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REVIEW ARTICLE

Medicinal Herbs as an Alternative Treatment in the Management of Hyperlipidemia

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Abstract

The medical disorder known as hyperlipidemia is characterized by unusually high amount of lipids in the blood (fatty substances). This illness is also associated with being overweight. Even though hypolipidemic drugs are commonly used to treat cardiovascular diseases and stroke, there is a possibility that they may cause undesirable side effects. Many different medicinal plants have been successfully utilized in the treatment of various conditions in India. The treatment of hyperlipidemia was the primary focus of this investigation into the therapeutic properties of a variety of plants.

Keywords: Cardiovascular Diseases, Hyperlipidemia, Hypolipidemic Drugs, Lipids, Medicinal Plants

1. Introduction

Abnormal levels of lipids and lipoproteins in the blood are linked to the prevalence of obesity, a leading public health issue (hyperlipidemia and hyperlipoproteinemia). Hyperlipidemia is characterized by elevated levels of lipids and cholesterol in the blood, which can point to several problems with lipoprotein metabolism[1]. Cholesterol and triglycerides are two types of lipids that can accumulate in excess in the blood and cause a condition called hyperlipidemia. The disease known as hyperlipoproteinemia occurs when there is an abnormally high concentration of triglyceride-protein complexes in the blood. Fat molecules in the bloodstream stay as liquid[2]. This lipid metabolic condition is characterized by elevated plasma concentrations of various lipid and lipoprotein fractions, principal risk factors for Cardiovascular Disease (CVD). Cholesterol esters, phospholipids, and triglycerides all rise as well. Heart disease can be avoided with a healthy lifestyle that includes regular exercise and a diet high in fruits, vegetables, and legumes.

The major cause of death in both emerging and industrialized nations is the predisposition to cardiovascular, cerebrovascular, and peripheral vascular artery disorders, which are mostly caused by abnormalities in plasma lipids[3].

Hyperlipidemia indicates alterations in serum lipid and lipoprotein profiles due to increased Total Cholesterol (TC), Low-Density Lipoprotein-Cholesterol (LDL-C), Very Low-Density Lipoprotein-Cholesterol (VLDL-C), and Triglyceride (TG) levels and decreased High-Density Lipoprotein-Cholesterol (HDL-C) levels. The WHO has created a list of 21,000 medicinal plants used in different parts of the world. India is home to over 2500 unique species, with 150 holding significant economic value. India is the largest producer of medicinal herbs, earning it the nickname "botanical garden of the world"[4,5]. Hypercholesterolemia (HC) is defined as elevated blood cholesterol levels. The expert panel of the National Cholesterol Education Program determined that blood cholesterol values below 200 mg/dL are desirable. Blood cholesterol levels between 200 and 239 mg/dL are considered borderline, whereas

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240 mg/dL levels are considered as hypercholesterolemic[6]. Environmental and genetic variables both play a role in the development of HC[7]. According to the theory of familial HC, the main environmental causes are obesity and high-fat diets, whereas the genetic factors include the cumulative effects of numerous genes or single-gene anomalies[8]. High blood cholesterol levels are associated with an increased risk of cardiovascular disease, stroke, and cognitive decline[9]. Peripheral vascular disease, in which fat builds up mainly in the arteries leading to the legs and feet, has also been linked to elevated cholesterol levels. HC has also been linked to metabolic syndrome and hypertension[10]. In addition to pharmaceutical interventions, lifestyle changes such as giving up tobacco, increasing physical activity, and adopting a diet rich in fibre and low in trans and saturated fats are beneficial for people with hypercholesterolemia. Cholesterol-lowering effects of red yeast rice and rice bran oil have been demonstrated. Cholesterol-lowering effects of a wide variety of herbs and spices, including ginger and turmeric, have also been investigated[11].

Important Omega-3 fatty acids for reducing TG and non-HDL cholesterol are Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA)[12]. The risk of atherosclerosis can be lowered by simultaneously reducing TC and TG levels[13,14]. Omega-3 fatty acids can improve metabolic problems related to non-alcoholic fatty liver in people with hyperlipidemia[15].

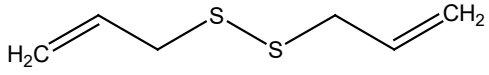
2. Hyperlipidemia Treatment using Herbs

2.1 Garlic (*Allium sativum*)

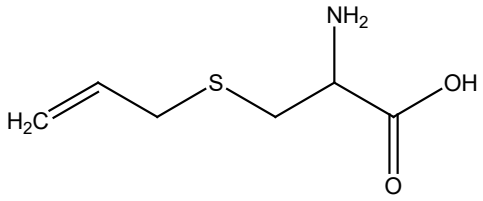
Garlic has been used for centuries as a culinary and medicinal herb. Use of this substance is widespread in traditional medicine. Garlic and its organosulfur bioactive components (including diallyl disulfide, S-allylcysteine, allin, and allicin) shown in Figure 1 A-D were found to play a significant impact in the regulation of serum lipid parameters in animal studies when administered in powder, extract, or oil form at varying doses. When exposed to high pressure and temperature, garlic showed improved organoleptic qualities and lipid-lowering activity[16-18].

Reliable clinical data on the likely justification for garlic usage in hyperlipidemia therapy was supplied by a meta-analysis consisting of 14 trials with a total of 1093 hyperlipidemic patients throughout the world. The studies lasted from 4 weeks to 10 months; and they utilized dosages of garlic from 0.3 to 20 g each day. Variations in TC, LDL-C, HDL-C, and TG levels occurred due to differences in garlic type, dosage form, and duration of study. Garlic's ability to reduce TC and LDL-C has been supported by statistical analysis[19].

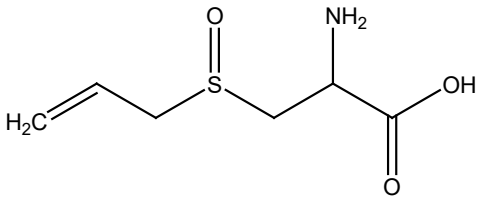
Similar to statins, garlic inhibited the liver enzyme 3-hydroxy-3 methylglutarylcoenzyme A (HMG-CoA) reductase, resulting in lower cholesterol synthesis[20,21]. Bioactive compounds in garlic, such as glucose



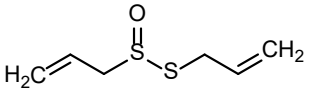
1A. Diallyl disulfide



1B. S-allylcysteine



1C. Allin



1D. Allicin

Figure 1. Structures of bioactive components of garlic.

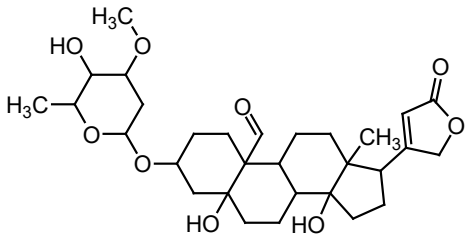


Figure 2. Structure of cymarine.

6-phosphate dehydrogenase, malic enzyme, and Fatty Acid Synthase (FAS), decrease cholesterol synthesis in addition to blocking HMG-CoA reductase[22].

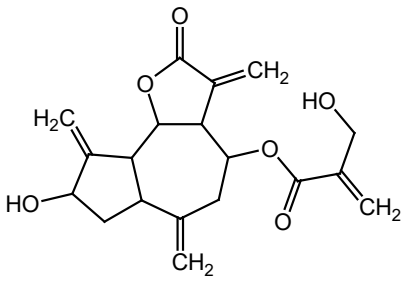
2.2 Artichoke (*Cynara scolymus*)

The *Cynara scolymus* leaf extract, sometimes known as artichoke thistle, is another herbal remedy for reducing high cholesterol levels. *Cynara cardunculus* var. *scolymus*, more often known as the globe artichoke, is cultivated for its edible leaves. It's a perennial plant native to the Canary Islands and the Mediterranean region of Southern Europe and Northern Africa. Artichoke is not only consumed in food forms but also beverages such as tea and liqueurs. Artichoke has been studied for its medicinal effects for over 60 years.

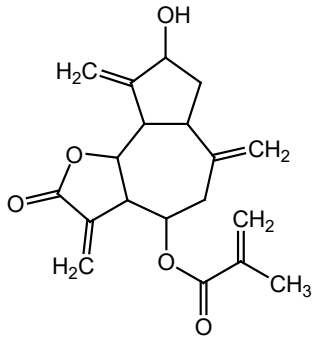
In vitro and *in vivo* research has shown that Artichoke Leaf Extract (ALE), specifically cymarine (Figure 2), can reduce plasma cholesterol levels. These studies were conducted on the extract's potential to do this[23-25]. In a dose-dependent way, the anti-atherosclerotic activity of luteolin-rich artichoke extract, similar to that of cymarine, reduces the amount of LDL oxidation[26]. The ALE treatment of primary cultures of rat hepatocytes significantly inhibited cholesterol synthesis[27].

Positive effects of ALE (1800 mg/day) on related hypertriglyceridemia in metabolic syndrome were observed in a recent randomized, double-blind, placebo-controlled trial involving 80 patients[28]. The levels of TC and LDL-C were not different from those of the placebo group, despite the considerable reduction in TG levels.

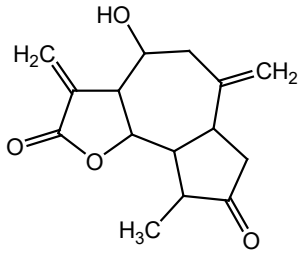
Studies on the possible in vitro mechanisms by which artichoke active principles reduce cholesterol levels were conducted primarily. In particular, sesquiterpens such as cynaropicrin, aguerin B, and grosheimin (Figures 3 A-C) and sesquiterpene glycosides like cynarascolosides A, B, and C (Figures 4 A-C) are responsible for artichokes' lipid-lowering effects. One theory proposed a mechanism whereby cholesterol levels could be lowered by suppressing cholesterol biosynthesis by inhibiting hepatic HMG-CoA reductase activity, TG formation could be stymied



3A. Cynaropicrin

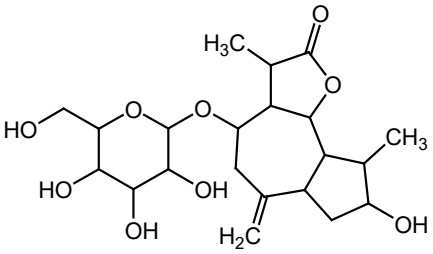


3B. Aguerin B

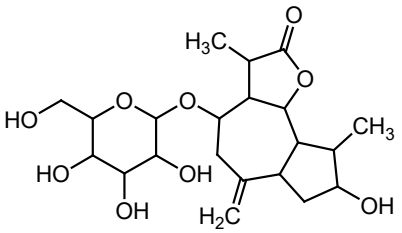


3C. Grosheimin

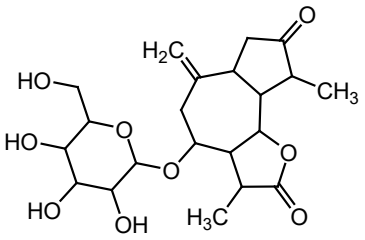
Figure 3. Structure of different sesquiterpens.



4A. Cynarascolosides A



4B. Cynarascolosides B



4C. Cynarascolosides C

Figure 4. Structure of cynarascolosides **A**, **B**, and **C**.

by decreasing Phosphatidate Phosphohydrolase (PAP) activity, and bile acids could be excreted more efficiently in the faeces[29-31].

In addition, the anti-atherogenic capabilities of artichoke aqueous extract were investigated in rats (fed a high-fat diet)[32]. In addition to reducing cholesterol, the polyphenols in artichoke extract exhibit anti-inflammatory effect by regulating pro-inflammatory and anti-inflammatory cytokines. This regulation safeguards the vascular system from atherosclerosis[31].

Additionally, it was hypothesized that the lipid-lowering effects were caused by a polymorphism in the intro 1 (Taq-IB) region of the Cholesteryl Ester Transfer Protein (CETP). Rezazadeh and colleagues investigated the effects of ALE extracts on CETP and cholesterol levels in a group of eighty individuals suffering from metabolic syndrome[28]. Taq IB-B1B1 male carriers showed decreased LDL-C levels after ALE intervention. However, there were no significant changes in CETP levels (1800 mg/day of ALE).

2.3 Fenugreek (*Trigonella foenum graecum*) Seeds

Fenugreek, or *Trigonella foenumgraecum*, has been shown to reduce both cholesterol and glucose levels in the blood. Its high fibre content has been linked to reduced blood and liver cholesterol[33,34]. Fenugreek seed's lipid-lowering activity is mediated by the presence of 4-hydroxyisoleucine (Figure 5), a branched-chain amino acid, and its action on adipocytes and liver cells, which results in reduced TG, TC, and LDL levels[35-37].

Fenugreek seed's major active ingredients are the steroid saponin and sapogenin extracts. Cholesterol is lowered through more than one component and likely more than one pathway through its interaction with bile acids in the digestive tract[38].

2.4 Turmeric (*Curcuma longa*)

Clinical evidence included in meta-analyses brought attention to turmeric, a yellow spice commonly used in Asia that is rich in curcuminoids (curcumin) shown in

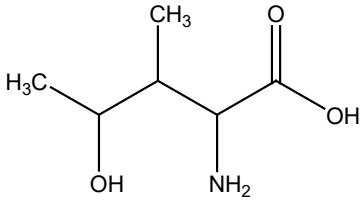


Figure 5. Structure of 4-hydroxyisoleucine.

Figure 6. Seven trials with a total of 649 participants, all of which were placebo or drug-controlled and randomized, are included in the analysis[39,40]. Patients were given curcumin for a period between four and six months, during which time they were divided into two groups: those with metabolic syndrome, and those with Type 2 diabetes. Patients who were at risk for cardiovascular disease had lower levels of LDL-C and TG in their blood after taking turmeric. The inaccuracy of the TC level readings, combined with doses that ranged from 70 mg/day to 1890 mg/day, made it difficult to draw any conclusions from the research on turmeric and its potential health benefits[39]. In the other meta-analysis, there were a total of 1427 people included; 737 of them were in the group that received curcuminoids, and 690 of them were in the control group. This meta-analysis was based on 20 studies, and it included people who were healthy, as well as people who had hyperlipidemia, metabolic syndrome, Non-Alcoholic Liver Disease (NAFLD), Type 2 diabetes, cardiovascular disease, and even chronic obstructive pulmonary disease. According to the findings, curcuminoids had a significant impact on lowering TG levels and increasing HDL-C levels in the blood. Despite this, neither total cholesterol nor low-density lipoprotein levels in the serum decreased much[39]. Both of these meta-analyses concluded that the components of turmeric have a positive impact on cholesterol levels. The possibility exists that the slight disparities in the results that were obtained are attributable to the varied eligibility requirements of the target group. In mice, supplementing their diet with curcumin extracts prevented both weight gain and pathological changes in hepatocytes and aorta walls, in addition to improving their blood cholesterol levels (significantly lowering total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol)[41]. With these findings, another study indicated that ingesting curcumin at a dose of 300 mg/kg/day reduced histological changes in the liver, body weight rise, and blood lipid markers (TC, TG, LDL-C, and HDL-C) in rats that were given streptozotocin in addition to a high-fat diet[42]. Curcumin treatment improved glucose tolerance and decreased blood sugar levels in rats. Analysis of oxidative stress markers and the expression of the Bcl-2 and Bax proteins indicated the importance of antioxidative and anti-apoptotic processes in the management of hyperglycemia and hyperlipidemia[42].

Possible lipid-lowering mechanisms discovered in animal studies include decreased cholesterol absorption in the duodenum and jejunum, decreased adipogenesis, and increased lipid catabolism. Lower levels of the NPC1L1 protein, which mediates intestinal cholesterol absorption, led researchers to uncover curcumin's effect on cholesterol absorption[43,44]. The reverse cholesterol transport system is essential for cholesterol clearance from peripheral tissues, and curcumin, like statins, influenced the components that controlled this mechanism. ABCA1 (involved in cellular cholesterol efflux), caveolin-1 (engaged in cholesterol transport), and HDL-mediated pathways for cholesterol elimination were all induced in response to PPARs activation[45].

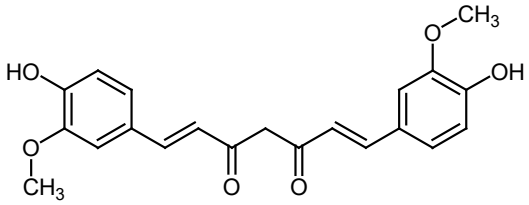


Figure 6. Structure of curcumin.

2.5 Green Tea (*Camelia sinensis*)

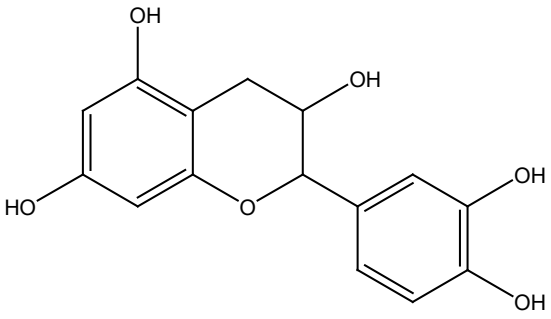
Green Tea (GT) is an extract of the Camellia sinensis plant that undergoes minimal processing and no fermentation. The catechins in GT, especially Epigallocatechin Gallate (EGCG) shown in Figure 7 A-B have been demonstrated to have biological activity at concentrations as high as 30-42 % in the dry weight of GT[46-48]. A meta-analysis of 14 randomized controlled experiments revealed evidence for an anti-hyperlipidemic effect of GT beverage and extract in humans[49]. All of the participants (1136) were either healthy, overweight, obese, or at risk for cardiovascular disease. The GT dosage ranged from 150 mg per day to 2500 mg per day, with the average daily dose being around 200 mg. GT had significant benefits in lowering TC and LDL-C, but had little effect on HDL-C levels. Moreover, the preparation type, the dose of catechins, the time period of the investigation, or the health status of the subgroup had no impact on the effect of GT. A small number of people had some discomfort, although this was the exception. In addition, a recent meta-analysis that focused on randomized controlled trials on overweight and obese patients indicated that GT significantly lowered TC and LDL-C with no significant changes in HDL-C or TG[50]. A total of 1704 persons participated throughout 21 investigations, and the EGCG doses used ranged from 39

mg/day to 856.8 mg/day. The longest treatment term was 24 weeks. Although the benefits of long-term GT intake in overweight and obese subjects were demonstrated, the authors did stress the necessity for further investigation into the dose effect of EGCG on blood cholesterol levels. There are a variety of mechanisms by which GT catechins reduce lipid levels and, by extension, reduce the risk of CVD. In animal studies, pure EGCG inhibited the production of cytokines and the absorption of cholesterol, demonstrating its anti-inflammatory properties[51]. Bioactive catechins found in GT extract lowered serum cholesterol levels in rats by blocking FAS and increasing AMPK activity[52]. The up-regulation of hepatic PPARa and aortic autophagy in ApoE mutant mice provided more evidence for the role of GT in lipid homeostasis[53].

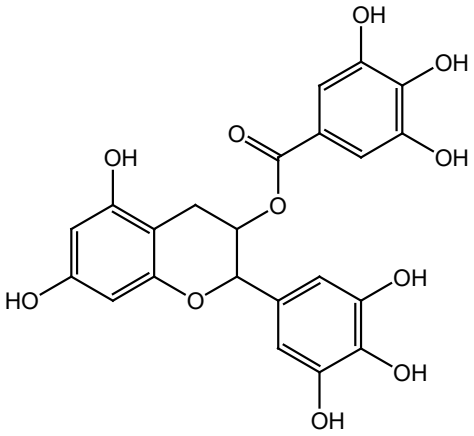
Finally, a human study has demonstrated that the catechins present in GT decaffeinated extract can inhibit oxidation of LDL, hence protecting against oxidative stress-induced atherosclerosis[54]. Both theaflavins (Figure 7 C) and catechins are responsible for green tea's health benefits. Micellar solubility and intestinal cholesterol absorption are reduced, faecal fat and cholesterol excretion are increased, hepatic cholesterol concentrations are lowered, and LDL receptor[38].

2.6 Red Yeast Rice (*Monascus purpueus*)

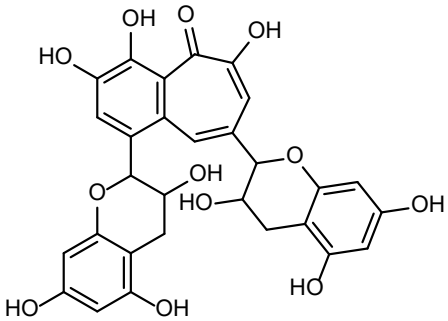
An ancient Asian staple, Red Yeast Rice (RYR) has been studied and refined as a nutraceutical for its potential to improve a wide range of health parameters in humans. It is fermented white rice, typically using *Monascus purpureus* but sometimes occasionally using other related yeasts[55]. Unsaturated fatty acids, phytosterols, tannins, and polyketides are all found in RYR, in addition to the pigments that give Monascus fungus their specific colour[56]. Due to its biochemical composition, RYR offers a number of health benefits, the most significant of which is its effect on cholesterol levels, which in turn has hypotensive, cardio-protective, and anti-diabetic effects[56].



7A. Catechin



7B. Epigallocatechin gallate



7C. Theaflavin

Figure 7. Structure of catechin, epigallocatechin gallate and theaflavins.

Monacolin K, the major polyketide in RYR, is a natural analogue of lovastatin (Figure 8) and has a hypolipidemic activity[57]. Statins like monacolin K are selective inhibitors of HMG-CoA reductase and thereby reduce cholesterol biosynthesis in the liver[58]. Dietary supplements based on RYR, which were initially approved in China and a few countries in Europe, typically include 5-10 mg of monacolin K, and its impact on decreasing cholesterol levels has been comprehensively proven in a meta-analysis of clinical evidence published up to the year 2005. According to the findings of Liu and colleagues, there was a notable reduction in total cholesterol, total fat, and LDL-C, in addition to a good effect on HDL-C[59]. When compared to a control group that followed the Mediterranean diet, a more recent multi-center, randomized clinical trial using 10 mg of monacolin K combined with 10 mg of coenzyme Q10 (CoQ10) found a significant reduction in blood levels of TC, total fat and LDL. Increases in HDL-C levels were not significantly affected in any way[60]. After 12 weeks of treatment, patients with borderline-high, untreated LDL-C who were given Monacolin K (3 mg, standardized in 200 mg of RYR) showed a substantial reduction in LDL-C compared to those given placebo[61]. In the same study, a saturated mechanism of cholesterol-lowering was suggested as a result of the fact that 53% of RYR-treated patients attained the LDL-C threshold level of 4.14 mmol/L, and 51% of them did so by the end of the study. In a clinical trial that was randomized, double-blind, and controlled with a placebo, a novel nutraceutical that contained 10 mg of monacolin K (along with phytosterols, hydroxytyrosol, and vitamin E) was shown to be beneficial and safe in the treatment of low to moderate, untreated CVD risk. The trial was carried out in patients who had not previously received any treatment for their CVD risk[62].

There were notable reductions in both TC and LDL-C (40 participants). Both the safety laboratory measurements and the side effect profiles remained unchanged. Patients with modest hypercholesteremic levels may not need hypercholesteremic drug therapy if they take RYR extract in combination with CoQ10, astaxanthin, policosanol, berberine, and folic acid[63]. Findings suggest that monacolin K, an active component of RYR, could be used as a safe and effective replacement for statins in both untreated and statin-intolerant people. It has been hypothesized that RYR is safe, with few musculoskeletal side effects[64].

It has been hypothesized that statin-induced muscle injury is mediated in part by the depletion of meyalonate metabolites distal to HMG-CoA reductase, such as intracellular isoprenoids and guanosine triphosphate-binding regulatory proteins. Other monacolins may have lipid-lowering effects or enhance those of monacolin K[38].

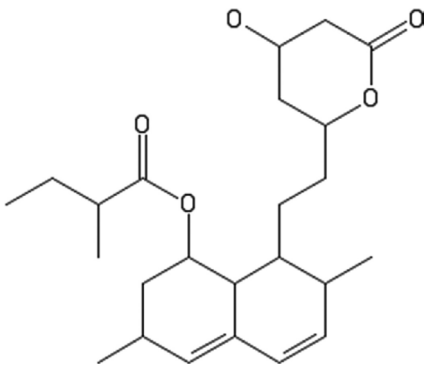


Figure 8. Chemical structure of monacolin K (lovastatin).

2.7 Grape (*Vitis vinifera*)

Grapes are widely used in traditional medicine and as part of the Mediterranean diet. Grape seeds are a rich source of the antioxidant polyphenols (including flavonoids and non-flavonoids), anthocyanidins, catechins, and phenolic acids[65]. Grape Seed Extracts (GSE) have been the subject of multiple meta-analyses due to its hypolipidemic potential. Asbaghi *et al.*, analyzed data from 15 researches, including 825 participants over the course of 4-25 weeks[66]. Daily doses of GSE ranged from 100 to 2000 mg for patients with hyperlipidemia, hypertension, T2DM, CVD, and other illnesses. Compared to controls, GSE dramatically decreased fasting plasma glucose, CRP, TC, LDL-C, and TG levels while having no effect on HDL-C[66]. Another meta-analysis looked at the effects of several grape products, including whole grape extract, grape juice, and raisins, amongst others[65]. On the other hand, the vast majority of them concentrated on GSE, and whole grape extract were included[66].

Some of the processes by which grape chemicals improved lipid status and atherosclerosis were decreased absorption and increased faecal excretion of lipids, which was mostly connected to the GSE, and decreased atheromatous plaque in the first stages of atherosclerosis[67,68]. Studies on both animals and humans have looked at the polyphenolic components of GSE, whose antioxidant properties underline the importance

of protecting LDL from oxidation in the fight against atherosclerosis[69-71].

2.8 Olive (*Olea europea*)

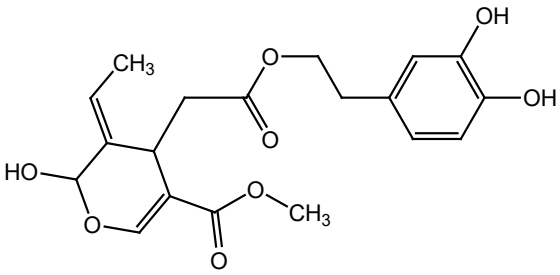
Some of the aforementioned supplements contain tyrosol, also known as hydroxytyrosol, which is derived from olive leaf extract. Combining them with RYR has shown promise as a therapy for hyperlipidemia in clinical trials[72-74]. By conducting a clinical trial with 61 participants, Lockyer *et al*., proved the efficacy of a commercially available olive leaf extract product. There was a considerable drop in LDL-C, TC, and TG levels compared to the control group, but there was no change in HDL-C. However, more clinical evidence of the lipid-lowering advantages of the olive extract is required[75].

The lipid-lowering effects of *Olea europea* are carried by secondary metabolites called phenolic compounds. The biophenol oleuropein and its hydrolysis products tyrosol and hydroxytyrosol were found in the greatest quantities in olive leaves (Figure 9 A-C)[76,77]. Due to its wide availability, fast absorption following oral treatment (detected in human plasma after 23-93 minutes), and elimination predominantly as conjugates of its metabolite hydoxytyrosol, oleuropein was offered as a significant pharmacological possibility[76,78].

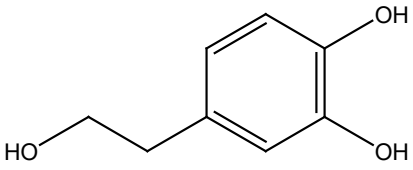
Active components in olive leaf extract (oleuropein and hydroxytyrosol) enhanced lipid profiles and reduced body mass and subcutaneous fat accumulated by chronic oral exposure to the endocrine disruptor bisphenol A in animal studies[79]. Antioxidant efficiency in anti-atherogenic pathways has been demonstrated in several animal studies using oleuropein and its derivatives[78]. Animals fed a cholesterol-rich diet were given olive leaf extract containing oleuropein, hydroxytyrosol, and oleuropein aglycone, which increased serum anti-oxidative potential, significantly restored hepatic antioxidant enzyme activities, and decreased TBARS levels, which are markers of polyunsaturated fatty acid peroxidation. Based on these results, *Olea europea* has some serious preventative value when it comes to metabolic illnesses and their consequences. Well-specified phenolic compounds and their doses, from a well-established source, in the formulation that would offer their highest bioavailability are needed for developing more reliable multicenter, placebo-controlled, randomized trials on hyperlipidemia patients[80,81].

2.9 Gum Residue Guggulipid

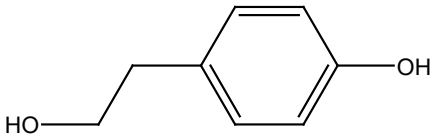
The *Commiphora mukul* tree, which yields a gum resin, has been used for centuries to manage weight problems and cholesterol problems. It has been established that the gum resin extract guggulipid lowers lipid levels in both normal and hyperlipidemic animals (rats, rabbits, and monkeys). Indian patients have been the subject of numerous investigations examining the response of gum resin gumsome to guggul therapy. One-eighth of patients responded to guggulipid treatment in American trials,



9A. Oleuropein aglycone



9B. Hydroxytyrosol



9C. Tyrosol

Figure 9. Chemical structures of (**A**). oleuropein aglycone, (**B**). hydroxytyrosol and (**C**). tyrosol.

with LDL levels decreasing by higher than 5%. Results from clinical trials may differ depending on participants' racial/ethnic/genetic/dietary/lifestyle characteristics.[82-85].

3. Conclusion

In conclusion, the findings of the research that was conducted and reviewed on the effects of herbs used for the prevention of and treatment of hyperlipidemia illustrate the benefits as well as the drawbacks of using alternative medicine. Herbal remedies are less likely to cause unwanted effects and are safer than statin drugs. Studies in humans showed no or mild adverse effects even when the herbs were given in large quantities for extended periods of time. This explains why more people are interested in and willing to try herbal remedies. Hyperlipidemia and related illnesses have made the quest for herbal compounds with therapeutic benefits a top research priority. Even though there has been growing interest in using herbs to treat hyperlipidemia, existing research is limited by the wide variety of people who have been studied (healthy subjects, patients with T2DM, hypertension and other CVD risks). Inconsistency in the results of meta-analyses of the same plant can also be attributed to factors such as the lack of standardization of herbal products, a wide range of doses applied in therapy, different dosage forms, and varying research lengths. Healthcare providers may be able to prescribe some promising herbs for treating hyperlipidemia if more large-scale, randomized, placebo-controlled studies are conducted.

4. References

1. Jain PG, Surana SJ. A review of Indian medicinal plants with hypolipidemic activity and their medicinal importance. World J Pharm Pharm Sci. 2015; 4(3):1477-93.
2. Edeoga HO, Okwu DE, Mbaebie BO. Phytochemical constituents of some Nigerian medicinal plants. Afr J Biotechnol. 2005; 4(7):685-8. https://doi.org/10.5897/AJB2005.000-3127
3. Bauman AE. Updating the evidence that physical activity is good for health: An epidemiological review 2000–2003. J Sci Med Sport. 2004; 7(1):6-19. https://doi.org/10.1016/S1440-2440(04)80273-1
4. Kaliora AC, Dedoussis GV, Schmidt H. Dietary antioxidants in preventing atherogenesis. Atherosclerosis. 2006; 187(1):1-7. https://doi.org/10.1016/j.atherosclerosis.2005.11.001
5. Berliner JA, Heinecke JW. The role of oxidized lipoproteins in atherogenesis. Free Radic Biol Med. 1996; 20(5):707-27. https://doi.org/10.1016/0891-5849(95)02173-6
6. Sempos CT. The expert panel on detection, evaluation and treatment of high blood cholesterol in adults. J Am Med Asso. 1993; 269:3009-14. https://doi.org/10.1001/jama.1993.03500230091035
7. Bhatnagar D, Soran H, Durrington PN. Hypercholesterolaemia and its management. Br Med J. 2008; 337. https://doi.org/10.1136/bmj.a993
8. Innerarity TL, Mahley RW, Weisgraber KH, Bersot TP, Krauss RM, Vega GL, *et al*. Familial defective apolipoprotein B-100: A mutation of apolipoprotein B that causes hypercholesterolemia. J Lipid Res. 1990; 31(8):1337-49. https://doi.org/10.1016/S0022-2275(20)42605-7
9. Grundy SM. George Lyman Duff Memorial Lecture; Multifactorial etiology of hypercholesterolemia. Implications for prevention of coronary heart disease. Arterioscler Thromb Vasc Biol. 1991; 11(6):1619-35. https://doi.org/10.1161/01.ATV.11.6.1619
10. Sniderman AD, Tsimikas S, Fazio S. The severe hypercholesterolemia phenotype: Clinical diagnosis, management, and emerging therapies. J Am Coll Cardiol. 2014; 63(19):1935-47. https://doi.org/10.1016/j.jacc.2014.01.060
11. Clark LT. Cholesterol and heart disease: Current concepts in pathogenesis and treatment. J Natl Med Assoc. 1986; 78:743-51.
12. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. New Eng J Med. 2014; 371(1):22-31. https://doi.org/10.1056/NEJMoa1307095
13. Khetarpal SA, Rader DJ. Triglyceride-rich lipoproteins and coronary artery disease risk: New insights from human genetics. Arterioscler Thromb Vasc Biol. 2015; 35(2):e3-e9. https://doi.org/10.1161/ATVBAHA.114.305172
14. Dewey FE, Gusarova V, O'Dushlaine C, Gottesman O, Trejos J, Hunt C, *et al*. Inactivating variants in ANGPTL4 and risk of coronary artery disease. New Eng J Med. 2016; 374(12):1123-33. https://doi.org/10.1056/NEJMoa1510926
15. Qin Y, Zhou Y, Chen SH, Zhao XL, Ran L, Zeng XL, *et al*. Fish oil supplements lower serum lipids and

glucose in correlation with a reduction in plasma fibroblast growth factor 21 and prostaglandin E2 in nonalcoholic fatty liver disease associated with hyperlipidemia: A randomized clinical trial. PLoS One. 2015; 10(7). https://doi.org/10.1371/journal.pone.0133496
16. Jafari-Dehkordi E, Seidkhani-Nahal A. Lipid-lowering effect of artichoke on liver phosphatidate phosphohydrolase and plasma lipids in hyperlipidemic rats. J Med Plant Res. 2011; 5(19):4918-24.
17. Sohn CW, Kim H, You BR, Kim MJ, Kim HJ, Lee JY, *et al*. High temperature-and high pressure-processed garlic improves lipid profiles in rats fed high cholesterol diets. J Med Food. 2012; 15(5):435-40. https://doi.org/10.1089/jmf.2011.1922
18. Sen DB, Sen AK, Patel KP, Balaraman R, Shah U, Maheshwari RA. Anti ulcer activities of herbal remedies as alternative therapy. J Nat Rem. 2022; 3:318-29. https://doi.org/10.18311/jnr/2022/30157
19. 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. 2018; 97(18). https://doi.org/10.1097/MD.0000000000010255
20. Sobenin IA, Myasoedova VA, Iltchuk MI, Zhang DW, Orekhov AN. Therapeutic effects of garlic in cardiovascular atherosclerotic disease. Chin J Nat Med. 2019; 17(10):721-8. https://doi.org/10.1016/S1875-5364(19)30088-3
21. Zhao Y, Chen ZY. Roles of spicy foods and their bioactive compounds in management of hypercholesterolemia. J Agric Food Chem. 2018; 66(33):8662-71. https://doi.org/10.1021/acs.jafc.8b02975
22. Alam MK, Nyeem MA, Samad MA. Effects of garlic on hyperlipidemia: A review. J Med Plant. 2018; 6(2):44-8.
23. Wojcicki J, Winter S. Effect of preparation Cynarex on the blood serum lipids level of the workers exposed to the chronic action of carbon disulphide. Medycyna Pracy. 1975; 26:213-7.
24. Wójcicki J. Effect of 1,5-dicaffeylquinic acid (cynarine) on cholesterol levels in serum and liver of acute ethanol-treated rats. Drug Alcohol Depend. 1978; 3:143-5. https://doi.org/10.1016/0376-8716(78)90028-5
25. Alkushi AG. Biological effect of Cynara carduncu-lus on kidney status of hypercholesterolemic rats. Pharmacogn Mag. 2017; 13:S430-S436. https://doi.org/10.4103/pm.pm_14_17
26. Brown JE, Rice-Evans CA. Luteolin- rich artichoke extract protects low density lipoprotein from oxidation in vitro. Free Rad Res. 1998; 29:247-55. https://doi.org/10.1080/10715769800300281
27. Gebhardt R. Inhibition of cholesterol biosynthesis in primary cultured rat hepatocytes by artichoke (*Cynara scolymus* L.) extracts. J Pharmacol Exp. 1998; 286:1122-8.
28. 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; 17:112-8. https://doi.org/10.1016/j.eujim.2017.12.008
29. Ahmed SF, Abd Al Haleem EN, El-Tantawy WH. Evaluation of the anti-atherogenic potential of Egyptian artichoke leaf extract in hypercholesterolemic rats. Arch Physiol Biochem. 2022; 128(1):163-74. https://doi.org/10.1080/13813455.2019.1669662
30. Gebhardt R. Inhibition of cholesterol biosynthesis in HepG2 cells by arti- choke extracts is reinforced by glucosidase pretreatment. Phytother Res. 2002; 16:368–72. https://doi.org/10.1002/ptr.960
31. Qiang Z, Lee SO, Ye Z, Wu X, Hendrich S. Artichoke extract lowered plasma cholesterol and increased fecal bile acids in Golden Syrian hamsters. Phytother Res. 201l; 26(7):1048-52. https://doi.org/10.1002/ptr.3698
32. Mocelin R, Marcon M, Santo GD, Zanatta L, Sachett A, Schönell AP, *et al*. Hypolipidemic and antiatherogenic effects of Cynara scolymus in cholesterol-fed rats. Revista Brasileira de Farmacognosia. 2016; 26:233-9. https://doi.org/10.1016/j.bjp.2015.11.004
33. Nadkarni KM. Trigonella foenum graecum: Indian materia. Médica. 1993; 1240:1249
34. Kumar K, Kumar S, Datta A, Bandyopadhyay A. Effect of fenugreek seeds on glycemia and dyslipidemia in patients with Type 2 diabetes mellitus. Int J Med Sci Public Health. 2015; 4(7):997-1000. https://doi.org/10.5455/ijmsph.2015.11032015202
35. Belaid Nouira Y, Bakhta H, Bouaziz M. Study on the lipid profile and the parieto-temporal lipid peroxidation in AlCl3 mediated neurotoxicity: The modulatory effect of the fenugreek seeds. Lipids Health Dis. 2012; 11(1):1-8. https://doi.org/10.1186/1476-511X-11-16
36. Jetle L, Harvey L, Eugeni K, Leven SN. The 4-hydroxy isoleucine plant-derived treatment for metabolic syndrome. Current opinion treatment for the metabolic syndrome. Curr Opin Investig Drugs. 2000; 10:353-8.
37. Sharma MS, Choudhary PR. Hypolipidemic effect of fenugreek seeds and its comparison with atorvastatin on experimentally induced hyperlipidemia. J Coll Physicians Surg Pak. 2014; 24(8):539-42.
38. Hasani-Ranjbar S, Nayebi N, Moradi L, Mehri A, Larijani B, Abdollahi M. The efficacy and

safety of herbal medicines used in the treatment of hyperlipidemia: A systematic review. Curr Pharm Des. 2010; 16;2935-47. https://doi.org/10.2174/138161210793176464
39. Qin S, Huang L, Gong J, Shen S, Huang J, Ren H, *et al*. Efficacy and safety of turmeric and curcumin in lowering blood lipid levels in patients with cardiovascular risk factors: A meta-analysis of randomized controlled trials. Nutr J. 2017; 16. https://doi.org/10.1186/s12937-017-0293-y
40. Simental-Mendía LE, Pirro M, Gotto Jr AM, Banach M, Atkin SL, Majeed M, *et al*. Lipid-modifying activity of curcuminoids: A systematic review and meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2019; 59(7):1178-87. https://doi.org/10.1080/10408398.2017.1396201
41. Sarker S, Haque MI, Sujan KM, Talukder MI, Miah MA. Curcumin attenuates butter fat induced hyperlipidemia in mice. J Bangladesh Agric Univ. 2019; 17(2):220-5. https://doi.org/10.3329/jbau.v17i2.41972
42. Xia ZH, Chen WB, Shi L, Jiang X, Li K, Wang YX, *et al*. The underlying mechanisms of curcumin inhibition of hyperglycemia and hyperlipidemia in rats fed a high-fat diet combined with STZ treatment. Molecules. 2020; 25(2):271. https://doi.org/10.3390/molecules25020271
43. Zou J, Zhang S, Li P, Zheng X, Feng D. Supplementation with curcumin inhibits intestinal cholesterol absorption and prevents atherosclerosis in high-fat diet–fed apolipoprotein E knockout mice. Nutr Res. 2018; 56:32-40. https://doi.org/10.1016/j.nutres.2018.04.017
44. Kim JH, Kim OK, Yoon HG, Park J, You Y, Kim K, *et al*. Anti-obesity effect of extract from fermented Curcuma longa L. through regulation of adipogenesis and lipolysis pathway in high-fat diet-induced obese rats. Food Nutr Res. 2016; 60(1):30428. https://doi.org/10.3402/fnr.v60.30428
45. Panahi Y, Ahmadi Y, Teymouri M, Johnston TP, Sahebkar A. Curcumin as a potential candidate for treating hyperlipidemia: A review of cellular and metabolic mechanisms. J Cell Physiol. 2018; 233(1):141-52. https://doi.org/10.1002/jcp.25756
46. Khan N, Mukhtar H. Tea polyphenols for health promotion. Life Sci. 2007; 81:519–3. https://doi.org/10.1016/j.lfs.2007.06.011
47. Sen AK, Sen DB, Zanwar AS, Balaraman R, Shah U, Maheshwari RA. Catechins and theaflavins: An overview on therapeutic applications. J Nat Rem. 2022; 3:330-46. https://doi.org/10.18311/jnr/2022/30181
48. Sen AK, Sen DB, Maheshwari RA. Extraction, isolation, and quantitative determination of flavonoids by HPLC. In Herbal Medicine in India, Singapore: Springer; 2020. p. 303-36. https://doi.org/10.1007/978-981-13-7248-3_21
49. Zheng XX, Xu YL, Li SH, Liu XX, Hui R, Huang XH. Green tea intake lowers fasting serum total and LDL cholesterol in adults: a meta-analysis of 14 randomized controlled trials. Am J Clin Nutr. 2011; 94(2):601-10. https://doi.org/10.3945/ajcn.110.010926
50. Yuan F, Dong H, Fang K, Gong J, Lu F. Effects of green tea on lipid metabolism in overweight or obese people: A metaanalysis of randomized controlled trials. Molecular Nutr Food Res. 2018; 62(1):1601122. https://doi.org/10.1002/mnfr.201601122
51. Chen YK, Cheung C, Reuhl KR, Liu AB, Lee MJ, Lu YP, *et al*. Effects of green tea polyphenol (−)-epigallocatechin-3-gallate on newly developed high-fat/Western-style diet-induced obesity and metabolic syndrome in mice. J Agric Food Chem. 2011; 59(21):11862-71. https://doi.org/10.1021/jf2029016
52. Huang HC, Lin JK. Pu-erh tea, green tea, and black tea suppresses hyperlipidemia, hyperleptinemia and fatty acid synthase through activating AMPK in rats fed a high-fructose diet. Food Func. 2012; 3:170–77. https://doi.org/10.1039/C1FO10157A
53. Ding S, Jiang J, Yu P, Zhang G, Zhang G, Liu X. Green tea polyphenol treatment attenuates atherosclerosis in high-fat diet-fed apolipoprotein E-knockout mice via alleviating dyslipidemia and up-regulating autophagy. PloS One. 2017; 12(8). https://doi.org/10.1371/journal.pone.0181666
54. Suzuki-Sugihara N, Kishimoto Y, Saita E, Taguchi C, Kobayashi M, Ichitani M, *et al*. Green tea catechins prevent low-density lipoprotein oxidation via their accumulation in low-density lipoprotein particles in humans. Nutr Res. 2016; 36(1):16-23. https://doi.org/10.1016/j.nutres.2015.10.012
55. Nguyen T, Karl M, Santini A. Red yeast rice. Foods. 2017; 6:19. https://doi.org/10.3390/foods6030019
56. Patel S. Functional food Red Yeast Rice (RYR) for metabolic syndrome amelioration: A review on pros and cons. World J Microbio Biotechnol. 2016; 32:87. https://doi.org/10.1007/s11274-016-2035-2
57. Burke FM. Red yeast rice for the treatment of dyslipidemia. Currt Atherosclerosis Rep. 2015; 17(4):495. https://doi.org/10.1007/s11883-015-0495-8
58. Sirtori CR. The pharmacology of statins. Pharmacol Res. 2014; 88:3-11. https://doi.org/10.1016/j.phrs.2014.03.002
59. Liu J, Zhang J, Shi Y, Grimsgaard S, Alraek T, Fønnebø V. Chinese red yeast rice (*Monascus purpureus*) for

primary hyperlipidemia: A meta-analysis of randomized controlled trials. Chin Med. 2006; 1(1):1-3. https://doi.org/10.1186/1749-8546-1-4
60. 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. Biomed Pharmacother. 2018; 105:992-6. https://doi.org/10.1016/j.biopha.2018.06.076
61. Heinz T, Schuchardt JP, Möller K, Hadji P, Hahn A. Low daily dose of 3 mg monacolin K from RYR reduces the concentration of LDL-C in a randomized, placebo-controlled intervention. Nutr Res. 2016; 36(10):1162-70. https://doi.org/10.1016/j.nutres.2016.07.005
62. Domenech M, Casas R, Ruiz-León AM, Sobrino J, Ros E, Estruch R. Effects of a novel nutraceutical combination (Aquilea Colesterol®) on the lipid profile and inflammatory biomarkers: A randomized control trial. Nutrients. 2019; 11(5):949. https://doi.org/10.3390/nu11050949
63. Sola R, Valls RM, Puzo J, Calabuig JR, Brea A, Pedret A, *et al*. Effects of poly-bioactive compounds on lipid profile and body weight in a moderately hypercholesterolemic population with low cardiovascular disease risk: A multicenter randomized trial. PLoS One. 2014; 9(8). https://doi.org/10.1371/journal.pone.0101978
64. Fogacci F, Banach M, Mikhailidis DP, Bruckert E, Toth PP, Watts GF, *et al*. Safety of red yeast rice supplementation: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2019; 143:1-6. https://doi.org/10.1016/j.phrs.2019.02.028
65. Ghaedi E, Moradi S, Aslani Z, Kord-Varkaneh H, Miraghajani M, Mohammadi H. Effects of grape products on blood lipids: A systematic review and dose–response meta-analysis of randomized controlled trials. Food Func. 2019; 10(10):6399-416. https://doi.org/10.1039/C9FO01248F
66. Asbaghi O, Nazarian B, Reiner Ž, Amirani E, Kolahdooz F, Chamani M, *et al*. The effects of grape seed extract on glycemic control, serum lipoproteins, inflammation, and body weight: A systematic review and meta-analysis of randomized controlled trials. Phytother Res. 2020; 34(2):239-53. https://doi.org/10.1002/ptr.6518
67. Nakamura Y, Tonogai Y. Effects of grape seed polyphenols on serum and hepatic lipid contents and fecal steroid excretion in normal and hypercholesterolemic rats. J Health Sci. 2002; 48:570-8. https://doi.org/10.1248/jhs.48.570
68. Pérez-Jiménez J, Saura-Calixto F. Grape products and cardiovascular disease risk factors. Nutr Res Rev. 2008; 21:158-73. https://doi.org/10.1017/S0954422408125124
69. Colica C, Milanović M, Milić N, Aiello V, De Lorenzo A, Abenavoli L. A systematic review on natural antioxidant properties of resveratrol. Nat Prod Commun. 2018; 13(9):1195-1203.
70. Rameshrad M, Razavi BM, Imenshahidi M, Hosseinzadeh H. *Vitis vinifera* (grape) seed extract and resveratrol alleviate bisphenol-A-induced metabolic syndrome: Biochemical and molecular evidences. Phytother Res. 2019; 33(3):832-44. https://doi.org/10.1002/ptr.6276
71. Razavi SM, Gholamin S, Eskandari A, Mohsenian N, Ghorbanihaghjo A, Delazar A, *et al*. Red grape seed extract improves lipid profiles and decreases oxidized low-density lipoprotein in patients with mild hyperlipidemia. J Med Food. 2013; 16(3):255-8. https://doi.org/10.1089/jmf.2012.2408
72. Cicero AF, 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. https://doi.org/10.1007/s12325-017-0580-1
73. D'Addato S, Scandiani L, Mombelli G, Focanti F, Pelacchi F, Salvatori E, *et al*. Effect of a food supplement containing berberine, monacolin K, hydroxytyrosol and coenzyme Q10 on lipid levels: A randomized, double-blind, placebo controlled study. Drug Des Devel Ther. 2017; 11:1585. https://doi.org/10.2147/DDDT.S128623
74. Muhindo CT, 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. Complement Ther Med. 2017; 35:140-4. https://doi.org/10.1016/j.ctim.2017.10.014
75. Lockyer S, Rowland I, Spencer JP, Yaqoob P, Stonehouse W. Impact of phenolic-rich olive leaf extract on blood pressure, plasma lipids and inflammatory markers: A randomised controlled trial. Eur J Nutr. 2017; 56(4):1421-32. https://doi.org/10.1007/s00394-016-1188-y
76. De Bock M, Thorstensen EB, Derraik JG, Henderson HV, Hofman PL, Cutfield WS. Human absorption and metabolism of oleuropein and hydroxytyrosol ingested as olive (*O lea europaea L.*) leaf extract. Mol Nutr Food Res. 2013; 57(11):2079-85. https://doi.org/10.1002/mnfr.201200795
77. Hassen I, Casabianca H, Hosni K. Biological activities of the natural antioxidant oleuropein: Exceeding

the expectation–A mini-review. J Funct Foods. 2015; 18:926-40. https://doi.org/10.1016/j.jff.2014.09.001
78. Omar SH. Oleuropein in olive and its pharmacological effects. Sci Pharm. 2010; 78:133-54. https://doi.org/10.3797/scipharm.0912-18
79. Mahmoudi A, Hadrich F, Feki I, Ghorbel H, Bouallagui Z, Marrekchi R, *et al*. Oleuropein and hydroxytyrosol rich extracts from olive leaves attenuate liver injury and lipid metabolism disturbance in bisphenol A-treated rats. Food Func. 2018; 9(6):3220-34. https://doi.org/10.1039/C8FO00248G
80. Jemai H, Bouaziz M, Fki I, El Feki A, Sayadi S. Hypolipidimic and antioxidant activities of oleuropein and its hydrolysis derivative-rich extracts from Chemlali olive leaves. Chem Biol Interact. 2008; 176(2-3):88-98. https://doi.org/10.1016/j.cbi.2008.08.014
81. Duric L, Medio-stojanoska M, Milosevic N. Herbs for treatment of hyperlipidemia: What is the evidence? Curr Top Nutraceutical Res. 2021; 19:1-11. https://doi.org/10.37290/ctnr2641-452X.19:146-156
82. Dev S. Ethnotherapeutics and modern drug development. The potential of Ayurveda. Curr Sci. 1997; 73:909-28.
83. Satyavati GV. Gum guggul (*Commiphora mukul*)-The success story of an ancient insight leading to a modern discovery. Indian J Med Res. 1988; 87:327-35.
84. Singh K, Chander R, Kapoor NK. Stimulation of low density lipoprotein receptor activity in liver membrane of guggulsterone treated rats. Pharmacol Res. 1990; 22:37-44. https://doi.org/10.1016/1043-6618(90)90741-U
85. Deng R. Therapeutic effects of guggul and its constituent guggulsterone: Cardiovascular benefits. Cardiovasc Drug Rev. 2007; 25:375-90. https://doi.org/10.1111/j.1527-3466.2007.00023.x