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Review Article

Phytochemicals effective in lowering Low-Density Lipoproteins

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Abstract: Cardiovascular diseases are the leading cause of morbidity and mortality around the globe. The key risk factor of cardiovascular diseases, hypercholesterolemia is expected to increase in the future. Phytochemicals, are natural compounds found in plants, having antioxidant properties. These antioxidant properties can be utilized to reduce the occurrence of chronic diseases and provide many health benefits in humans. Phytochemicals such as Indoles, plant sterols, flavonoids and lignans have been extracted and studied widely. It is because of their antioxidant properties they can be used in preventing hypercholesterolemia. This review illustrates and summarizes various phytochemicals and their mechanisms in lowering LDL cholesterol levels. The progress and the results achieved in studies relevant to the hypocholesterolemic effects of these phytochemicals are also illustrated. It was interpreted that on the availability of sufficient and confirmatory data about the efficacy of phytochemicals in lowering LDL cholesterol levels, plant-based diets or drugs containing extracts of phytochemicals can then be deployed in the treatment of hypercholesterolemia.

INTRODUCTION

Chronic diseases like cancers, diabetes and cardiovascular diseases (CVD) are health problems, which cause mortality and morbidity to millions of people around the world. Cardiovascular diseases are the leading cause of deaths around the globe. Cardiovascular diseases are related to heart and/or blood vessels of the human body. There are various risk factors associated with cardiovascular disease (CVD). Hypercholesterolemia has been investigated as a major risk factor for cardiovascular diseases [1]. Hypercholesterolemia refers to a medical condition characterized by high levels of cholesterol in the blood. High levels of cholesterol increase the risks of heart disease and stroke. Worldwide, one third of ischemic heart disease is caused by high cholesterol level. Overall, raised cholesterol is estimated to cause 2.6 million deaths (4.5% of total) [2]. WHO has stated CVD as the primary reason of deaths throughout the world (CVD contributes more than 30% of all deaths). An important step in reducing coronary morbidity and mortality is the prevention of cardiovascular diseases (CVD) by the treatment of hypercholesterolemia [3].

Lipoproteins are a combination of lipid and protein and are classified into two types - LDL (Low-Density Lipoproteins) and HDL (High-Density Lipoproteins). LDL is called as "bad" cholesterol because a high LDL level causes a build-up of cholesterol in the arteries. A high LDL level indicates too much LDL cholesterol in the blood and this extra LDL, along with other substances, forms plaque. The plaque builds up in the arteries leading to a condition called atherosclerosis. Both genetic and environmental factors affect plasma concentrations of LDL and other risk factors of CVD. Since, it is difficult to modify genetic factors; environmental factors like dietary patterns could be aimed to lower the risk factors. International guidelines issued by the WHO state that dietary saturated fat and cholesterol intakes when reduced can be measures to prevent hypercholesterolemia. In various studies, diets involving fruit and vegetable showed decrease in LDL concentration in subjects with hypercholesterolemia [4]. This preventive role can be attributed to the phytochemicals present in them. Phytochemicals can be defined as chemical compounds synthesized by plants through several chemical pathways [5]. Phytochemicals are a rich source of antioxidants in plants. Their antioxidant activity is of significance, because the increased production of oxidants in the human body takes part in the pathogenesis of various chronic diseases [6].

In this review paper, we have briefly discussed phytochemical compounds by analyzing their sources, mode of actions, and the available evidences in support of their effects on cholesterol levels in the blood.

INDOLES

Indoles are present in cruciferous vegetables, such as, cauliflower, broccoli, Brussels sprouts, cabbage, turnips, etc. Indole-3-carbinol (I3C) is found to be a major derivative of Glucobrassicin. Glucobrassicin is found commonly in the vegetables of the class Cruciferae [7]. Glucobrassicin converts to Indole-3-carbinol by autolysis during maceration (breakdown of ingested food into chime). After ingestion, it yields various oligomeric derivatives, due to the presence of stomach acid (Fig. 1) [8].

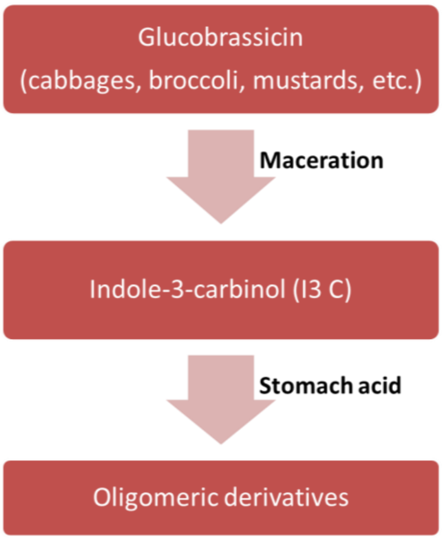

Fig. 1: Breakdown of Glucobrassicin to oligomeric derivatives [8]

When cholesterol is absorbed by the intestinal epithelial cells, it is subjected to esterification with long chain fatty acids in the presence of the enzyme Acyl-CoA: cholesterol acyltransferase (ACAT) [9]. A cholesteryl ester is formed and is legible to be transported to the liver with the help of chylomicrons [10]. In the liver, this cholesteryl ester is de-esterified by the enzyme called Cholesterol ester hydrolase. The elimination of this free cholesterol from our body can occur by conversion to bile acids or by affiliation with bile acid/phosphatidylcholine micelles [11]. Also, re-esterification of the free cholesterol can occur by hepatic ACAT. Thus, by inhibiting ACAT, the cholesterol levels in the blood can be reduced, because by inhibiting ACAT, the uptake of cholesterol can be hindered and the free cholesterol can be made available for elimination (Fig. 2) [12].

Results from the study of Dunn et al. 1993 indicate likelihood of lowering of LDL/VLDL cholesterol in blood on consumption of glucobrassicin-rich vegetables. Further, derivative products of I3C after acid condensation showed to inhibit ACAT activity at micromolar concentration [8]. Those results indicate a possible hypocholesterolemic action of I3C. In the experiments of Geoffrey et al. 2007, I3C was found to reduce the secretion of apoB, which is the major structural component of LDL. In the presence of I3C, production of triglycerides and cholesterol esters was observed to be reduced. Moreover, ACAT activity decreased in the cells subjected to I3C [13].

According to the in-vitro and in-vivo experiments performed by Okulicz et al. 2009, I3C demonstrated inhibition of basal lipogenesis at three different concentrations while I3C was unable to modify phospholipids, total and esterified cholesterol in the serum and liver cholesterol [14]. In a nutshell, it can be observed that beneficial effects of plant indoles on lipid metabolism may have a potential in cardiovascular protection. Indole-3-carbinol supplements are already available in the market and are used as a preventive measure for various types of cancer and other illnesses. But further research studies are still required in humans to demonstrate confirmatory hypocholesterolemic activity of plant indoles.

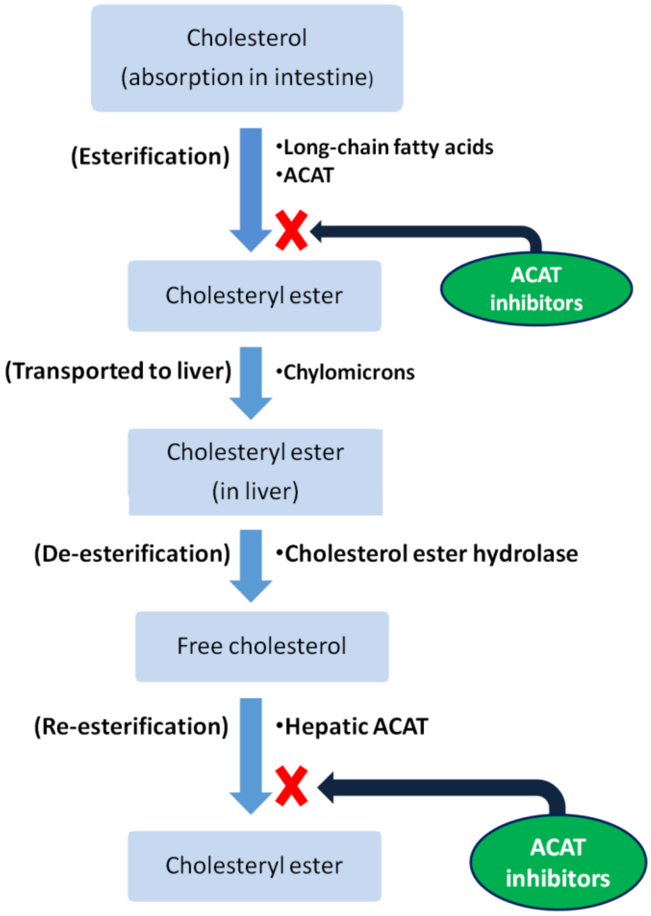

Fig. 2: Cholesterol absorption and the effect of ACAT inhibitors [9-12]

PLANT STEROLS AND STANOLS

Plant sterols and stanols, collectively called Phytosterols are naturally occurring compounds present in cell membranes of plants. Whole grains, dried peas, beans, peanuts, almonds, oranges, apples, cauliflower, broccoli, etc. are some of the rich sources of phytosterols. Phytosterols are similar in structure to our cholesterol. Phytosterols can be believed to lower cholesterol levels by inhibiting cholesterol absorption [15]. It is believed that inhibition of absorption of cholesterol occurs due to the high affinity of plant sterols for micelles than cholesterol, reducing the pool of absorbable cholesterol, thereby resulting in lowering of serum cholesterol levels (Fig. 3) [16].

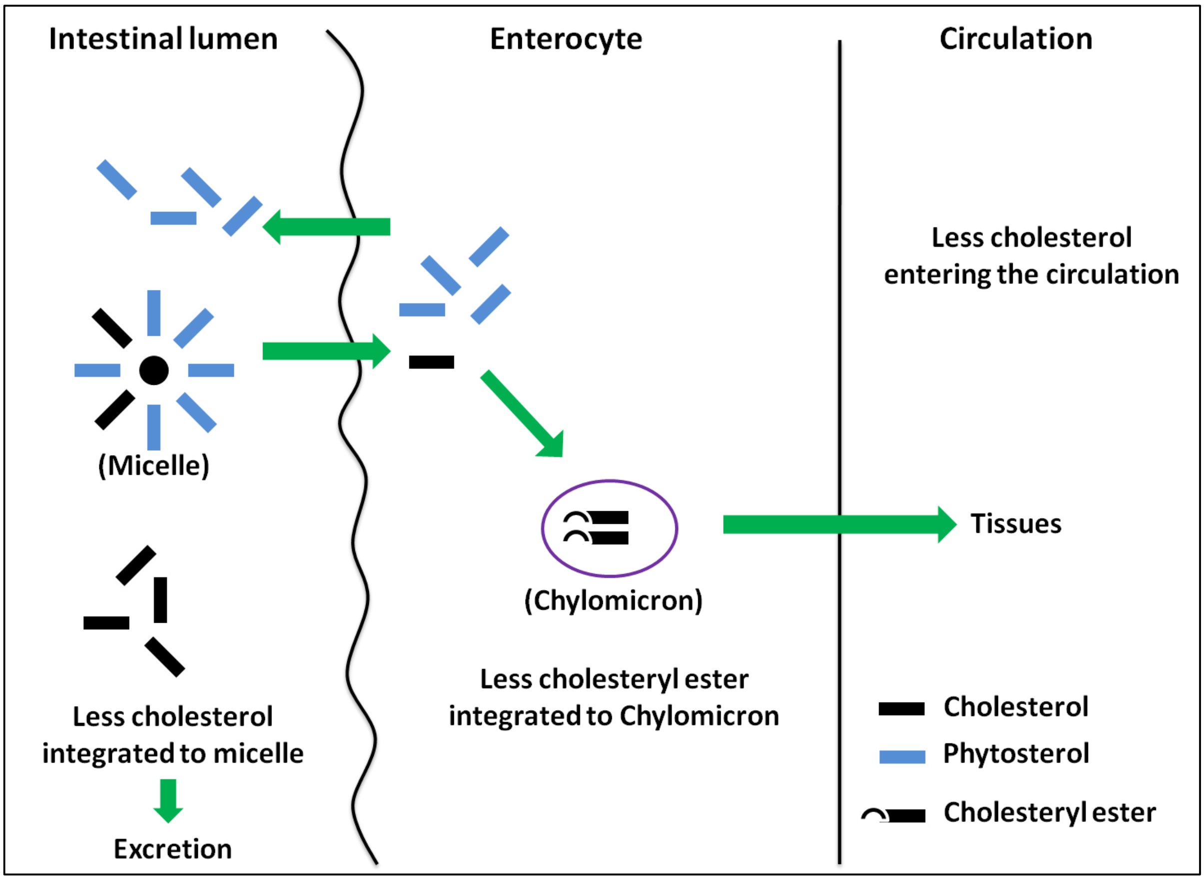

Fig. 3: Lowering of serum cholesterol levels due to the effect of phytosterol on intestinal cholesterol absorption [17]

As reported by Plat et al. 2005, when products enriched with plant sterols/stanols are taken between 2 to 2.5 g/day, LDL cholesterol levels in the plasma decreased by 10% to 14%, with no side effects observed [18]. In another study by Mensink et al. 2010, serum LDL cholesterol levels decreased linearly up to 17.4% when plant stanols up to 9g were utilized on a daily basis [19]. In a study by Rouyanne et al. 2014, it was found that the plant sterols decreased LDL cholesterol concentrations in a dose-dependent manner. Moreover, increased intake of plant sterols upto 3g per day led to lowering of LDL cholesterol levels by 12% [20]. There are limited evidences indicating that effectiveness in lowering cholesterol levels are not affected by use of different sources of plant sterols. A study involving comparison of LDL cholesterol lowering effect between soybean oil, tall oil or a mix of tall and rapeseed oil as the sources of plant sterols was done by Clifton et al. It was concluded that after three weeks of 1.6g per day intake followed by three weeks of 3g per day intake led to 7-11 % decrease in cholesterol levels, commensurable amongst the three sources [21]. Recently, the development of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors is of important consideration. The role of PCSK9 gene in hypercholesterolemia was first discovered by Abifadel et al. He studied that missense mutations in the PCSK9 was responsible for autosomal hypercholesterolemia, which is characterized by increase in the LDL-cholesterol levels [22]. At this point, due to the lack of definitive data, it can be suggested that phytosterol supplements efficiently decrease plasma LDL cholesterol levels along with influencing PCSK9 expression (Fig. 4) to decrease cholesterol absorption by intestine [24]. PCSK9 inhibitors prove to be a compelling agent to reduce LDL-Cholesterol and have led to a new generation of cholesterol lowering therapies. As far as the current evidences from various clinical studies, it was summarized that on consuming around 2g of phytosterols per day can reduce the LDL-cholesterol levels significantly.

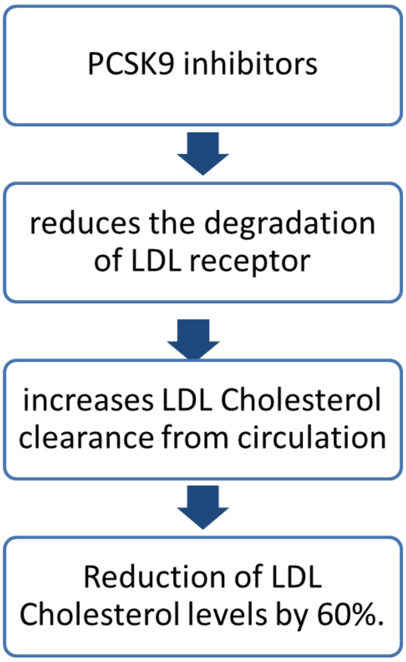

Fig. 4: Role of PCSK9 inhibitors in reducing LDL cholesterol levels [23]

The National Cholesterol Education Program which is managed by the National Heart, Lung and Blood Institute, a division of the National Institutes of Health with a goal to reduce increased cardiovascular disease rates due to hypercholesterolemia in the United States of America, recommends phytosterol supplementation of 2g per day. The clinical and safety testing of phytosterols is of importance, although sufficient evidence is present to enhance usage of phytosterols in patients with high LDL cholesterol, with a variety of plant sterol supplements already being marketed for use to reduce LDL cholesterol levels.

FLAVONOIDS

Flavonoids belong to the phytochemical group of Polyphenols. Flavonoids are natural substances having phenolic structures and are abundantly found in foods and beverages of plant origin, such as fruits, vegetables, tea, cocoa and wine [25]. Flavonoids are classified into flavonols, flavones, flavanols, flavanones, anthocyanidins, and isoflavonoids [26]. According to epidemiological studies, risk of heart diseases can be decreased when flavonoid-rich diets are consumed [27]. Flavonoids are proposed to lower serum LDL cholesterol owing to their antioxidant capacity with respect to Copper-triggered LDL oxidation [28]. Copper is a free radical and is involved in the formation of reactive oxygen species that oxidizes LDL [29]. The oxidized low-density lipoprotein (LDL) is a potentially harmful as it moves rapidly into arterial walls and swells them with cholesterol [30]. Flavonoids are antioxidants that may affect the initial steps in the pathogenesis of atherosclerosis as they chelate the copper ions and prevent them from oxidizing LDL (Fig. 5) [29,31,32].

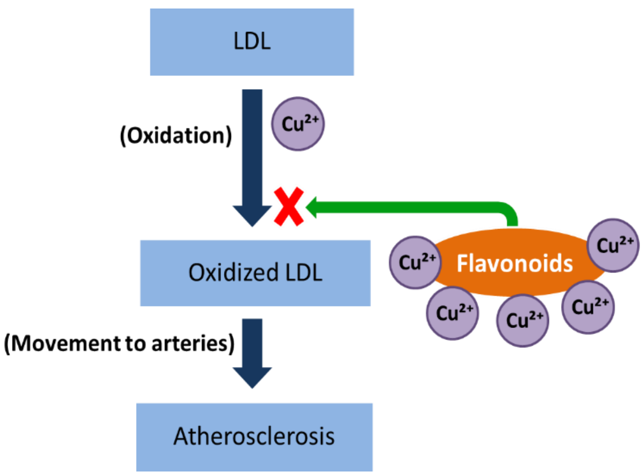

Fig. 5: - Role of flavonoids in preventing atherosclerosis [29,31-33]

Even though there exists evidence of flavonoids in improving cholesterol in various animal models, the mechanism through which lipid profile is improved in humans in unclear [34]. It is also demonstrated that Isoflavones, flavones, and flavanones decrease blood cholesterol levels by two means, i.e., inhibiting cholesterol synthesis and increasing expression of LDL receptors [35]. Various meta-analyses of clinical trials and cross-sectional studies have indicated that a variety of flavonoids- in food sources or supplements are effective in improving LDL cholesterol levels. For example, a meta-analysis on effects of cocoa products or dark chocolates on serum lipids was conducted by Tokede et al. Cocoa products, which contain plant phytochemicals, are rich in flavonoids. The study proposed that the significant reduction in LDL cholesterol and total cholesterol levels after intervention of cocoa products/dark chocolates may be linked to the flavonoids present in them [36]. Another meta-analysis done by Zhuo et al., concluded that on consumption of soy protein, having a high isoflavone content, lead to hypocholesterolemic effects, the intensity of which was stronger than in the same diet with a low isoflavone concentration [37]. Similar results were obtained by Zhan et al. wherein 23 randomized control trials were meta-analysed and Soy protein with isoflavones was observed to decrease plasma total cholesterol, LDL cholesterol, triglycerides and a concomitant increase in HDL cholesterol, though the effects were linked to the duration of intake, sex and the initial serum lipid levels of the subjects [38].

Conversely, few interventions demonstrated less or no improvement in cholesterol levels on intake of selected flavonoids. A meta-analysis done by Hooper et al. shows that the epidemiological results on the effects of flavonoids on cardiovascular system are somehow mixed [39]. As far as the interpretation for the hypocholesterolemic effects of flavonoids go, only cocoa products and soy have remained the mainstream focus of attention. Although studies indicate a possible relation between flavonoid intake and blood cholesterol levels, but the availability of data on effectiveness of the sub-classes is less. Further studies and clinical trials are required to assess the effectiveness of other subclasses of flavonoids in decreasing blood cholesterol levels.

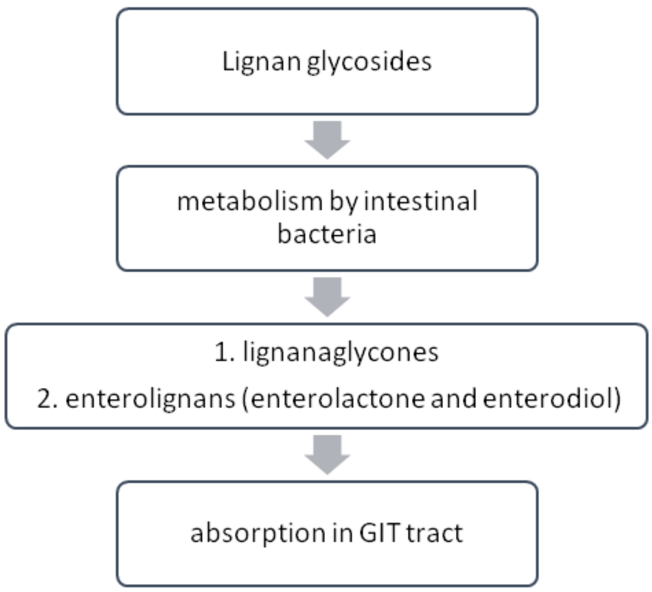

Fig. 6: Lignan metabolism [44,45]

LIGNANS

Lignans are a group of phytochemicals belonging to Polyphenols and are widely distributed in plants. Lignans are found in fruits and vegetables, legumes, whole grain cereals and oil seeds [40]. The seed of flax plant is called flaxseed. Flaxseed is particularly the richest known source of lignans with secoisolariciresinol diglucoside (SDG) being the principal lignan compound [41,42]. Lignans are present in plants in two forms – (i) aglycones (without sugars) and (ii) glycosides (with sugars) (Fig. 6) [43].

Similarly, the lignan glycoside present in flax, i.e., secoisolariciresinol diglucoside (SDG) is hydrolyzed by gut microbes to lignan aglycones and then to enterolignans (Fig. 7) [46].

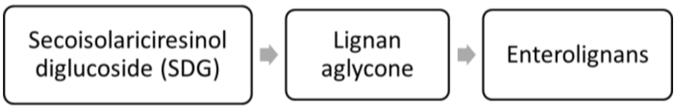

Fig. 7: Bacterial metabolism of SDG in the gut [46]

The levels of enterolignans in the blood and urine are used as biomarkers for plant lignan intakes, while the biochemical properties of enterolignans in reduction of blood LDL levels is still unclear [45, 47].

It is observed that many factors affect the efficiency of the conversion steps, and differs from person to person [44]. Although lignan metabolism in the tissues is regulated by genetic factors, these are not well understood [48]. Human and animal studies have indicated that SDG's cholesterol lowering ability can be linked to decreased absorption of circulating cholesterol and increased biliary excretion. Further, SDG decrease oxidative stress due to their advanced anti-oxidant defences [49].

A study done by Fukumitsu et al. demonstrated that moderately hypercholesterolemic men showed a significant decrease in LDL/HDL ratio with no adverse effects being reported by the subjects on taking 100mg SDG for a period of 12 weeks [50]. A clinical trial conducted by Zhang et al. concluded that plasma cholesterol levels were significantly lowered in hypercholesterolaemic subjects on intake of dietary SDG-rich flaxseed extract. However, the effect produced was in a dose-dependent manner. Further, the subjects were entirely Chinese who would be more genetically homogenous [42]. The available evidences show promise of the ability of flaxseed in decreasing LDL cholesterol levels; however, the effects are dependent on sex, profile/type of subjects and dose-dependent relationships. Further studies should be undertaken to explore the efficiency of flaxseed in lowering cholesterol levels in men and women and hence in prevention of hypercholesterolemia.

Table 1: Sources, proposed mechanism and the inference drawn from studies relevant to lowering LDL cholesterol for the four phytochemicals.

Phytochemical	Plant sources	Proposed mechanism to reduce LDL levels	Inference from the studies	Ref.
Indoles	Broccoli, cabbage, Brussels sprouts, cauliflower, turnips.	Inhibitors of ACAT activity	Further confirmatory studies required.	[8,51]
Phytosterols	Legumes (cereals, and seeds), broccoli, almonds, cauliflower, carrots, avocado, oranges, apples, and oils.	Inhibiting cholesterol absorption in the intestine	Sufficient evidence is present to enhance usage of phytosterols to lower LDL levels.	[15,52]
Flavonoids	Beverages (green tea, cocoa, coffee, red wine), fruits (berries, apple, citrus), and vegetables (onions, hot peppers, broccoli, snap beans, kale, and lettuce)	Antioxidant activity with respect to oxidation of LDL by Copper ions	Less data about the effectiveness of sub classes is available.	[28, 53, 54]
Lignans	Oilseeds (flax, soy, rapeseed, and sesame), whole-grain cereals (wheat, oats, rye, and barley), legumes, various vegetables and fruits (particularly berries), beverages (coffee, tea, and wine).	Reducing the absorption of circulating cholesterol and increasing biliary excretion.	Although, there is promising evidence of their ability to decrease LDL cholesterol levels, further studies are required to assess their efficiency without any dependency on the profile of the subject.	[49,55]

CONCLUSION

Hypercholesterolemia is a major factor in cardiovascular diseases. Various literature works illustrate that diets having high content of plant-based foods prove to be protective against various cardiovascular diseases. Through the employment of phytochemicals, which are found in plants, the cholesterol levels in blood can be lowered. The paper provided brief aspects of 4 types of phytochemicals namely, indoles, plant sterols, flavonoids and lignans (Table 1). The available non-clinical and clinical data was presented that illustrate the beneficial aspects of these phytochemicals. These phytochemicals utilize their anti-oxidant properties in treating various chronic diseases, of which cardiovascular diseases form a major part. It is recommended to eat more fruits and vegetables, since they contain various essential antioxidant phytochemicals. As outlined in this paper, these phytochemicals show promise in lowering blood cholesterol levels, even though there exists some contradictory and inefficient results. Further research studies are required to fully illustrate the effectiveness of these phytochemicals. Various mixtures of phytochemical extracts can then be employed as interventions in reducing blood cholesterol levels.

ETHICAL STATEMENT

No ethical issue to be declared

COMPETING INTERESTS

No conflicts of interest

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