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PHYTOSTEROLS AS A MEAN TO ALTER CHOLESTEROL LEVELS

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review paper

Summary

Cholesterol is a molecule wich represents the basic building part of every cell. Its homeostasis is crucial for proper cellular and systemic functions and it is very important to maintain it within reference values. Altered cholesterol balance causes cardiovascular diseases as well as other diseases, like neurodegenerative and cancer. High level of cholesterol can be aleviated with medical therapy but also with a diet rich in phytosterols. The main sources of phytosterols are vegetable oils, nuts, and legumes, but positive effect on lipid profile have fruits and vegetables, and some medicinal plants. Additionally, positive effect was found for combination of phytosterols with read yeast rice and in combination with probiotic bacteria. The most important property of phytosterols is reduced absorption of endogenous and exogenous cholesterol in the body. According to a number of studies their sufficient intake can significantly alter absorption of cholesterol from foods in the small intestine.
Conclusion: Daily diet that includes foods containing phytosterols can maintain normal blood cholesterol levels and prevent diseases due to hypercholesterolemia, which are still te main cause of death in Croatia and surrounding countries.

Keywords: cholesterol, phytosterols, hypercholesterolemia

Introduction

Cholesterol is considered as one of the most important structural components of cell membranes and is the basic building part of every cell (Cerqueira et al., 2016). In certain organs cholesterol has specific roles such as: synthesis of bile acids in hepatocytes, synthesis of steroid hormones in the cortex of adrenal glands and gonads, transport of liposoluble (A, D, E and K) vitamins (Lemke et al., 2007). It is a chemically rigid and almost planar molecule with a steroid skeleton of four fused rings, three six-membraned and one five-membraned (Carqueira et al., 2016). Cholesterol is the most widespread sterol in the human body, and as far as its origin is concerned, it can be endogenous and egzogenous . Most cells in human body have the ability to synthesize cholesterol on their own , which is called endogenous cholesterol, while its other source can be food through which cholesterol is introduced externally, so called exogenous cholesterol. Given the ability of the body to create it in the large quantities, it is sufficient to consume 150-300 mg of cholesterol daily from outside. Children need a proportionally larger amount, since it plays a significant role as a structural element of all cellular and intracellular membranes (Voet, 2005).
Most of the cholesterol is produced in the liver, while its synthesis can also occur in the intestinal mucosa and adrenal gland, from where it is transported by bloodstream to the cells of the body. Like other lipids cholesterol is also insoluble in water. Cholesterol is transported in the bloodstream by binding proteins, thus building lipoproteins. There are several types of lipoproteins and they are divided by density, so we have: chylomicrons which are the largest in diameter and have the lowest density, very low density lipoprotein (VLDL), intermediate (transitional) density lipoprotein (IDL), low density lipoprotein (LDL) and large lipoprotein density (HDL). Lipoproteins which contain more lipids in their composition have a lower density. Cholesterol is present in the blood in free and esterified form, when it is bound with one fatty acid molecule. Cholesterol esterification is carried out in plasma under the action of the enzyme lecithin-cholesterol-acetyltransferaze (LCAT), which is found in blood plasma. In plasma, approximately 75% of cholesterol is esterified, most often with a polyunsaturated fatty acid, namely linoleic acid. Cholesterol is eliminated from the body through bile, conversion into cholic acids, peeling of the skin, a small amount is lost through urine, while lactation women lose a certain amount throuhg milk (Parket et al., 2006).
The harmful effect of cholesterol is manifested when it is present in blood in significantly higher than normal concentrations. Increased food intake increases its concentration in the blood. It has been proven that with every 100 mg of increased dietary cholesterol intake, the cholesterol value in the blood of adults increases by 0.25 mmol/l. Other factors such as genetic, endrocine and some others can influence the

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increase of its concentration in the blood (AJCN, 1997).

Hypercholesterolemia is a condition that indicates the presence of high levels of cholesterol in the blood. It is also a form of hyperlipidemia (high level of lipids in the blood), hyperlipoproteinemia (high level of lipoproteins in the blood) and dyslipidemia (any abnormality of lipids and lipoproteins in the blood). Elevated levels of LDL in the blood can be due to diet, obesity, genetic disease (such as LDL receptor mutations in familial hypercholesterolemia), or the presence of other diseases such as type 2 diabetes mellitus and an underactive thyroid gland (Durrington, 2003).

All animal cells produce cholesterol and use it at the same time to build their membranes, while plant cells produce phytosterols in smaller amounts, which are similar to cholesterol (Behrman et al., 2005). All lipoproteins carry cholesterol, but elevated levels of all lipoproteins except HDL are associated with an increased risk of atherosclerosis and coronary heart disease, especially elevated levels of LDL (Carmena et al., 2004). On the other hand an elevated level of HDL has a protective effect (Kontush et al., 2006). In most European cantries, cholesterol is measured in mmol/l. For healty adults, the recommended upper limit for total cholesterol is 5.2 mmol/l, of which the upper limit for LDL is 3.3 mmol/l (MC, 2022). Increased intake of soluble fiber has been shown to lower LDL levels, with each additional gram of soluble fiber lowering LDL by an average of 2.2 mg/dl (0.057 mmol/l) (Brown, 1999). Increased consumption of whole grains also reduces blood LDL levels, with whole grain oats being particulary effective (Hoolaender, 2015). Phytosterols which encourage from plants also showed great importance in reducing LDL levels (Ito et al., 2011). A meta-analysis of randomized controlled trials in adults was preformed to establish a continuous dose-response relationship that would allow prediction LDL-lowering efficacy at different doses of phytosterols. As a result of the study, it was found that phytosterol at an average dose of 2.15 g/day reduces LDL by an average of 8,8% (Demonti et al., 2009).

Sitosterolemia is a hereditary lipid disorder manifested by elevated serum sitosterol and may result in an increased risk of premature cardiovascular disease. Since sitosretol cannot be accurately measured by routine diagnostic tests, this means that the diagnosis of sitosterolemia can often be difficult, especially with many clinical features that overlap with familial hypercholesterolemia. Lipid testing including sitosterol is recommended in children, especially those with uncontrolled hyprecholesterolemia, to identify potential patients with sitosterolemia who would otherwise be overlooked (Lee et al., 2020).

Phytosterols

Phytosterols are a group of steroid alcohols that occur naturally in plants (Ramamutrthi et al., 1993). They are structurally and physiologically similar to cholesterol and represent a large group of steroid triterpens. They are necessary to maintain normal function in the cell membrane of the plant. Phytosterols can lower the intestinal absorption of cholesterol and on that way reduce the serum level od LDL and the risk of atherosclerosis (Wang, 2011). Phytosterols have been observed to displace cholesterol from micelles by dynamic competiton where unabsorbed cholesterol is eliminated in the stool, in which case its absorption and blood levels are reducing (AbuMweis et al., 2014). The most common phytosterols in the human diet are sitosterols, stigmasterols and campesterols and can be found in free form, as a fatty/cinnamic acid esters or as glycosides processed by pancreatic enzymes. Accumulating evidence reveals that phytosterols and diets enriched in them can control glucose and lipid metabolism, as well as insulin resistence (Prasad et al., 2022).

Plant sterols have a potential preventive function in aterosclerosis due to their ability to lower cholesterol (Han et al., 2015). Experimental and clinical studies have demonstrated the effect of phytosterols on lowering blood cholesterol and plasma LDL, but the effects of plant sterols beyond cholesterol lowering are still questionable. Since inflammation and endothelial dysfunction are involved in the phatogenesis of atherosclerosis, studies aim to evaluate the effect of phytosterols on biomarkers involved in the progression of aterosclerosis and are this effects independed of changes in plasma LDL (Ilha, 2020). In one stady that aimed to evaluate the effect of low-fat products enriched with plant sterols along with the diet Step 1 of the National Cholesterol Education Program on serum lipids and lipoproteins. The study was a double-blind, randomized, placebo-controlled crossover design with a run-in period and 2 intervention periods, each lasting 4 weeks. A total of 46 subjects with mild hypercholerolemia completed the study. The tested products consised of 20 g of low-fat margarine and 250 ml of low-fat milk, which supplied a total of 2.3 g of plant sterols. As a result of the study, total serum cholesterol and LDL were significantly reduced, by 5.5% and 7.7% compared to placebo. Serum apolipoprotein B was significantly reduced, by 4.6%, and apolipoprotein B/apolipoprotein A-I by 3.4%. The conclusion is that the combination of low-fat margarin and milk enriched with plant sterols significantly reduces total serum cholesterol, LDL, apolipoprotein B and the ratio of apolipoprotein B to apolipoprotein A-I in humans with mild hypercholesterolemia, but without affecting C-reactive protein (Madsen et al., 2007).

One systemic review analyzed the cholesterol-lowering efficacy of phytosterols/stanols in normocholesterolemic and hypercholesterolemic subjects. It is important to note that familial hypercholesterolemia is characterized by high concentrations of LDL and is considered a global public health problem due to the high frequency of premature coronary heart disease in these patients. Six of the 13 reviewed studies were of sufficient quality. Studies have used fat spreads as a carrier with doses ranging from 1.6-2.8 g/day phytosterols/stanol. The subjects were heterozygotes aged 2 to 69 years. The duration of the study was from 4 weeks to 3 months. Fat spreans enriched with 2.3 +/- 0.5 g of phytosterols/stanols per day significantly reduced triglycerides, an average reduction of 0.65 mmol/l and LDL od 10-15% with an average reduction of 0.64 mmol/l (Moruisi et al., 2006).

In order to charachterize the effect of plant sterols/stanols on serum lipids in people with hypercholesterolemia who are on statin therapy, a meta-analysis of randomized controlled trials was conduced. The analysis evaluetes the use of plant sterols/stanols in combination with statins i hypercholesterolemic subjects who reported efficacy data on total cholesterol , LDL, HDL or triglycerides. The results of 8 studies (n=306 patients) had satisfied the inclusion criteria. After a meta-analysis, it was concluded that the use of plant sterols/stanols in combination with statin therapy significantly lowers the values of total cholesterol and LDL, but not HDL or triglycerides (Scholle et al., 2009).

In a pilot study involving children and adolescents with hypercholesterolemia, the effects of a combination of plant sterols, fish oil and B vitamins on the levels of four independent risk factors for cardiovascular disease were investigated; LDL ccholesterol, triacylglycerol, C-reactive protein and homocysteine. In one study 25 participants with an average age of 16 years with BMI of 23 participated in the study and recived a daily emulsified preparation consisting of plant sterol esters (1300 mg), fish oil (providing 1000 mg of EPAplus DHA), vitamin B12 (50 μg), B6 (2.5mg), folic acid (800 μg) and coenzyme Q10 (3mg) for 16 weeks. Atherogenic and inflammatory risk factors, lipophilic vitamins in plasma, provitamins and fatty acids were measured at the beginning of the 8th and 16th week. The results showed that the levels of total serum cholesterol, LDL, VLDL, LDL-2 subfractions, IDL-1, IDL-2 and homocysteine in plasma were significantly reduced at the end of the intervention ($p<0.05$). Triacylglycerol levels were reduced by 17.6% but did not reach a significant value. No significant changes in high-sensivity C-reactive protein, HDL and apolipoprotein A-1 were observed during the study period. Based on the obtained results, it is concluded that the daily intake of a combination of plant sterols, fish oil and B vitamins can modulate the lipid profile of hyprecholesterolemic children and adolescents (Garaiova et al. 2013).

The efficacy of phytosterols and fish oil on a high-oleic sunflower oil diet was evaluated in growing hypercholesterolemic rats. During 8 weeks, the control group received a standard diet, while the experimental rats were fed an atherogenic diet for period of 3 weeks, after which they were devided into four groups fed a diet with monounsaturated fatty acids (MUFA) for 5 weeks. The diet did not change weight or growth, but rats showed a decrease in total cholesterol, non-HDL and triglycerides, and an increase in HDL levels (Alsina et al., 2016).

The main sources of phytosterols are vegetable oils (linseed, olive, soybean, sesame, wheat germ), nuts (walnut, almond, pistachio, cashew, Brazil nut, hazelnut, macadamia), legumes (bean, pea), fruit (apple, cranberry, blueberry, red grapes), vegetables (broccoli, cabbage, cauliflower, garlic, onion, tomato), plants (cocoa, artichoka). A beneficial effect of phytosterols in combination with red yeast rice and in combination with probiotic bacteria was also recorded.

Flaxseed oil

Flax seeds are one of the most important sources of dry oils, with an oil content od 31% to 43%. Flaxseed is a rich source of omega-3 fatty acids, namely α-linolenic acid (ALA), short-chain polyunsaturated fatty acids (PUFA), soluble and insoluble fiber, phytoestrogen ligands, proteins and oxidases (Ivanova et al., 2012; Singh et al., 2011; Oomah, 2001; Toure et al., 2010). Flaxseed oil contains 58% α-linolenic acid, which is a powerful antioxidant (Perumal et al., 2019). It also contains stearic, oleic, linoleic and palmitic acid and vitamin E (Moallen, 2018). Flaxseed oil protects the human body from cardiovascular diseases, inhibits pro-inflammatory mediators, reduces LDL, plays a significant role in bone health and reducing the risk of hormonally mediated cancers (Nelsor et al, 2019). A recent meta-analysis of 62 randomized controlled trials with a total of 3772 participants suggests that flaxseed supplementation can reduce total serum

cholesterol, triglycerides and LDL in individuals with high baseline blood lipids (Hadi et al., 2020).
The protein content of flaxseed varies from 20% to 30%, comprising approximately 80% globulin (lignin and kinlinin) and 20% glutelin (Hall et al., 2006). Active peptides with cholesterol-lowering properties have been isolated from flaxseed proteins, which are by-products of the industrial production of flaxseed oil, which significantly improved the economic and medical value of flaxseed proteins. The most effective isolated peptide Ile-Pro-Pro-Phe (IPPF) inhibits intestinal absorption of cholesterol by modulating the expression of cholesterol transporters and reduces cholesterol synthesis in the liver by inhibiting the mevalonate pathway. According to research, IPPF can be used as a new type of food-derived intestinal cholesterol absorption inhibitor to reduce dietary cholesterol absorption and cholesterol synthesis inhibitor and has the same pharmacological mechanism as statins (Bao et al., 2022).

Olive oil

The therapeutic effects of olive (*Olea europaea* L.) for a long time have been recognized; it leads to a decrease in blood sugar, cholesterol and uric acid levels (Hawkely et al., 2010). The most important nutritional elements of olives are MUFA an PUFA. Consumption of MUFAs such as oleic acid reduces several cardiovascular risk factors (Schwingshackl et al., 2012), while the presence of omega-3 and omega-6 fatty acids emphasizes the importance of olives as an important food source of essential fatty acids. In addition of fatty acids and phenolic compounds, the nutritional value of olives is also related to other lipids such as phytosterols and non-lipid compounds such as tocopherols and carotenoids (Boskou et al., 2015). Olive oil mainly consists of triacylglycerols, which represent a diverse group of glycerol esters with different fatty acids. The predominant fatty acid is monounsaturated oleic acid, up to 83%. Palmitic acid, linoleic acid, stearic acid and palmitoleic acid are also present (Boskou, 2009; Luchetti, 2002; Ramirez-Tortosa et al., 2006). Research results suggest that supplementing the diet with olive oil and plant sterols esterified to fatty acids of olive oil favorably alters the plasma lipid profile and may reduce the susceptibility of LDL to lipid peroxidation in individuals with hypercholesterolemia (Chen et al., 2007).

Soybean and soyabean products

Soy (*Glycine max*) is a plant species from the leguminosus group which is an important source of plant proteins, isoflavones, phytoestrogens and polyphenols that have ability to inhibit LDL oxidation (Maki et al., 2010). Raw soy contains 20% fat including saturated fat (3%), monounsaturated (4%) and polyunsaturated fat, mainly in the form of linoleic acid. Soybean oil is one of the main term by-product in the soybean processing process and is rich in phytosterols (Ramamurthi et al., 1993). Just like cholesterol in animals, phytosterols regulate the fluidity of plant cell membranes and characteristics in cell differentiation and proliferation (Piironen et al., 2000). The FDA has stated that daily intake of moderate amounts of phytosterols may reduce the risk of heart disease. Long-term intake of foods rich in phytosterols could effectively reduce plasma cholesterol levels and the risk of atherosclerosis (Ostlud et al., 2003). In a randomized, controlled, palallel trial, soy was shown to have a cholesterol-lowering effect in 65 men and women with moderate hypercholesterolemia who experienced a reduction in total LDL (Maki et al., 2010). In a randomized crossover study of 24 subjects , soy consumption reduced lipid peroxidation *in vivo* and increased LDL resistance to oxidation (Wiseman et al., 2000). In a meta-analysis of eight randomized studies, scientists found that participants who consumed high concentrations of isoflavones had LDL concentrations approximately 6mg/dl lower than participants who consumed the same amount of soy protein with low concentrations of isoflavones ($P<0.0001$). Similar effects were observed when patients who were normocholesterolemic were analyzed separately. Becouse soy is generally associated with reduced serum cholesterol concentrations (Belleville et al., 2002). In a 4-week double blind, placebo-controlled, cross-over study, 38 moderately hypercholesterolemic volunteers (58±12 years, LDL $\geq$ 130 mg/dl) participated and were randomly assigned to consume 400 ml/day of soy milk or soy milk + phytosterols (1,6 g/day). Blood samples were collected and lipid profile and biomarkers for inflammation and endothelial dysfunction were determined. The results showed that treatment with phytosterol reduced the concentration of endothelin-1 in plasma by 11% ($p=0.02$) independent of the variations in plasma LDL level. Phytosterol reduced the concentration of total cholesterol in plasma (-5,5%, $p < 0{,}001$), LDL (-6,4%, $p < 0{,}05$), without changing the concentration of HDL ($p > 0.05$). Therefore, it can be seen that supplementation with phytosterols effectively lowers endothelin-1 independently of the reduction of LDL levels in plasma, contributing to the understanding of the effect of plant sterols on endothelial function and prevention of cardiovascular disease (Ilha, 2020). The FDA has approved a daily intake of 25g of soy protein in a diet low in saturated fat and cholesterol as a means of reducing the risk of cardiovascular disease. Soy is also advocated in the treamtent of hypercholesterolemia (FDA, 1999).

Sesame oil

Sesame (Sesamum indicum) yields an oil rich in MUFA and PUFA. Many studies have revealed that sesame oil contains lignans such as sesamin, sesamolin and several antioxidant compounds such as sesaminol (Egbekun et al., 1997). Lignans are metabolites formed from two phenylpropanoid molecules. In sesame, lignan synthesis involves the fusion of oxopropane side chains of cinnamyl alcohol to the furan core, and these metabolites are designated as furofuran lignans (Wu et al., 2019). In addition to lignans, several bioactive compounds such as phenols, phytosterols, phytates and tocopherol have been identified in sesame (Pathak et al., 2017). Sesamin has been shown to reduce total serum cholesterol and LDL levels in patients with hypercholesterolemia (Hirata et al., 1996). A randomized, placebo-controlled study in overweight men and woman, given sesame seed equivalents containing 50 mg of sesamin per day, showed no reduction in blood lipids or blood pressure, and markers of systemic inflammation and lipid peroxidation were unaffected, although urine excretion confirmed that lignans were absorbed and metabolized (Penavlo et al., 2006). On the other hand, administration of sesame to postmenopausal women reduced their serum cholesterol and androgen precursor levels and increased the ratio of tocopherol (Wu et al., 2006).

Wheat germs

Wheat (*Triticum aestivum*) is one of the most widely consumed edible whole germs in the world. Wheat consist of abouth 80% endosperm, 15% bran and 5% germ (Savin, 2004). It is rich in starch, fiber, minerals, vitamins and phytochemicals such as phenolic compounds, phytosterols and swingolipids and most of them are concentrated in the outer layers (bran) of the grain (Cheng et al., 2021). Weath germ (embryo) is a concentrated source of antioxidans such as polyphenols, carotenoids and tocopherols (the most common natural sources of vitamin E) (Vaher et al., 2010; Zhu et al., 2011). Nomerous *in vivo* and *in vitro* studies have investigated various health aspects of weath germ, especially wheat germ oil (Arshad et al., 2013; Kherd et al., 2017) which can improve lipid metabolism (Khalil et al., 2010). In the conducted research, wheat germs with a high concent of phytosterols in relation to total fat were selected for one group as a trial food with a low fat content, while the other group of respondents used wheat germs without phytosterols. Absorption of cholesterol from meals containing wheat germ with phytosterols is significantly lower than absorption of cholesterol from foods with wheat germ that does not contain phytosterols. This suggests that endogenous phytosterols in wheat germ and possibly other low-fat vegetable foods may have important effects on cholesterol absorption and metabolism that are independent of major nutrients (Ostlud et al., 2003).

Nuts

Nuts are a food rich in energy and contain a complex matrix of beneficial nutrients and bioactive substances including MUFAs and PUFAs, high-quality proteins, fiber, non-sodium minerals, tocopherols, phytosterols and antioxidant phenols (Ros et al., 2021). They contain a number of phytochemicals including carotenoids, phenolic acid, phytosterols and polyphenolic compounds such as flavonoids, proanthocyanidins and stilbenes, as well as phytates, sphingolipids, lignans. The phytochemical content of nuts can very significantly depending on the type of nuts, genotype, pre-harvest and post-harvest conditions, as well as storage conditions. Genotype affects phenolic acid, flavonoids, stilbenes and phytosterols. Phytochemicals found in nuts are associated with antioxidant, anti-inflammatory, antiproliferative, antiviral, chemopreventive and hypocholesterolemic effects (Bolling et al., 2011). Phytosterols in nuts range from 95-280 mg/100 g. Walnuts are particulary rich in total phenols with 1625 mg gallic acid equivalents/100 g. Stilbene resveratrol is found in peanuts and pistachios in amounts of 84 and 115 µg/100 g. Proanthocyanins are found in almonds, cashews, hazelnuts, pistachios, peanuts and walnuts with concentrations varying from 9-494 mg/100 g (Chen et al., 2008). Randomized control trials consistently show that nuts lower cholesterol. It is also an interesting fact that although foods are rich in energy, they do not predispose to obesity, even on the contrary, they can help weight loss. Level 1 evidence from the PREDIMED trial showed that consumption of 30 g of nuts per day significantly reduced the risk of the composite endpoint of major adverse cardiovascular events (Ross et al., 2021). In the conducted study, the effects of nuts on risk factors for major cardiovascular diseasee were investigated. The effects of nuts (walnuts, pistachios, macadamias, cashews, almonds, hazelnuts and Brazil nuts) on blood lipids were investigated. The results showed that nut intake (portion/day) lowered total cholesterol (-4.7 mg/dl) and LDL (-4.8 mg/dl). The dose-response between nut intake and total cholesterol and LDL was non-linear (P-non-linearity <0.001each), with stronger effects observed for ≥60 g nuts/day. No significant heterogeneity was observed by nut type or other factors. It is concluded that the intake of nuts lowers total cholesterol and LDL. The main determinant of cholesterol lowering appears to be the dose of nuts rather than the type (Gobbo et al., 2015).

Leguminos (fabaceae)

Legumes are a good source of bioactive compounds such as polyphenols, phytosterols, indigestible carbohydrates and have an important physiological and metabolic role. Ferulic acid is the most abundant phenolic acid present in legumes, while flavonol glycosides, anthocyanins and tannins are responsable for the color of the seed coat. Sitosterol (which is also the most abundant), stigmasterol and compesterol are the main phytosterols present in legumes. Fiber, resistant starch and oligosaccharides function as probiotic and possess several other health benefits such as anti-inflammatory and antitumor effects and lowering blood glusose and lipid levels. Beans and peas contain higher amounts of oligosaccharides than other legumes (Singh et al., 2017). Consuming soluble fiber in the diet is associated with health benefits, including the reduction in lipid levels. By consuming water-soluble fibers that from viscosity, the level of total cholesterol and LDL can be reduced by about 5-10 %, and minimal changes in HDL have been observed. The cholesterol-lowering properties of soluble fibers depend on their physical and chemical properties, and medium to high molecular weight fibers are more effective in lowering lipid levels (Suramoudi et al., 2016).

Fruits (apple, cranberry, blueberry, grapes) as a source of phytochemicals

Epidemiological studies indicate that fertile consumption of foods rich flavonoids is associated with a reduced risk of cardiovascular diseases, which is probably the result of their antioxidant activity and ability to inhibit endogenous cholesterol synthesis (Kruger et al., 2014). Fruits and vegetables are a good source of flavonoids, so the recommended intake of five a day would have a positive effect on the level of lipids in the blood.

It was experimentally shown that in hamsters fed cholesterol-enriched food, the consumption of anthocyanin can reduce the concentration of LDL in the plasma and increase the concentration of HDL by manifesting antiatherogenic effects (Liang et al., 2013). Similar results were observed in humans after 3 months of anthocyanin supplementation (160 mg twice daily) in a double-blind, randomized, placebo-controlled tial of 120 subjects with dyslipidemia (Qin et al., 2009).

Quercetin is one of the main flavonoids found in food, and it is associated with the prevention of LDL oxidation and atherosclerosis by exhibiting anti-inflammatory, antiproliferative and antioxidative effects (Liang et al., 2013; Qin et al., 2009). In a double-blind cross-over study on 49 healthy male subjects, it was determined that quercetin intake (150 mg/day) reduced postprandial triglyceride concentrations and increased HDL concentrations (Pfeuffer et al., 2013). It was found that the consumption of a functional drink rich in fruit poyphenols (apple, cranberry, blueberry) for two week can significantly reduce the concentration of triglycerides, total cholesterol and cholesterol in the liver in experimental sponthaneously hypertensive rats fed an atherogenic diet (Gunathilake et al., 2013).

Cranberry (Vaccinium macrocarpon)

Cranberry as one of the main sources of polyphenols has found its place for widespread use due to its antioxidant properties. It contains a number of phytochemicals including three classes of flavonoids (flavonols, anthocyanins and proantocyanins), catechins and phenolic acids, substances associated with a wide range of biologocal effects, including antioxidant activity, madulation of enzyme activity and regulation of genetic expression (Neto, 2007). The nutritional attributes of cranberry make it one of the most important nutritional targets in the prevention of cardiovascular disease by having a beneficial effect on cardiovascular disease risk factors that include dyslipidemia, oxidative stresa, hypertension, inflammation and endothelial dysfunction. After long-term cranberry use, clinical studies have shown significant improvment in lipid profile, apoA-I and oxidative stress, and reduction in apoB, fasting plasma glucose and C-reaktive protein (Shidfar et al., 2012; Daffey et al., 2015).

Grapes (Vitis vinifera)

Grapes are a good source of polyphenol antioxidant. A 6-week randomized, double-blind, placebo-controlled study was conducted to evaluate the effects of integral grape extract on antioxidant status and lipid profile in 24 prehypertensive, obese, and/or prediabetic subjects. The results showed an increase in HDL, a decrease in the ratio of total cholesterol to LDL and improved antioxidant capacity (Evans et al., 2014).

Vegetables (cabbage, garlic, onion, tomato) as a source of phytochemicals

Cabbage (Cruciferae, Brassicaceae)

Plants which belongs to the Brassicaceae family (cabbage, brussels sprouts, broccoli and cauliflower) contain glucosinolates, polyphenols, carotenoids and phytosterols which are anti-inflammatory and antioxidant nature. In an intervention study, 38 healthy volunteers (23 woman and 15 man) were fed portion of 300 g/day of blach and red cabbage for a period of two weeks. The results showed a significant increase in plasma carotenoid concentration (lutein and β-carotene) and total antioxidant capacity. A decrease in blood glucose and an improved lipid profile were observed, along with a decrease in total an LDL cholesterol and LDL oxidation (Bacchetti et al., 2014).

Garlic (Allium sativum)

Bioactive compounds in garlic are enzymes (eg. allinase) and sulfur-rich compounds such as enzymatically produced allin and its compounds (eg. allicin). Allicin concentrations in garlic vary depending on the metod of its processing. Since allicin is an unstable compound it is quickly transformed into various chemicals. However, even in the abstance of allicin, garlic still retains its positive effects on the cardiovascular system. Clinically , the benefits of garlic have been reported to alleviate several conditions, including hypertension, hypercholesterolemia, diabetes and atherosclerosis. The possible antibacterial, antihypertenzive and antitrombotic properties of garlic also make it an important antiatherogenic agent (Majewski, 2014).

Onion (Allium cepa)

Onion take a high place among vegetables that are rich in flavonoids, mainly containing quercetin. Its most significant benefits associated with cardiovascular disease include lowering blood pressure and oxidized LDL, and acting as aninflammatory marker. However, the best effects od onion are observed when approximately 150 mg of quercetin is consumed, which corresponds to an intake of approximately 700 mg/day of onions (Toh et al., 2013).

Tomato (Lycopersicon esculentum)

Tomato is one of the most consumed vegetables in the world and is a rich source of carotenoids and flavonoids (Hanson et al., 2004). It is a key component of the Mediterranean diet and its consumption is directly related to the reduction of the risk of inflammatory processes, various chronic diseases and carcinogenesis, as well as the inhibition of LDL oxidation, which helps to lower blood cholesterol levels (Pinela et al., 2016). A randomized, single-blind, controlled clinical trial in humans showed that raw tomato consumption had a beneficial effect on HDL concentrations in overweight women (Cuevas-Ramos et al., 2013).

Plants (artichoke, cacao) as a source of phytosterols

Artichoke (Cynara scolyms)

Due to significant amount of polyphenols in its artichoke extracts, artichoka can exhibit a hypercholesterolemic effects (Arnaboldi et al., 2022). A trial was conducted to evaluate the effects of artichoke leaf extract on plasma lipid levels and general well-being in otherwise healthy adults with mild to moderate hypercholesterolemia. Number of 131 individuals were tested for total plasma cholesterol in range 6.0-8.0 mmol/l, with 75 appropiate volunteers randomized into the trial. Vounteers consumed 1280 mg of a standardized artichoke leaf extract per day or a matching placebo for 12 weeks. Total cholesterol in the plasma of the treated group decreased by an average of 4,2% (from 7.16 mmol/l to 6.86 mmol/l) and increased in the control group by an average of 1.9% (6.90 mmo/l to 7.03 mmol/l), where the difference between the groups is statistically significant ($p=0.025$). No significant differences were observed between groups for LDL, HDL or triglyceride levels. Consumption of artichoke leaf extract resulted in a modest but beneficial statistically significant difference in total cholesterol after 12 weeks (Bundy et al., 2008).

Cacao (Theobroma cacao)

Cacao contains polyphenols that reduce LDL oxidation, act as anti-inflammatory, antioxidant, moderate immune response, improve vascular function and reduce thrombocytes adhesion (Schinella et al., 2010). Antioxidants in cacao polyphenols change the glycemic response, change the lipid profile and reduce thrombocytes aggregation, inflammation and blood pressure, and can alleviate intestinal inflammation by reducing neutrophil infiltration and the production of proinflammatory enzymes and cytokines (Mohamed 2014). In a study in which 25 woman and 25 man participated, the effects of a three-week consumption of 50 g of flavonoid-rich dark chocolate on the oxidative stress of lipoproteins *in vivo* and *in vitro* were investigated, and the results were that the lipoprotein profile was improved with greater beneficial effects in women that in men (Nanetti et al., 2012).

Nutraceuticals with subchapters: red yeast rice and probiotic bacteria

RED YEAST RICE

Phytosterols and red yaest rice are very often studied nutraceuticals for lowering cholesterol, that is inhibiting intestinal absorption and hepatic synthesis of cholesterol (Cicero et al., 2017). The cholesterol-lowering effectiveness of red yeast rice is directly related to the amount of monacolin K in the extract (up to 10mg per day). Consuming macrolin K on a daily basis lowers LDL levels, where any reduction in LDL is accompanied by a similar raduction in total cholesterol. Although it has a mechanism of action that is similar to statins, daily consumption between 3 and 10 mg of macrolin K causes minimal risk, and mild myalgias are seen only in the weakest patients (Cicero et al., 2019). A study was conducted that aimed to examine the effects of phytosterols and red yeast rice on the lipid profile and their relationship. A double-blind, clinical trials was conducted randomizing 90 subjects with moderate hypercholesterolemia to treatment with phytosterols 800 mg (group 1), red yeast rice standardized to contain 5 mg macrolin from Monscus purpureus (group 2), or both in combination with nutraceuticals (group 3). The results obtained after 8 weeks of treatment in group 1 did not reveal significant variations in lipid parameters. In group 2 there was a significant raduction ($p < 0.001$) of LDL (-20.5% compared to the initial value) and apolipoprotein B (-14.4% compared to the initial value) as occurred in group 3 (LDL versus baseline: -27.0% apolipoprotein B versus baseline: -19.0%) ($p < 0.001$). Changes in LDL and apolipoprotein B were significantly different comparing group 2 with group 1 ($p < 0.05$). The change in LDL was also significantly higher in group 3 than in group 2 ($p <005$). The obtained results indicate that the combination of phytosterols and red yeast rice has an additive effect on lowering cholesterol, achieving a clinically significant reduction of LDL in patients with mild hypercholesterolemia (Cicero et al., 2017).

Probiotic bacteria

Phytosterols and probiotic bacteria are natural hypocholesterolemic agents with potential cardiovascular benefits. Accordingly, a stady was conducted to evaluate the effects of probiotic and phytosterols supplementation alone or in combination on serum and liver lipid profiles and thyroid hormones in hypercholesterolemic rats. The probiotic treatment consisted of 8 probiotic strains: 2 each of *Lactobacillus acidophilus*, *Lacrobacillus casei*, *Lactobacillus gasseri* and *Lactobacillus reuteri*. Rats were fed for 8 weeks and treatment with a high-cholesterol basal diet to induce hypercholesterolemia. The results of the study showed that supplementation significantly reduced serum total cholesterol, LDL, HDL and tryglicerides compared to control groups. The symbiotic treatment was more effective in lowering LDL, while the mix probiotic treatment was more effective in lowering serum total cholesterol and LDL than the treatment containing phytosterols. Treatment containing phytosterols induced increased thyroid activity, which was evident by increased levels of serum total thyroxine, total triiodothyronine and free triiodothyronine. Based on the obtained results, it can be concluded that the lipid profile can be effectively reduced in order to reduce the incidence of cardiovascular diseases by using a combination of *Lactobacillus*-based probiotics and phytosterols in functional food (Awaisheh et al., 2013).

Conclusion

Food that is rich in phytosterols show favorable effects on the lipid profile in the blood, and therefore food that containing phytosterols and/or nutritional supplements should be included in the daily diet. Such a diet would have far-reaching effects on the entire population, not only on people who have hypercholesterolemia, because cardiovascular deseases and strokes are the main cause of death in Croatia and the countries of the region.

References

AbuMweis S.S., Marinangeli C.P.F., Frohlich J., Jones P.J. (2014): Implementing phytosterols into medical practice as a cholesterol-lowering strategy: overview of efficacy, effectiveness, and safety, *Can J Cardiol.* 30(10), 1225–32.

Alhassane T., Xu X.M. (2010): Flaxseed Lignans: Source, Biosynthesis, Metabolism, Antioxidant Activity, Bio-Active Components and Health Benefits, *Compr Rev Food Sci Food Saf*. 9(3), 261–269.

Alsina E., Macri E.V., Lifshitz F., Bozzini C., Rodriguez P.N., Boyer P.M., Friedman S.M. (2016): Efficacy of phytosterols and fish-oil supplemented high-oleic-sunflower oil rich diets in hypercholesterolemic growing rats, *Int J Food Sci Nutr.* 67(4), 441-53.

American Journal of Clinical Nutrition (1997): „Health effects of trans fatty acids“ review article. 66, 1006S-1010S.

Arnaboldi L., Corsini A., Bellosta S. (2022): Artichoke and bergamot extract : a new opportunity for the menagement od dyslipidemia and related risk factors, *Minerva. Med*. 113(1), 141-157.

Arshad M.S., Anjum F.M., Khan M.I., Shahid M. (2013): Wheat germ oil and α-lipoic acid predominantly improve the lipid profile of broiler meat, *J. Agric. Food Chem.* 20;61(46), 11158–65.

Awaisheh S.S., Khalifeh M.S., Al-Ruwaili M.A., Khalil O.M., Al-Ameri O.H., Al-Groom R. (2013): Effects of Supplementation of probiotics and phytosterols alore or in combination on serum and hepatic lipid profiles and thyroid hormones of hypercholesterolemic rats, *J Dairy Sci.* 96(1), 9-15.

Bacchetti T., Tullii D., Masciangelo S., Gesuita R., Skrami E., Brugè F., Silvestri S., Orlando P., Tiano L., Ferretti G. (2014): Effect of black and red cabbage on plasma carotenoid levels, lipid profile and oxidized low density lipoprotein, *J Funct Foods.* 8, 128–37.

Bao X., Yuan X., Li X., Liu X. (2022): Flaxseed-deriverd peptide, IPPF, inhibits intestinal cholesterol absorption in Caco-2 cells and hepatic cholesterol syntesis in HepG2 cells, *J Food Biochem*. 46(1), e14031.

Behrman. E. J., Gopalan, Vrnkat (2005): Cholesterol and Plants, *Journal of Chemical Education* 82(12), 1791.

Belleville J. (2002): Hypocholesterolemic effect of soy protein, *Nutrition* 18(7-8), 684-6.

Bolling B.W., Chen C-Y.O., McKay D.L., Blumberg J.B. (2011): Tree nut phytocemicals: composition, antioxidant, capacity, bioactivity, impact factors. A systemic review of Almond, Brazils, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts, *Nutr Res Rev.* 24(2), 244-75.

Boskou D. (2009): Olive Oil: Minorconstituents and Health. CRC Press; Boca Raton, FL, USA: *Other important minor constituents*; pp. 45-54.

Boskou D., Camposeo S., Clodoveo M.L. (2015): Table olives as sources of bioactive compunds. In: Boskou D., editor. Olive and Olive Oil Bioactive Constituents. AOCS Press; Urbana, IL, USA: pp. 215-259.

Brown L., Rosner B., Willett W.W., Snack F.M. (1999): Cholesterol-lowering effects of dietary fiber; a meta analysis, *Am J Clin Nutr.* 69(1), 30-42.

Bundy R., Walker A.F., Middleton R.W., Wallis C., Simpson H.C. (2008): Artichoke leaf extract (*Cynara scolymus*) reduces plasma cholesterol in otherwise healthy hypercholesterolemic adults: A randomized, double blind placebo controlled trial, *Phytomedicine* 15(9), 668–75.

Carmena R., Duriez P., Fruchart J.C. (2004): Atherogenic lipoprotein particles in atherosclerosis, *Circulation* 15;109(23 Suppl), III2-7.

Cerqueira N.M.F.S.A., Oliveira E.F., Gesto D.S., Santos-Martins D., Moreira C., Moorthy H.N., Ramos M.J., Fernandes P.A. (2016): Cholesterol Biosynthesis: A Mechanistic Overview, *Biochemistry* 4;55(39), 5483–5506.

Chan Y.M., Demonty I., Pelled D., Jones P.J.H.(Sep., 2007): Olivae oil containing olive oil fatty acid esters of plant steros and dietary diacylglycerol reduces low-density lipoprotein cholesterol and decreases the tendency for peroxidation in hypercholesterolaemic subjects, *Be J Nutr*. 98(3), 563-70.

Chen C-Y O, Blumberg JB. (2008): Phytochemical composition of nuts, *Asia Pac J Clin Nutr*.;17 Suppl 1, 329-32.

Cheng W., Sun Y. J., Fan M. C., Li Y., Wang L., Qian H. F. (2021): Wheat bran, as the resource of dietary fiber: a review, *Crit. Rev. Food Sci. Nutr*. 3, 1–28.

Cicero A.F.G., Fogacci F., Rosticci M., Parini A., Giovannini M., Varonesi M., D'Addato S., Borghi C. (2017): Effects of short –term dietary supplementation with phytosterols, red yeast riceor both on lipid pattern in moderately hypercholesterolemic subjects: a three-arm, double-blind, randomized clinical trial, *Nutr Metab (Lond.)* 25;14, 61.

Cicero A.F.G., Fogacci F., Banach M. (2019): Red Yeast Rice for Hypercholesterolemia, *Methodist Debakey Cardiovasc J.* 15(3), 192-199.

Cuevas-Ramos D, Almeda-Valdés P, Chávez-Manzanera E, Meza-Arana CE, Brito-Córdova G, Mehta R, Pérez-Méndez O, Gómez-Pérez FJ. (2013): Effect of tomato consumption on high-density lipoprotein cholesterol level: a randomized, single-blinded, controlled clinical trial, *Diabetes Metab Syndr Obes*. 26;6, 263–73.

Demonti I., Ras R.T., van der Knaap H.C., Duchateau G.S., Mejier L., Zock P.L., Geleijnse J.M., Trautwein E.A. (2009): Continuous dose-response relationship of the LDL-cholesretol lowering effect of phytosterol intake, *J Nutr.* 139(2), 271-84.

Diagnosing High Cholesterol. (Retrieved 2013) NHS Choices.

Duffey K..J, Sutherland L.A. (2015): Adult consumers of cranberry juice cocktail have lower C-reactive protein levels compared with nonconsumers, *Nutr Res*. 35(2), 118–26.

Durrington P. (2003): Dyslipidaemia, *The Lancet*. 30;362(9385), 717-31.

Egbekun M.K., Ehieze M.U. (1997): Proximate composition and functional properties of full fat and defatted beniseed (Sesamum indicum L.) flour, *Plant Foods Hum Nutr.* 51(1), 35-41.

Evans M., Wilson D., Guthrie N. (2014): A randomized, double-blind, placebo-controlled, pilot study to evaluate the effect of whole grape extract on antioxidant status and lipid profile, *J Funct Foods* 7, 680–91.

Food and Drug Administration, HHS. Final rule. Fed Regist. (1999): Food labeling: health claims; soy protein and coronary heart disease, 64, 57700-33.

Garaiova I., Muchova J., Nagyova Z., Mišlanova C., Oravec S., Dukat A., Wang D., Plummer S.F., Duračkova Z. (2013): Effect of a plant sterol, fish oil and B vitamin combination on cardiovascular risk factors in hypercholesterolemic children and adolescents: a pilot study, *Nutr J.* 8;12, 7.

Gobbo L.C.D., Falk M.C., Feldman R., Lewis K., Mozaffarian D. (2015): Effacts of tree nuts on blood lipids, apolipoproteins, and blood preassure: systematic review , meta-analysis, and dose –response od 61 controlled intervention trials, *Am J Clin Nutr*.;102(6), 1347-56.

Grundy S.M. (1986): Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol, *N. Engl. J. Med*.20;314(12), 745–8.

Gunathilake K.D.P.P., Wang Y., Vasantha Rupasinghe H.P. (2013): Hypocholesterolemic and hypotensive effects of a fruit-based functional beverage in spontaneously hypertensive rats fed with cholesterol-rich diet, *J Funct Foods*;5, 1392-401.

Hadi A., Askarpour M., Salamat S., Ghaedi E., Symonds M.E., Miraghajani M. (2020): Effect of flaxseed supplementation on lipid profile: An updated systematic review and dose-response meta-analysis of sixty-two randomized controlled trials, *Pharmacol. Res.*152, 104622.

Hall C., Tulbek M.C., Xu Y. (2006): Flaxseed, *Adv Food Nutr Res.* 51, 1-97.

Han H., Yan P., Chen L., Luo C., Gao H., Deng Q., Zheng M., Shi Y., Liu L. (2015): Flaxseed Oil Containing α-Linolenic Acid Ester of Plant Sterol Improved Atherosclerosis in ApoE Deficient Mince, *Oxid Med Cell Longev.* 958217.

Hanson P., Yang R., Wu J., et al. (2004): Variation for Antioxidant Activity and Antioxidants in Tomato, *J. Ame. Soc. Hort. Sci*.;129, 704-711.

Hasan S.T., Zingg J.M., Kwan P., Noble T., Smith D., Meydani M. (2014): Curcumin modulation of high fat diet-induced atherosclerosis and steatohepatosis in LDL receptor deficient mice, *Atherosclerosis.* 232(1), 40-51.

Hawkley L.C., Cacioppo J.T. (2010): Loneliness Matters: A Theorectical and Empirical Review of Consequences and Mechanisms, *Ann Behav Med.* 40(2), 218-27.

Hirata F., Fujita K., Ishikura Y., Hosoda K., Ishikawa T., Nakamura H. (1996): Hypocholesterolemic effect of sesame lignan in humans, *Atherosclerosis.* 26;122(1), 135–36.

Holleander, Pernille L.B., Ross, Alastair B., Kristensen, Mette (2015): Whole grain and blood lipid changes in apparently healthy adults: a systemic review and meta-analysis of randomized controled studies, *The Am J Clin Nutr.* 102(3), 556-72.

Ilha A.O.G., Nunes V.S., Alfonso M. S., NakandakareE. R., Ferreira G.S., Bombo R.P.A., Giorgi R.R., Machado R.M., Quintao E.C.D., Lottenberg A.M. (2020): Phytosterols Supplementation Reduces Endothelin-1 Plasma Concentration in Moderately Hypercholesterolemic Individuals Independently of Their Cholesterol-Lowering Properties, *Nutritiens* 22;12(5), 1507.

Ito M.K., McGowan M.P., Moriarty P.M. (2011): Menagement of familial hypercholesterolemias in adult patients: recommendations from the National Lipid Association Expert Panel on Familial hypercholesterolenia, *J Clin Lipidol*. 5(3 Suppl), S38-45.

Ivanova S., Rashevskaya T., Makhonina M. (2011): Flaxseed additive application in dairy products production, *Procedia Food Sci.* 1, 275.

Khalil F., Khalifa F., Barakat H., Hessin M. (2010): Ameliorative effect of wheat germ and/or grape seed oils on hematological, kidney functions and lipid profiles in rats co-administreted chlorpyrifos, *Vet. Med. J. Giz.* 58,365–380.

Khedr NF. (2017): Fish oil and wheat germ oil supplementation modulates brain injury in streptozotocin-induced diabetic rats, *J. Diabetes* 9(11), 1012–1022.

Kontush A., Chapman M.J. (2006): Antiatherogenic small, dense HDL-guardian angel of the arterial wall?, *Nat Clin Prac Cardiovasc Med*: 3(3), 144-53.

Keuger M.J., Davies N., Myburgh K.H., Lecour S. (2014): Proanthocyanidins, anthocyanins and cardiovascular diseases, *Food Res Int* . 59, 41-52.

Lee J.H., Song D.Y., Jun S.H., Song S.H., Shin C.H., Ki C.S., Lee K., Song J. (2020): High prevalence of increased sitosterol levels in hypercholesterolemic children suggest underestimation of sitosterolemia incidence, *PloS One.* 26;15(8), e0238079.

Lemke L.T., Williams D.A., ur. (2007). „Chapter : Adenocorticoids". Foye's Principles of Medicinal Chemistry (6 izd.). *Baltimore: Lippincott Williams & Wilkins*. ISBN 0-7817-6879-9.

Liang Y., Chen J., Zuo Y., Ma K.Y., Jiang Y., Huang Y., Chen ZY. (2013): Blueberry anthocyanins at doses of 0.5 and 1% lowered plasma cholesterol by increasing fecal excretion of acidic and neutral sterols in hamsters fed a cholesterol-enriched diet, *Eur J Nutr.* 52(3), 869-75.

Luchetti F. (2002): Importance and future of olive oil in the world market—An introduction to olive oil, *Eur. J. Lipid Sci. Technol.* 104, 559–563.

Madsen M.B., Jenesn A.M., Schmidt E.B. (2007): The Effect of combination of plant-sterol –enriched foods in mildly hypercholesterolemic subjects, *Clin Nutr.* 26(6), 792-8.

Majewski M. (2014): *Allium sativum*: facts and myths regarding human health, *Rocz Panstw Zakl Hig.* 65, 1–8.

Maki KC, Butteiger DN, Rains TM, Lawless A, Reeves MS, Schasteen C, Krul ES. (2010): Effects of soy protein on lipoprotein lipids and fecal bile acid excretion in men and women with moderate hypercholesterolemia, *J Clin Lipidol.* 4(6), 531-42.

Mayo Clinic. Retrived (2022): „High Cholesterol-Diagnosis and treatment".

Moallen U. (2018): Roles of dietary n-3 fatty acids in performance, milk fat composition, and immune system in dairy cattle, *J. Dairy Sci.* 101(10), 8641–8661.

Mohamed S. (2014): Functional foods against metabolic syndrome (obesity, diabetes, hypertension and dyslipidemia) and cardiovasular disease, *Trends Food Sci Technol* 35, 114–28.

Moruisi K.G., Oosthuizen W., Opperman A.M. (2006): Phytosterols/stanols lower cholesterol concentration in familiar hypercholesterolemic subjects: a systematic review with meta-analysis, *J Am Coll Nutr.* 25(1), 41.8.

Nanetti L, Raffaelli F, Tranquilli AL, Fiorini R, Mazzanti L, Vignini A. (2012): Effect of consumption of dark chocolate on oxidative stress in lipoproteins and platelets in women and in men, *Appetite*. 58(1), 400-5.

Nelson J.R., Raskin S. (2019): The eicosapentaenoic acid: Arachidonic acid ratio and its clinical utility in cardiovascular disease, *Postgraduate Med.* 131(4), 268–277.

Neto CC. (2007): Cranberry and blueberry: evidence for protective effects against cancer and vascular diseases, *Mol Nutr Food Res.* 51(6), 652–64.

Oomah BD. (2001): Flaxseed as a functional food source, *J Sci Food Agric.* 81(9), 889–894.

Ostlund, R.E.; Racette, S.B. & Stenson, W.F. (2003). Inhibition of Cholesterol Absorption by Phytosterol-replete Wheat Germ Compared with Phytosterol-depleted Wheat Germ, *Am J Clin Nutr*. 77(6), 1385-9.

Parker K., Brunton L., Goodman, Stanford L., Lazo, JohnS., Gilman, Alfred (2006). Googman and Gilman's The Pharmacological Basis of Therapeutics (11 izdanje). *New Yorf: MaGraw-Hill.* ISBN 0-07-142280-3.

Pathak N., Bhaduri A., Rai A.K. (2017): Sesame: Bioactive compounds and health benefits. In: Mérillon J.M., Ramawat K., editors. *Bioactive Molecules in Food. Springer; Cham, Switzerland*: pp. 1–20. (Reference Series in Phytochemistry).

Penalvo J.L., Hopia A., Adlercreutz H. (2006): Effect of sesamin on serum cholestrol and triglycerides level in LDL-receptor-deficient mice, *Eur. J. Nutr.* 45(8), 439–44.

Perumal P., Chang S., Khate K., Vupru K., Bag S. (2019): Flaxseed oil modulates semen production and its quality profiles, freezability, testicular biometrics and endocrinology profiles in mithun, *Theriogenology.* 15;136, 47–59.

Pfeuffer M, Auinger A, Bley U, Kraus-Stojanowic I, Laue C, Winkler P, Rüfer CE, Frank J, Bösch-Saadatmandi C, Rimbach G, et al. (2013): Effect of quercetin on traits of the metabolic syndrome, endothelial function and inflammation in men with different APOE isoforms, *Nutr Metab Cardiovasc Dis.* 23(5), 403-9.

Piironen, V.; Lindsay, D.G.; Miettinen, T.A.; Toivo, J. & Lampi, A.M. (2000). Plant Sterols: Biosynthesis, Biological Function and Their Importance to Human Nutrition, *Journal of the Science of Food and Agriculture*, 80, 939-966.

Pinela J., Oliveira M.B.P., Ferreira I.C.F. (2016): Natural Bioactive Compounds from Fruits and Vegetables as Health Promoters Part II. Volume 2. Bentham Science Publishers; Sharjah, United Arab Emirates: Chapter 3 Bioactive Compounds of Tomatoes as Health Promoters; pp. 48–91.

Prasad M, Jayaraman S, Eladl MA, El-Sherbiny M, Abdelrahman MAE, Veeraraghavan VP, Vengadassapathy S, Umapathy VR, Hussain SFJ, Krishnamoorthy K, Sekar D, Palanisamy CP, Mohan SK, Rajagopal P. (2022): A Comprehensive Review on Therapeutic Perspectives of Phytosterols in insulin Resistance: A Mechanistic Approach, *Molecules*. 28;27(5), 1595.

Qin Y, Xia M, Ma J, Hao Y, Liu J, Mou H, Cao L, Ling W. (2009): Anthocyanin supplementation improves serum LDL- and HDL-cholesterol concentrations associated with the inhibition of cholesteryl ester transfer protein in dyslipidemic subjects, *Am J Clin Nutr.* 90(3), 485-92.

Ramamurthi, S. & McCurdy, A.R. (1993): Enzymatic Pretreatment of Deodorizer Distillate for Concentration of Sterols and Tocopherols, *Journal of the American Oil Chemists Society*, 70,287-295.

Ramirez-Tortosa M.C., Granados S., Quiles J.L. (2006): Chemical composition, types and characteristics of olive oil, *Olive Oil Health*. 45–61.

Riaz Mian N. (2006): Soy Applications in Food. Boca Raton, FL: CRC Press. ISBN 0-8493-2981-7.

Ros E, Singh A, O'Keefe JH. (2021): Nuts: Natural Pleiotropic Nutraceuticals, *Nutritients* 19;13(9), 3269.

Schinella G, Mosca S, Cienfuegos-Jovellanos E, Pasamar MA, Muguerza B, Ramón D, Ríos JL. (2010): Antioxidant properties of polyphenol-rich cocoa products industrially processed, *Food Res Int* 43, 1614-1623.

Scholle J.M., Baker W.L., Talati R., Coleman C.I. (2009): The effect of adding plant sterols to statin therapy in hypercholesterolemic patients: systematic review and meta-analysis, *J Am Coll Nutr*. 28(5), 517-24.

Schwingshackl L., Hoffmann G. (2012): Monounsaturated fatty acids and risk of cardiovascular disease: Synopsis of the evidence available from systematic reviews and meta-analyses, *Nutrients*. 11;4(12), 1989–2007.

Shidfar F, Heydari I, Hajimiresmaiel SJ, Hosseini S, Shidfar S, Amiri F. (2012): The effects of cranberry juice on serum glucose, apoB, apoA-I, Lp(a), and paraoxonase-1 activity in type 2 diabetic male patients, *J Res Med Sci.* 17(4), 355-60.

Singh B, Singh JP, Shevkani K, Singh N, Kaur A. (2017): Bioactive constituents in pulses and their health benefits, *Foof Sci Technol.* 54(4), 858-870.

Singh KK, Mridula D, Rehal J, Barnwal P. (2011): Flaxseed- a potential source of food, feed and fiber, *Crit Rev Food Sci Nutr.* 51(3), 210-22.

Slavin J. (2004): Whole grains and human health, *Nutr. Res. Rev.* 17(1), 99-110.

Surampudi P, Enkhmaa B, Anuurad E, Berglund L. (2016): Lipid loweringwith Soluble Dietary Fiber, *Curr Atheroscler Rep*. 18(12), 75.

Toh JY, Tan VM, Lim PC, Lim ST, Chong MF. (2013): Flavonoids from fruit and vegetables: a focus on cardiovascular risk factors, *Curr Atheroscler Rep.* 15(12), 368.

Toure A., Xu X. (2010): Flaxseed lignans: Source, Biosynthesis, Metabolism, Antioxidant activity, Bio-Active Components and Health Benefits, *Compr Rev Food Sci Food Saf*. 9(3), 261–269.

Voet D., Judith G. Voet (2005): Biochemistry. Wiley str 394. ISBN 978-0-471-19350-0.

Vaher M., Matso K., Levandi T., Helmja K., Kaljurand M. (2010): Phenolic compounds and the antioxidant activity of the bran, flour and whole grain of different wheat varieties, *Procedia Chem.* 2, 76-82.

Wiseman H, O'Reilly JD, Adlercreutz H, Mallet AI, Bowey EA, Rowland IR, Sanders TA. (2000): Isoflavone phytoestrogens consumed in soy decrease F(2)-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in humans, *Am J Clin Nutr.* 72(2), 395-400.

Wu D., Wang X.-P., Zhang W. (2019): Sesamolin Exerts Anti-proliferative and apoptotic effect on human colorectal cancer cells via inhibition of JAK2/STAT3 signaling pathway, *Cell Mol. Biol.* 31;65(6), 96–100.

Wu W.H., Kang Y.P., Wang N.H., Jou H.J., Wang T. (2006): Sesame ingestion affects sex hormones, antioxidant status, and blood lipids in postmenopausal women, *J. Nutr.* 136(5), 1270–5.

Zhu K-X, Lian C-X, Guo X-N, Peng W, Zhou H-M. (2011): Antioxidant activities and total phenolic contents of various extracts from defatted wheat germ, *Food Chem.* 126, 1122–1126.