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Contrasting actions of various antioxidants on hyperlipidemia: A review and new concepts

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ABSTRACT

Hyperlipidemia can lead to disorders that result in the onset of various diseases, including cardiovascular diseases which are the leading cause of death in many industrialized countries. Antioxidants are recommended in the treatment of various diseases, particularly atherosclerosis. However, the results of the studies are inconclusive and do not provide strong evidence that antioxidants have a substantial effect on disease. From the results of the studies presented in this paper it might be concluded that although antioxidants might be beneficial in patients with atherosclerosis or other cardiovascular diseases, however, single or even combination of a few antioxidants are not reliable agents for this purpose. This might be due to the complexity of free radicals which are produced and work as a continuous chain. It is known that after scavenging electron, if an antioxidant is not restored by the following antioxidant in the chain, it usually changes to a pro-oxidant. In this situation, the final effect of such supplementation would be no or a damaging effect. In this review study, other than presenting and discussing the studied antioxidants on hyperlipidemia and cardiovascular diseases, the possible reasons for the opposing actions of different antioxidants are discussed in detail.

Key words: Antioxidants, Hyperlipidemia, Medicinal herbs, traditional medicine

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INTRODUCTION

Hyperlipidemia has been shown to contribute in development and severity of atherosclerosis and cardiovascular diseases. The level of cholesterol transporting by lipoproteins like chylomicrons, the very-low-density lipoproteins (VLDL) and the low density lipoproteins (LDL), is a risk factor for the incidence of cardiovascular disease [1].

Lipids in the cell membrane, act as energy storage, additionally, act as hormones and secondary messengers. Plasma lipid concentrations at any time reflect the balance between production, storage and consumption. Cardiovascular diseases are considered as the leading cause of death in many industrialized countries [2]. The prevalence of hyperlipidemia in the world is 15.2% [3]. Hyperlipidemia as a major risk factor for cardiovascular system directly or indirectly increases the production of oxygen free radicals and thus the progress of atherosclerosis plaques causing cardiovascular and of coronary artery atherosclerotic [2, 4].

Free radicals are considered as constant threats to the human bodies [5]. Free radicals are wide groups of highly reactive molecules which may cause damage to cell structures. Reactive oxygen species (ROS) are considered as the most abundant free radicals which are usually formed as natural byproducts of normal metabolism in the body. ROS have crucial role in homeostasis and cell signaling [6].

Free radicals are present and produced in many chemical configurations, shapes and sizes. They all have high

appetite to capture electrons and stealing them from any nearby substances. Free radicals can damage the instructions of DNA or oxidize the molecule of circulating low-density lipoprotein (LDL), making it suitable to be trapped in an artery wall [7].

If we consider that free radicals can accelerate atherosclerosis, hence antioxidants should be able to prevent atherosclerosis [8,9]. However, some large clinical trials have declared that antioxidants have no positive effect and even sometimes destructing effects have been observed. In contrast, a lot of medicinal plants have been shown to possess antioxidant activity and seem to be effective substances and good source for new drugs [10, 11]. Herbs have a long history of use [12] and most of them have few side effects [13]. These substances in addition to hyperlipidemia, are used in prevention [13,14] or treatment [15,16] of other cardiovascular disorders [17,18], as well as in many other incurable diseases like diabetes [19,20], hypertension [21,22], ulcers and burns [23,24], bacterial diseases [25,26], cancer [27,28] or parasitic infections [29,30]. Herbs can also confront the toxic effects of other drugs [31,32]or toxins [33,34].

In this review study, other than presenting and discussing the studied antioxidants on hyperlipidemia and cardiovascular diseases [35,36], the possible reasons for the opposing actions of different antioxidants are discussed in detail.

The role of antioxidant supplementation on atherosclerosis and heart disease

The role of vitamins C or E, beta-carotene and other complementary antioxidants against heart disease and stroke are not as they were hoping for. Large vitamin E trials on patients with coronary disease or at high risk for it, have shown no benefit. In a large study, about 40000 healthy women were administered placebo or 600 IU of vitamin E every other day. The incidence of cardiovascular events was not significant different control group and those took vitamin E for 10 years. However, there was 24 percent reduction in total cardiovascular mortality which may represent an important outcome [37].

In another study, the rate of cardiovascular events was not different in placebo (20.6 percent and vitamin E (21.5 percent) groups, However, the participants who took vitamin E had higher risks of heart failure and hospitalization for heart failure [38]. In another trial, the results showed no preventive effects after more than three years consumption of vitamin E among heart attack survivors [39] Beta-carotene, which is an antioxidant, also did not show any significant effect against heart disease or stroke [40].

In contrast to the above mentioned papers, in a recently published trial in Middle East, vitamin E resulted in a significant reduction in coronary heart disease among people with type 2 diabetes mellitus [41]. Notably, different isoforms of tocopherol (vitamin E isoforms) have shown contrasting effects on lung function this study demonstrated that higher level of serum alpha tocopherol was associated with higher spirometric parameters, however, high level of serum gamma tocopherol was associated with lower spirometric parameters. The same results may be achieved in hyperlipidemia [42].

In antioxidant combination studies the results are complicated, too. In French, 13,000 people who took a single daily capsule of placebo or the one containing 120 mg vitamin C, 30 mg vitamin E, 6 mg beta-carotene, 20 mg zinc and 100 mg selenium for more than seven years showed no significant effect on overall rates of cardiovascular disease [43]. In another study the combination of vitamin C, vitamin E, and/or beta-carotene showed the same effect as a placebo on coronary revascularization, stroke, myocardial infarction or cardiovascular death [44].

RESULTS

Effects of medicinal plants with antioxidant activity on hyperlipidemia

Recently a rapid rise is seen in the use of medicinal plants for the treatment of hyperlipidemia which may indicate that botanical supplements can prevent atherosclerosis [1,45]. The anti-hyperlipidemic activities of plants have been evaluated and confirmed in a lot of animal Models, and human beings. Some clinical trials have also confirmed that foods rich in antioxidants may play an essential role in the prevention of cardiovascular disease [46,47]. Consumption of Cereals, plant sterols and stanols as well as viscous soluble dietary fibers is recommended. Hence the information on some plants which their antioxidant and hypolipidemic activities have been confirmed are presented in table 1.

Table 1. Medicinal plants with antioxidant activity used in hyperlipidemia

Row	Scientific name of Plant	Therapeutic effect	References
1	*Amirkabiria odorastissima Mozaffarian*	Reducing blood lipids in hypercholesterolemic rabbit model	[48]
2	*Rheum ribes* L	Stimulating liver and gall bladder, regulation the blood cholesterol .In clinical studies, consumption 27 gram of stem of *Rheum ribes* L for four weeks caused the decrease in cholesterol and LDL.	[49]
3	Pistacia atlantica	Feeding 20 percent of the Pistacia atlantica in period 3 weeks led to reduction in cholesterol- LDL	[50]
4	*Allium sativum* L.	Consumption of garlic and the garlic coated tablets caused the decrease in cholesterol and LDL . Garlic caused the decrease in formation of Atherosclerosis.	[51,52]
5	Guggul (*Commiphora mukul*)	Receiving 100 mg daily for 12 weeks Guggul caused the decreased total cholesterol to the amount of 12. 7 percent , LDL 12.7 % , triglycerides 12% and the ratio of cholesterol to LDL decreased about 11.1 %.	[53]
6	*Trigonella foenum graecum* L.	Consumption of a warm extraction of plant for 2 months caused the decrease in serum triglycerides.	[54]
7	Red yeast rice	Stimulating blood cycle and digestion by thought-provoking secretion and increase HDL and reduce triglycerides and LDL .	[55]
8	*Cynara scolymus*	Stimulating the liver and gallbladder and bile secretion and is prescribed to reduce cholesterol levels. Improves digestion problems due to lack of bile secretion and increased secretion of bile to help digest fats. Inhibit cholesterol synthesis in the liver cells and protects the liver from chemical toxins damage.	[56]
9	*Cyamopsis tetragonoloba (*Guar gum)	Reduce intestinal absorption of fat in food and fecal steroid excretion and bile production increased by using this plant.	[57]
10	Oat	Leading to lower LDL cholesterol levels and inhibiting LDL oxidation and antioxidant properties which are dose dependent.	[58]
11	L-cavanin	Alfalfa seeds reduce blood cholesterol levels. Regular use of old alfalfa seed for one year by monkey, reduce cholesterol levels and no side effects from it yet Report.	[59]
12	*Silybum marianum* L.	LDL cholesterol levels were reduced by 10%, LDL / HDL ratio improves and also reduces triglyceride levels.	[60]
13	Dietary fiber	Effects of dietary fiber on blood lipid dropping in both laboratory and clinical research has proven.	[61]
14	*Glycine max* L.	Medicinal plant Silybum marianum seed extract (silymarin) is an herbal remedy to lowering blood cholesterol in patients with hypercholesterolemia. Silymarin also reduces blood cholesterol and increase the HDL.	[62]
15	*Juglans regia*	Anti-lipid effects of walnuts in humans has been demonstrated.	[63]
16	*Brassica napus L*	Cooked turnip extract decrease triglycerides, cholesterol, LDL-cholesterol and the level of HDL-Cholesterol increases.	[64]
17	Citrus extracts	Short-term and long-term consumption of grapefruit, orange and pineapple (citrus) on lipids and lipoproteins were determined in normolipidemic mice. In short term period, plasma triglycerides were reduced with consumption pineapple and grapefruit, but did not change the amount of total cholesterol and VLDL. Citrus fruits such as orange juice include an excellent food source of hydrophilic and lipophilic phytochemicals. Pectin is a soluble fiber found in citrus fruits that are capable of binding and uptake of bile acids and has the ability to form high viscosity solutions. This increases the viscosity of gastrointestinal tumors. Finally, the level of total cholesterol improved in patients hypercholestrolemic.	[65,66]
18	*Solanum lycopersicum* & *Solanum Melongena*	Tomatoes, nightshade and husk tomato contain lycopene, which is effective in the treatment of hypertension and reduction the risk of heart disease. Because lycopene and fiber prevents bad cholesterol of blood and possibly increased wasting by releasing of cholesterol and thereby reduces blood cholesterol levels. A Glycoalkaloid steroid in tomatoes reduces the low-density lipoprotein cholesterol, but does not cause the change the high-density lipoprotein cholesterol concentrations. The fruit of this plant (husk tomato) contain ascorbic acid, citric acid and sugar and vitamin C content of this plant is about twice comparison the lemons. Fruit of Physalis alkekengi in traditional medicine have been prescribed orally as a diuretic and to treat kidney stones and jaundice. Most plants in this family such as eggplant, reduce blood cholesterol levels, this effect was not only due to niacin (a powerful antioxidant), but also because of their phytotrines (phenolic compounds, acids cafic and cholovegeniac) is in addition to the alkaloid, inhibits cholesterol synthesis.	[67-69]
19	Ginseng	Daily intake of 150 mg per kg body weight of ginseng extract for 6 weeks in rats reduced 40% cholesterol.	[70]
20	*Brassica Oleraceae Italica*	Broccoli sprout powder has a positive effect in improving blood lipid levels in diabetic patients. So that daily consumption of 10 grams of broccoli sprouts for 4 weeks caused a significant 13.5% reduction in triglycerides and a significant increase in HDL-C in patients with type 2 diabetes is. The 12.2% decrease in total cholesterol at the end of four weeks, a significant reduction occurred in the ratio of total cholesterol to cholesterol- LDL, cholesterol - LDL to cholesterol-HDL.	[71]
21	*Olea europaea*	Olive oil consumption increased HDL, decreased LDL and cholesterol, reducing triglycerides and LDL-cholesterol ratio.	[72]

22	*Sesamus indicum*	Daily consumption of 30 grams of sesame oil for 6 weeks caused a significant reduction in total cholesterol, LDL, fasting blood glucose and glycosylated hemoglobin in type II diabetics.	[73]
23	*Citrus limetta*	Studies show that rats fed lemon peel have concluded the lower level liver and plasma cholesterol, which suggested this decrease is related to the flavonoids.	[74]
24	S*accharum officinarum*	Hamsters fed policosanol revealed 25-15% reduction of serum total cholesterol and increased HDL-Cholestrol levels by as much as 16.8 to 7 percent.	[75]

DISCUSSION

Antioxidants are important part of diets for patients with hypercholesterolemia [76]. However, the results of the studies are inconclusive and do not provide strong evidence that antioxidants have a substantial effect on disease. From the results of the studies presented in this paper it might be concluded that although antioxidants might be beneficial in patients with hyperlipidemia or other cardiovascular diseases, however, single or even combination of a few antioxidants are not reliable agents for this purpose [37-44].

Free radicals have been shown to contribute to a wide range of complications including atherosclerosis [77,78]. diabetes mellitus [79,80], cognitive and other neurological disorders [81-87] and infectious diseases [88-96]. The results of preclinical and clinical trials, especially, the results of cohort studies do not show that all compounds with antioxidant activities will definitely fix the problem. Some scientists believe that antioxidants do not exert benefit when they are prepared synthetically or when taken out of their natural context [37-44].

Abundant evidence suggests that consumption of medicinal plants, whole grains, vegetables, and fruits, rich in antioxidants provide protection against these complications [97-100]. They possess a wide variety of phytochemicals with antioxidant activities including flavonoids, tocopherols, tannins, anthocyanins, carotenoids, as well as vitamins C and E [101-105]. All of these have antioxidant activities which can help prevent atherosclerosis. However, they have some other compounds which may act by various mechanisms to reduce cardiovascular diseases [106-108].

Polyphenols donate phenolic hydrogen atoms to free radicals and inhibit the oxidation of lipids and proteins. Flavonoids decrease the apo B secretion in hepatocytes by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA). Tannins enhance the synthesis of nitric oxide, which relaxes the vascular segments. Anthocyanins suppress the genes involved in proliferation, angiogenesis and inflammation. They also inhibit oxidation of low density lipoproteins. Vitamins C and E prevent membrane peroxidation by scavenging free radical species [109,110].

Medicinal plants with these and some other compounds as well as antioxidant activities have been shown to be effective against a wide range of diseases [111-115]. The reason for contrasting actions of different antioxidants on oxidative stress induced complications is an important question which should be answered.

Free radicals are substances which come in a wide variety of configurations, shapes and sizes. They have appetite to steal electrons from any nearby substances. However, this happens as redox reaction or oxidation-reduction reaction. Redox reaction has some similarities to acid-base reaction. Redox reaction is a reaction which causes transfer of electron between different species. Reduction refers to the gain and oxidation refers to the loss of electron. Redox reaction, the same as acid-base reactions, is a matched set. It means that we have an oxidation reaction and a reduction reaction which happen at the same time [6,116].

The balance between generation and elimination of free radicals is maintained by several complex mechanisms. Dysfunction of these mechanisms usually leads to alterations in cellular redox status. An increase in production of free radical or a decrease in the scavenging of free radical disrupts redox homeostasis, leading to oxidative stress. Increase in oxidative stress can cause a variety of pathologic conditions including cancer, neurodegenerative diseases, and aging [117,118]. Excessive free radicals constantly attack DNA, proteins and lipids, leading to severe oxidative damage [119,120]. The presence of complex antioxidants, but usually not one or two, will scavenge the free radicals at various stages [6,7].

A redox reaction or oxidation-reduction reaction is comprised of two parts, in which an oxidized half and a reduced half, and usually occur together. The oxidized half losses electrons while the reduced half gains electron. This usually continues, making a chain of redox reactions.

From the literature review it might be conclude that the medicinal plants fruits and vegetables are nearly almost beneficial, but this is not the case for diet supplementations. The reason is not established yet, however, in the diets and medicinal plants, there are complex of antioxidants working as a continuous chain, while supplementation is

usually given using one or two antioxidants. Therefore, the antioxidant chain is not completely available [6,7]. It is known that after scavenging free radicals, if an antioxidant is not restored by the following antioxidant in the chain, it usually changes to a pro-oxidant. In this situation, the final effect of such supplementation would be no or a damaging effect [121]. This may explain that why in antioxidant therapy, complimentary antioxidants cannot always substitute the medicinal plants, fruits and vegetables high in antioxidants.

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