGW et al. Systematic review of low-density lipoprotein cholesterol apheresis for the treatment of familial hypercholesterolemia. J Am Heart Association. 2016;5(7).
18. Blood cholesterol and. Vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. Lancet. 2007;370(9602):1829–39.
19. Bhatnagar D, Soran H, Durrington PN. Hypercholesterolaemia and its management. BMJ. 2008;337(aug21 1):a993–3.
20. Civeira F, Arca M, Cenarro A, Hegele RA. A mechanism-based operational definition and classification of hypercholesterolemia. J Clin Lipidol. 2022;16(6):813–21.
21. Bilitou A, Were J, Farrer A, Rabe A, Ming SWY, Haq I, et al. Prevalence and Patient Outcomes of Adult Primary Hypercholesterolemia and Dyslipidemia in the UK: Longitudinal Retrospective Study using a primary care dataset from 2009 to 2019. ClinicoEconomics Outcomes Res. 2022;14:189–203.
22. Gao Y, Isakadze N, Duffy E, Sheng Q, Ding J, MacFarlane ZT, et al. Secular trends in Risk profiles among adults with Cardiovascular Disease in the United States. J Am Coll Cardiol [Internet]. 2022;80(2):126–37. Jul 12 [cited 2022 Sep 4];.
23. Holven KB, Ulven SM, Bogsrud MP. Hyperlipidemia and cardiovascular disease with focus on familial hypercholesterolemia. Curr Opin Lipidol. 2017;28(5):445–7.
24. Kim H, Kim S, Han S, Rane PP, Fox KM, Qian Y et al. Prevalence and incidence of atherosclerotic cardiovascular disease and its risk factors in Korea: a nationwide population-based study. BMC Public Health [Internet]. 2019;19(1). https://bmcpublichealth.biomedcentral.com/articles/https://doi.org/10.1186/s12889-019-7439-0
25. Jandari S, Ghavami A, Ziaei R, Nattagh-Eshtivani E, Rezaei Kelishadi M, Sharifi S, et al. Effects of Momordica charantia L on blood pressure: a systematic review and meta- analysis of randomized clinical trials. Int J Food Prop. 2020;23(1):1913–24.
26. Mills EJ, WU P, Chong G, Ghement I, Singh S, Akl EA, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials. QJM. 2010;104(2):109–24.
27. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. BMJ. 2013;346(may23 4):f2610–2610.
28. Users'. Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice, 3rd ed | JAMAevidence.
29. DeMars MM, Perruso C. MeSH and text-word search strategies: precision, recall, and their implications for library instruction. Journal of the Medical Library Association [Internet]. 2022;110(1). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8830400/?report=reader
30. Banach M, Patti AM, Giglio RV, Cicero AFG, Atanasov AG, Bajraktari G, et al. The role of Nutraceuticals in Statin intolerant patients. J Am Coll Cardiol. 2018;72(1):96–118.
31. Falagas ME, Pitsouni EI, Malietzis GA, Pappas G. Comparison of PubMed, Scopus, Web of Science, and Google Scholar: Strengths and Weaknesses. The FASEB Journal [Internet]. 2008;22(2):338–42. https://faseb.onlinelibrary.wiley.com/doi/full/10.1096/fj.07-9492LSF
32. Kleibel V, Mayer H. Literaturrecherche für Gesundheitsberufe. 2011.
33. Stam-Slob MC, van der Graaf Y, Greving JP, Dorresteijn JAN, Visseren FLJ. Cost-effectiveness of intensifying lipid-lowering Therapy with statins based on individual Absolute Benefit in Coronary Artery Disease patients. J Am Heart Assoc. 2017;6(2):e004648.
34. Sirtori CR. The pharmacology of statins. Pharmacol Res. 2014;88:3–11.
35. Shah A, Sharma K, Rawal S, Sisodia R, Bhatt P, Christian C et al. Commentary: Beyond 10-year risk: A cost-effectiveness analysis of statins for the primary prevention of cardiovascular disease. Front Cardiovasc Med [Internet]. 2022 [cited 2023 Jul 27];9. https://www.frontiersin.org/articles/https://doi.org/10.3389/fcvm.2022.916695
36. Laffin LJ, Bruemmer D, Garcia M, Brennan DM, McErlean E, Jacoby DS, et al. Comparative effects of Low-Dose Rosuvastatin, Placebo, and Dietary supplements on lipids and inflammatory biomarkers. J Am Coll Cardiol. 2023;81(1):1–12.
37. Law M, Rudnicka AR. Statin Safety: a systematic review. Am J Cardiol. 2006;97(8):S52–60.
38. Cheon DY, Jo SH. Adverse effects of statin therapy and their treatment. Cardiovasc Prev Pharmacother. 2022;4(1):1–6.
39. Rausch R. DAZ.online. 2021 [cited 2023 Jul 27]. Das Statin-Roulette. https://www.deutsche-apotheker-zeitung.de/daz-az/2021/daz-38-2021/das-statin-roulette
40. Birtcher K. When compliance is an issue—how to enhance statin adherence and address adverse effects. Curr Atheroscler Rep. 2014;17(1):471.
41. Zhu B, Qi F, Wu J, Yin G, Hua J, Zhang Q et al. Red Yeast Rice: A Systematic Review of the Traditional Uses, Chemistry, Pharmacology, and Quality Control of an Important Chinese Folk Medicine. Frontiers in Pharmacology [Internet]. 2019 Dec 2 [cited 2021 Apr 13];10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6901015/table/T1/?report=objectonly
42. Patel S. Functional food red yeast rice (RYR) for metabolic syndrome amelioration: a review on pros and cons. World J Microbiol Biotechnol. 2016;32(5):87.
43. SR 817.022. 14 - Verordnung des EDI vom 16. Dezember 2016 über Nahrungsergänzungsmittel (VNem) [Internet]. [cited 2023 Jul 27]. https://www.fedlex.admin.ch/eli/cc/2017/155/de
44. Nahrungsergänzungsmittel | EFSA [Internet]. 2022 [cited 2023 Jul 27]. https://www.efsa.europa.eu/de/topics/topic/food-supplements
45. Cicero AFG, Fogacci F, Banach M. Red Yeast Rice Hypercholesterolemia. 2019;15(3):192.
46. Cicero AFG, Fogacci F, Bove M, Veronesi M, Rizzo M, Giovannini M, et al. Short-term effects of a combined nutraceutical on lipid level, fatty liver biomarkers, hemodynamic parameters, and estimated Cardiovascular Disease Risk: a Double-Blind, placebo-controlled Randomized Clinical Trial. Adv Ther. 2017;34(8):1966–75.
47. Gerards MC, Terlou RJ, Yu H, Koks CHW, Gerdes VEA. Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but safety is uncertain – A systematic review and meta-analysis. Atherosclerosis. 2015;240(2):415–23.
48. Mazzanti G, Moro PA, Raschi E, Da Cas R, Menniti-Ippolito F. Adverse reactions to dietary supplements containing red yeast rice: assessment of cases from the Italian surveillance system. Br J Clin Pharmacol. 2017;83(4):894–908.
49. Farkouh A, Baumgärtel C. Mini-review: medication safety of red yeast rice products. Int J Gen Med. 2019;12:167–71.
50. Peng D, Fong A, van Pelt A. Original Research: the effects of red yeast Rice supplementation on cholesterol levels in adults. AJN Am J Nurs. 2017;117(8):46.
51. Iskandar I, Harahap Y, Wijayanti TR, Sandra M, Prasaja B, Cahyaningsih P. Efficacy and tolerability of a nutraceutical combination of red yeast rice, guggulipid, and chromium picolinate evaluated in a randomized, placebo-controlled, double-blind study. Complement Ther Med. 2020;48:102282.
52. Schütz K, Kammerer D, Carle R, Schieber A. Identification and quantification of caffeoylquinic acids and flavonoids from Artichoke (Cynara scolymus L.) heads, juice, and pomace by HPLC-DAD-ESI/MS n. J Agric Food Chem. 2004;52:4090–6.
53. Salem MB, Affes H, Ksouda K, Dhouibi R, Sahnoun Z, Hammami S, et al. Pharmacological studies of Artichoke Leaf Extract and their health benefits. Plant Foods Hum Nutr. 2015;70(4):441–53.
54. Rondanelli M, Castellazzi AM, Riva A, Allegrini P, Faliva MA, Peroni G, et al. Natural Killer Response and Lipo-Metabolic Profile in adults with low HDL-Cholesterol and mild hypercholesterolemia: Beneficial effects of Artichoke

Leaf Extract Supplementation. Evid Based Complement Alternat Med. 2019;2019:e2069701.
55. Sahebkar A, Pirro M, Banach M, Mikhailidis DP, Atkin SL, Cicero AFG. Lipid-lowering activity of artichoke extracts: a systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2018;58(15):2549–56.
56. Osadnik T, Goławski M, Lewandowski P, Morze J, Osadnik K, Pawlas N, et al. A network meta-analysis on the comparative effect of nutraceuticals on lipid profile in adults. Pharmacol Res. 2022;183:106402.
57. Rezazadeh K, Rezazadeh F, Ebrahimi-Mameghani M. The effect of artichoke leaf extract supplementation on lipid and CETP response in metabolic syndrome with respect to taq 1B CETP polymorphism: a randomized placebo-controlled clinical trial. Eur J Integr Med. 2018;17:112–C8.
58. Mollace V, Sacco I, Janda E, Malara C, Ventrice D, Colica C, et al. Hypolipemic and hypoglycaemic activity of bergamot polyphenols: from animal models to human studies. Fitoterapia. 2011;82(3):309–16.
59. Mollace V, Scicchitano M, Paone S, Casale F, Calandruccio C, Gliozzi M, et al. Hypoglycemic and Hypolipemic effects of a new lecithin formulation of bergamot polyphenolic fraction: a double blind, randomized, placebo- controlled study. Endocr Metab Immune Disord - Drug Targets. 2019;19(2):136–43.
60. Viktoria I. Arzneimittel-Interaktionen mit Nahrungsmitteln [Internet]. Gelbe-liste.de. Vidal MMI Germany GmbH; 2019 [cited 2024 Oct 8]. https://www.gelbe-liste.de/arzneimitteltherapiesicherheit/nahrungsmittel-interaktionen
61. Rossi M, Aktar S, Davis M, Hefter Feuss E, Roman-Holba S, Wen K et al. The Grapefruit Effect: Interaction between Cytochrome P450 and Coumarin Food Components, Bergamottin, Fraxidin and Osthole. X-ray Crystal Structure and DFT Studies. Molecules [Internet]. 2020;25(14):3158. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7397038/
62. Ribas SA, Grando RL, Zago L, Carvajal E, Fierro IM. Overview of Flaxseed Patent Applications for the reduction of cholesterol levels. Recent Pat Food Nutr Agric. 2016;8(2):116–23.
63. Akrami A, Nikaein F, Babajafari S, Faghih S, Yarmohammadi H. Comparison of the effects of flaxseed oil and sunflower seed oil consumption on serum glucose, lipid profile, blood pressure, and lipid peroxidation in patients with metabolic syndrome. J Clin Lipidol. 2018;12(1):70–7.
64. Kanikowska D, Korybalska K, Mickiewicz A, Rutkowski R, Kuchta A, Sato M et al. Flaxseed (Linum Usitatissimum L.) Supplementation in Patients Undergoing Lipoprotein Apheresis for Severe Hyperlipidemia—A Pilot Study. Nutrients [Internet]. 2020 Apr 1 [cited 2023 Mar 5];12(4):1137. https://www.mdpi.com/2072-6643/12/4/1137#B22-nutrients-12-01137
65. Katare C, Saxena S. Evaluation of flaxseed formulation as a potential therapeutic agent in mitigation of dyslipidemia. Biomedical Journal [Internet]. 2014 [cited 2021 Oct 8];37(6):386. http://biomedj.cgu.edu.tw/pdfs/2014/37/6/images/BiomedJ_2014_37_6_386_126447.pdf
66. Kanikowska D, Malińska A, Mickiewicz A, Zawada A, Rutkowski R, Pawlaczyk K, et al. Effect of Flaxseed (Linum usitatissimum L.) supplementation on vascular endothelial cell morphology and function in patients with Dyslipidaemia—A Preliminary Observation. Nutrients. 2022;14(14):2879.
67. Skoczyńska AH, Gluza E, Wojakowska A, Turczyn B, Skoczyńska M. Linseed oil increases HDL3 cholesterol and decreases blood pressure in patients diagnosed with mild hypercholesterolaemia. Kardiologia Polska [Internet]. 2018 [cited 2021 Oct 24];76(8):1242–50. https://pubmed.ncbi.nlm.nih.gov/29688571/
68. Hadi A, Askarpour M, Salamat S, Ghaedi E, Symonds ME, Miraghajani M. Effect of flaxseed supplementation on lipid profile: an updated systematic review and dose-response meta-analysis of sixty-two randomized controlled trials. Pharmacol Res. 2020;152:104622.
69. Valls RM, Companys J, Calderón-Pérez L, Salamanca P, Pla-Pagà L, Sandoval-Ramírez BA, Bueno A, Puzo J, Crescenti A, Bas JMD, Caimari A, Salamanca A, Espinel AE, Pedret A, Arola L, Solà R. Effects of an optimized aged Garlic Extract on Cardiovascular Disease Risk factors in moderate hypercholesterolemic subjects: a randomized, crossover, Double-Blind, Sustainedand Controlled Study. Nutrients. 2022;14(3):405. https://doi.org/10.3390/nu14030405. PMID: 35276764; PMCID: PMC8838962.
70. Villaño D, Marhuenda J, Arcusa R, Moreno-Rojas JM, Cerdá B, Pereira-Caro G, Zafrilla P. Effect of black garlic consumption on endothelial function and lipid Profile: a before-and-after study in Hypercholesterolemic and non-hypercholesterolemic subjects. Nutrients. 2023;15(14):3138. https://doi.org/10.3390/nu15143138. PMID: 37513556; PMCID: PMC10385333.
71. Jung ES, Park SH, Choi EK, Ryu BH, Park BH, Kim DS, Kim YG, Chae SW. Reduction of blood lipid parameters by a 12-wk supplementation of aged black garlic: a randomized controlled trial. Nutrition. 2014;30(9):1034-9. https://doi.org/10.1016/j.nut.2014.02.014. Epub 2014 Mar 12. PMID: 24976429.
72. Isaacsohn JL, Moser M, Stein EA, Dudley K, Davey JA, Liskov E, Black HR. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. Arch Intern Med. 1998;158(11):1189-94. https://doi.org/10.1001/archinte.158.11.1189. PMID: 9625398.
73. Sun YE, Wang W, Qin J. Anti-hyperlipidemia of garlic by reducing the level of total cholesterol and low-density lipoprotein: a meta-analysis. Med (Baltim). 2018;97(18):e0255.
74. Ried K, Toben C, Fakler P. Effect of garlic on serum lipids: an updated meta-analysis. Nutr Rev. 2013;71(5):282–99.
75. Gyawali D, Vohra R, Orme-Johnson D, Ramaratnam S, Schneider RH. A systematic review and Meta-analysis of Ayurvedic Herbal preparations for Hypercholesterolemia. Med (Mex). 2021;57(6):546.
76. Ruscica M, Pavanello C, Gandini S, Macchi C, Botta M, Dall'Orto D et al. Nutraceutical approach for the management of cardiovascular risk – a combination containing the probiotic Bifidobacterium longum BB536 and red yeast rice extract: results from a randomized, double-blind, placebo-controlled study. Nutr J. 2019;18(1).
77. Cicolari S, Pavanello C, Olmastroni E, Puppo MD, Bertolotti M, Mombelli G, et al. Interactions of Oxysterols with atherosclerosis biomarkers in subjects with Moderate Hypercholesterolemia and effects of a nutraceutical combination (Bifidobacterium longum BB536, red yeast Rice Extract) (Randomized, Double-Blind, placebo-controlled study). Nutrients. 2021;13(2):427.
78. Guerrero-Bonmatty R, Gil-Fernández G, Rodríguez-Velasco FJ, Espadaler-Mazo J. A Combination of Lactoplantibacillus plantarum Strains CECT7527, CECT7528, and CECT7529 Plus Monacolin K Reduces Blood Cholesterol: Results from a Randomized, Double-Blind, Placebo-Controlled Study. Nutrients [Internet]. 2021;13(4):1206. https://pubmed.ncbi.nlm.nih.gov/33917503/
79. Mazza A, Lenti S, Schiavon L, Di Giacomo E, Tomasi M, Manunta R et al. Effect of Monacolin K and COQ10 supplementation in hypertensive and hypercholesterolemic subjects with metabolic syndrome. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie [Internet]. 2018;105:992–6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6361161/
80. Cicero AFG, Morbini M, Rosticci M, D"Addato S, Grandi E, Borghi C. Middle-Term Dietary supplementation with red yeast Rice Plus Coenzyme Q10 improves lipid pattern, endothelial reactivity and arterial stiffness in moderately hypercholesterolemic subjects. Annals Nutr Metabolism. 2016;68(3):213–9.
81. Tshongo Muhindo C, Ahn SA, Rousseau MF, Dierckxsens Y, Hermans MP. Efficacy and safety of a combination of red yeast rice and olive extract in hypercholesterolemic patients with and without statin-associated myalgia. Complementary Therapies in Medicine [Internet]. 2017 Dec 1 [cited 2023 Oct 20];35:140–4. https://pubmed.ncbi.nlm.nih.gov/29154060/
82. Cimaglia P, Vieceli Dalla Sega F, Vitali F, Lodolini V, Bernucci D, Passarini G et al. Effectiveness of a novel nutraceutical compound containing red yeast Rice, Polymethoxyflavones and antioxidants in the modulation of cholesterol levels in subjects with Hypercholesterolemia and Low-Moderate Cardiovascular Risk: the NIRVANA Study. Front Physiol. 2019;10.
83. Pecchioli V, Cicero AFG, Lomartire N, Gemmiti MP, Colangeli A, Germanò R et al. A double-blind, placebo-controlled clinical trial to assess the effects of a combined nutraceutical on endothelial function in patients with mild-to-moderate hypercholesterolaemia. Archives of Medical Sciences Atherosclerotic Diseases [Internet]. 2020 [cited 2023 Oct 20];5:e36–42. https://pubmed.ncbi.nlm.nih.gov/32529103/
84. Barrat E, Zaïr Y, Sirvent P, Chauveau P, Maudet C, Housez B, et al. Effect on LDL-cholesterol of a large dose of a dietary supplement with plant extracts in subjects with untreated moderate hypercholesterolaemia: a randomised, double-blind, placebo-controlled study. Eur J Nutr. 2012;52(8):1843–52.
85. Cicero AFG, D'Addato S, Borghi CA, Randomized. Double-Blinded, Placebo-Controlled, clinical study of the effects of a nutraceutical combination (LEVELIP DUO®) on LDL Cholesterol Levels and lipid pattern in subjects with suboptimal blood cholesterol levels (NATCOL Study). Nutrients. 2020;12(10):3127.
86. Gonnelli S, Caffarelli C, Stolakis K, Cuda C, Giordano N, Nuti R. Efficacy and tolerability of a nutraceutical combination (red yeast Rice, Policosanols, and Berberine) in patients with low-moderate risk hypercholesterolemia: a Double-Blind, placebo-controlled study. Curr Therapeutic Res. 2015;77:1–6.
87. Mollace R, Macrì R, Tavernese A, Gliozzi M, Musolino V, Carresi C et al. Comparative Effect of Bergamot Polyphenolic Fraction and Red Yeast Rice Extract in Rats Fed a Hyperlipidemic Diet: Role of Antioxidant Properties and PCSK9 Expression. Nutrients [Internet]. 2022 Jan 1 [cited 2022 Apr 26];14(3):477. https://www.mdpi.com/2072-6643/14/3/477/htm.

88. Cicero AFG, Fogacci F, Tocci G, D'Addato S, Grandi E, Banach M et al. Three arms, double-blind, non-inferiority, randomized clinical study testing the lipid-lowering effect of a novel dietary supplement containing red yeast rice and artichoke extracts compared to Armolipid Plus® and placebo. Archives of medical science: AMS [Internet]. 2023 [cited 2023 Oct 20];19(5):1169–79. https://pubmed.ncbi.nlm.nih.gov/37732047/
89. Cicero AFG, Derosa G, Pisciotta L, Barbagallo C. Testing the short-term efficacy of a lipid-lowering nutraceutical in the setting of clinical practice: a Multicenter Study. J Med Food. 2015;18(11):1270–3.
90. Xiong Z, Cao X, Wen Q, Chen Z, Cheng Z, Huang X, Zhang Y, Long C, Zhang Y, Huang Z. An overview of the bioactivity of monacolin K / lovastatin. Food Chem Toxicol. 2019;131:110585. https://doi.org/10.1016/j.fct.2019.110585. Epub 2019 Jun 15. PMID: 31207306.
91. Li J, Inoue J, Choi JM, Nakamura S, Yan Z, Fushinobu S, Kamada H, Kato H, Hashidume T, Shimizu M, Sato R. Identification of the Flavonoid Luteolin as a Repressor of the transcription factor hepatocyte nuclear factor 4α. J Biol Chem. 2015;290(39):24021–35. https://doi.org/10.1074/jbc.M115.645200. Epub 2015 Aug 13. PMID: 26272613; PMCID: PMC4583009.
92. Cicero AFG, Fogacci F, Bove M, Giovannini M, Borghi C. Three-arm, placebo-controlled, randomized clinical trial evaluating the metabolic effect of a combined nutraceutical containing a bergamot standardized flavonoid extract in dyslipidemic overweight subjects. Phytother Res. 2019;33(8):2094–2101. doi: 10.1002/ptr.6402. Epub 2019 Jun 21. PMID: 31225673.
93. Kajla P, Sharma A, Sood DR. Flaxseed-a potential functional food source. J Food Sci Technol. 2015;52(4):1857–71. https://doi.org/10.1007/s13197-014-1293-y. Epub 2014 Feb 28. PMID: 25829567; PMCID: PMC4375225.
94. Banerjee SK, Maulik SK. Effect of garlic on cardiovascular disorders: a review. Nutr J. 2002;1:4. https://doi.org/10.1186/1475-2891-1-4. PMID: 12537594; PMCID: PMC139960.
95. Cicero AFG, Fogacci F, Zambon A. Red yeast Rice for Hypercholesterolemia: JACC Focus Seminar. J Am Coll Cardiol. 2021;77(5):620–8.
96. Berg JM, Held A, Stryer L, Lange C, Mahlke K, Maxam G et al. Stryer Biochemie [Internet]. Springer Berlin Heidelberg; 2012. https://books.google.de/books?id=PWxJLgEACAAJ
97. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR * trial). Am J Cardiol. 2003;92(2):152–60.
98. Schoeneck M, Iggman D. The effects of foods on LDL cholesterol levels: a systematic review of the accumulated evidence from systematic reviews and meta-analyses of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2021;31(5):1325–38.
99. Younes M, Aggett P, Aguilar F, Crebelli R, Dusemund B, Filipič M et al. Scientific opinion on the safety of monacolins in red yeast rice. EFSA J. 2018;16(8).
100. Affairs O, of R. Advisory Letters [Internet]. FDA. 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/advisory-letters
101. Swissmedic. 2019 C. Human health [Internet]. www.swissmedic.ch. [cited 2023 Oct 17]. https://www.swissmedic.ch/swissmedic/en/home/services/questions-on-delimitation/humanbereich.html
102. Zhu B, Qi F, Wu J, Yin G, Hua J, Zhang Q et al. Red Yeast Rice: A Systematic Review of the Traditional Uses, Chemistry, Pharmacology, and Quality Control of an Important Chinese Folk Medicine. Front Pharmacol [Internet]. 2019 [cited 2023 Jul 27];10. https://www.frontiersin.org/articles/https://doi.org/10.3389/fphar.2019.01449
103. Lattanzio V, Kroon PA, Linsalata V, Cardinali A. Globe artichoke: a functional food and source of nutraceutical ingredients. J Funct Foods. 2009;1(2):131–44.
104. Deng A, Liu F, Tang X, Wang Y, Xie P, Yang Q, Xiao B. Water extract from artichoke ameliorates high-fat diet-induced non-alcoholic fatty liver disease in rats. BMC Complement Med Ther. 2022;22(1):308. https://doi.org/10.1186/s12906-022-03794-9. PMID: 36424606; PMCID: PMC9686119.
105. Santos HO, Bueno AA, Mota JF. The effect of artichoke on lipid profile: a review of possible mechanisms of action. Pharmacol Res. 2018;137:170–8.
106. Hoving L, de Vries M, de Jong R, Katiraei S, Pronk A, Quax P, et al. The prebiotic inulin aggravates accelerated atherosclerosis in Hypercholesterolemic APOE*3-Leiden mice. Nutrients. 2018;10(2):172.
107. Toth PP, Patti AM, Nikolic D, Giglio RV, Castellino G, Biancucci T, Geraci F, David S, Montalto G, Rizvi A, Rizzo M. Bergamot reduces plasma lipids, Atherogenic Small Dense LDL, and subclinical atherosclerosis in subjects with moderate hypercholesterolemia: a 6 months prospective study. Front Pharmacol. 2016;6:299. https://doi.org/10.3389/fphar.2015.00299. PMID: 26779019; PMCID: PMC4702027t.
108. Leopoldini M, Malaj N, Toscano M, Sindona G, Russo N. On the inhibitor effects of bergamot juice flavonoids binding to the 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) enzyme. J Agric Food Chem. 2010;58(19):10768-73. https://doi.org/10.1021/jf102576j. PMID: 20843083.
109. Gliozzi M, Walker R, Muscoli S, Vitale C, Gratteri S, Carresi C, et al. Bergamot polyphenolic fraction enhances rosuvastatin-induced effect on LDL-cholesterol, LOX-1 expression and protein kinase B phosphorylation in patients with hyperlipidemia. Int J Cardiol. 2013;170(2):140–5.
110. Riva A, Petrangolini G, Allegrini P, Perna S, Giacosa A, Peroni G, et al. Artichoke and Bergamot Phytosome Alliance: a Randomized double blind clinical trial in mild hypercholesterolemia. Nutrients. 2022;14(1):108.
111. Arnaboldi L, Corsini A. Bellosta S. Artichoke and bergamot extracts: a new opportunity for the management of dyslipidemia and related risk factors. Minerva Med. 2022;113(1).
112. Pan A, Yu D, Demark-Wahnefried W, Franco OH, Lin X. Meta-analysis of the effects of flaxseed interventions on blood lipids12. Am J Clin Nutr. 2009;90(2):288–97.
113. Prasad K, Khan AS, Shoker M. Flaxseed and its components in treatment of Hyperlipidemia and Cardiovascular Disease. Int J Angiol. 2020;29(04):216–22.
114. Ursoniu S, Sahebkar A, Andrica F, Serban C, Banach M. Effects of flaxseed supplements on blood pressure: a systematic review and meta-analysis of controlled clinical trial. Clin Nutr. 2016;35(3):615–25.
115. Sadat Masjedi M, Mohammadi Pour P, Shokoohinia Y, Asgary S. Effects of Flaxseed on blood lipids in healthy and dyslipidemic subjects: a systematic review and Meta-analysis of Randomized controlled trials. Curr Probl Cardiol. 2022;47(7):100931.
116. Borlinghaus J, Albrecht F, Gruhlke M, Nwachukwu I, Slusarenko A, Allicin. Chemistry and Biological Properties. Molecules [Internet]. 2014;19(8):12591–618. https://www.mdpi.com/1420-3049/19/8/12591/htm
117. Fitó M, Guxens M, Corella D, Sáez G, Estruch R, de la Torre R, Francés F, Cabezas C, López-Sabater MDC, Marrugat J, García-Arellano A, Arós F, Ruiz-Gutierrez V, Ros E, Salas-Salvadó J, Fiol M, Solá R, Covas MI. PREDIMED Study Investigators. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. Arch Intern Med. 2007;167(11):1195–1203. https://doi.org/10.1001/archinte.167.11.1195. PMID: 17563030.
118. Yeh YY, Liu L. Cholesterol-lowering effect of garlic extracts and Organosulfur compounds: human and animal studies. J Nutr. 2001;131(3):989S993S.
119. Lawson LD, Garlic. A Review of Its Medicinal Effects and Indicated Active Compounds. ACS Symposium Series. 1998;176–209.
120. Ryu K, Ide N, Matsuura H, Itakura Y. Nα-(1-Deoxy-D-fructos-1-yl)-L-Arginine, an antioxidant compound identified in aged Garlic Extract. J Nutr. 2001;131(3):972S976S.
121. Banerjee SK, Maulik SK. Effect of garlic on cardiovascular disorders: a review. Nutrition Journal [Internet]. 2002 Nov 19 [cited 2019 Aug 27];1(1). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC139960/

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