REVIEW ARTICLE

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Fruit Flavonoids and Cardiovascular Health

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Fruits and vegetables have been used as medicinal agents because of their health promoting properties attributed by different compounds, which primarily includes flavonoids. Flavonoids, the secondary polyphenols have been suggested to prevent atherosclerosis by its antioxidant property. Oxidation of low density lipoprotein may play a significant role in atherosclerosis. Various flavoniods in different fruits such as catechin, myricetin and quercetin (grapes); tannins and anthocyanins (pomegranate); quercetin, catechin and phyloridizin (apple); hesperedin and naringenin (citrus fruits); myricetin and kampferol (berries) are considered as potent antioxidants of low density lipoprotein.The status of antioxidants in such fruits is reviewed in detail.

All fruits that contains one or more substances with physiological and biochemical functions, which benefit human health, are considered as functional foods as reported by Ferrari and Torres[1]. Fruits and vegetables have been used as a medicinal agents, their health promoting properties have been attributed by modern research to several different compounds such as terpenoids, lignans, polyphenols, carotenoids, saponins, sterols, vitamins. Among them however, the flavonoids are in foreground because of their biological properties as reported by Spignoli[2].

Flavonoids, a group of phenolic compounds found naturally in fruits, vegetables, nuts, flowers, seeds and bark are an integral part of the human diet. Mojzisova and Kuchta[3] have been reported that flavonoids exhibit a wide range of biological effects including antiinflammatory, antiallergic, antiviral, anticarcinogenic, antiischemic, antiplatelet, antilipoperoxidant or gastro protective action. Furthermore flavonoids are potent antioxidants, free radical scavengers, and metal chelators and inhibit lipid peroxidation. Oxidation of low-density lipoprotein plays a significant role in atherosclerosis.

Atherosclerosis and coronary heart diseases are associated with elevated levels of cholesterol in low-density lipoproteins, circulating in blood. It was reported by Frankel *et al.*[4] that oxidation of LDL may play a significant role in atherosclerosis. A reduced incidence of coronary heart diseases and other vascular diseases is well related to a high dietary intake of flavonoids from fresh fruits and vegetables.

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Role of fruit flavonoids in prevention of atherosclerosis:

Wang *et al.*[5] reported that fruits and vegetables provide protection against diseases, including cancer, cardiovascular and cerebrovascular diseases, that has been attributed to the various antioxidants contained in them. Fruits and vegetables contain many different antioxidant components. Majority of their antioxidant capacity may be from compounds other than vitamin C, vitamin E or β-carotene. For example some flavonoids (including isoflavones, flavonones, anthocyanins, catechins and isocatechins) that are frequent components of the human diet demonstrated strong antioxidant activities as reported by Hanasaki *et al.*[6].

The beneficial health effects attributed to the consumption of fruit and vegetables are related, at least in part, to their antioxidant activity. Of special interest is the inverse relationship between the intake of daily nutrients rich in polyphenols and cardiovascular diseases. This effect is attributed to polyphenols ability to inhibit LDL oxidation, macrophage foam cell formation and atherosclerosis as reported by Aviram *et al.*[7]. This review focuses the effects of five different common fruits on antiatherosclerosis property.

Grapes (*Vitis vinifer*, Family- Vitaceae):

Grapes are ancient edible fruit within the Vitaceae family. The major species currently consumed is *Vitis vinifera* and most red wines are made from this variety only. The French paradox that represents the low incidence of cardiovascular events inspite of high unsaturated fat, was attributed to the regular drinking of red wine in southern France as reported by Renaud and Lorgeril[8]. Wine has been part of human culture for over 6000 years, serving dietary and socio-religious functions.

The beneficial effect of red wine consumption against the development of atherosclerosis was attributed to the antioxidant activity of its flavonoids. According to Hertog *et al.*[9], red wine contains flavonoids, quercetin and myricetin (10 to 20 mg/l), catechins and epicatechins (up to 270 mg/l) and also polymeric anthocyanins such as cyanidin, delphinidin, peonidin, petunidin, malvidin, pelargonidin and reservetrol.

A number of epidemiological studies have suggested a special protective effect of red wine, and this hypothesis has been supported by experimental research. Bentzon *et al.*[10] has recently show that red wine flavonoids protect LDL from oxidation *ex vivo* and inhibit smooth muscle cell proliferation *in vivo*. Both properties could mediate anti atherogenic effect.

In red wines, the dominant component catechins, epicatechins and gallic acid were particularly active as antioxidants in inhibiting LDL oxidation *in vitro* as reported by Frankel *et al.*[4] Catechin oligomers and procyanidin dimers (B2 B3, B4, B6, and B8) and trimers (C1 and C2) extracted from grape seeds were also shown to posses significant anti oxidant activity towards LDL oxidation *in vivo* according to Teissedre *et al.*[11].

The most valuable flavonoids in grape seed extracts are procyanidolic oligomers (also known as proanthocyanidins). Grape seed extract may help to reduce the risk of heart attack and stroke with its potent antioxidants, which is believed to prevent the plaque development that can clog arteries. Proanthocyanidins may function as effectively as aspirin in keeping blood cells from sticking together and forming blood clots (called as anticoagulant effect) (www.wholehealthmd.com/refshelf/substances_view/1,1525,793,00.html#What_Is_It).

Phenolic compounds extracted from fresh grapes were able to inhibit significantly the *in vitro* LDL oxidation at micro molar phenol concentration. The antioxidant potency of grape extracts in inhibiting LDL oxidation was in the same order as that of wine. Thus, extracts of grapes exerted between 22 and 60 percent inhibition at 10 μm total phenols as gallic acid equivalents (GAE). Wine tested under the same conditions had antioxidant activities ranging from 27 percent to 65 percent inhibition at 10 μm GAE as reported by Meyer *et al.*[12].

In addition to LDL oxidation, aggregation of LDL is also an atherogenic modification of the lipoproteins, since aggregated LDL is taken up by macrophages by phagocytosis at increased rate, leading to foam cells formation. LDL aggregation can result from interaction between the lipoprotein hydrophobic domains. Flavonoids, which are multidentate ligands, are able to bind simultaneously to more than one molecule on the lipoprotein surface and thus can reduce the susceptibility of LDL to aggregation. Aviram and Fuhman[13] reported that consumption of quercetin and red wine or catechin by mice specimen also resulted in a reduced susceptibility of their LDL to aggregation by 48, 50, or 63 percent respectively in comparison to LDL from placebo treated mice.

Red wine polyphenols do not reduce mature atherosclerosis. This discrepancy is not due to differences in polyphenols profiles between the used wines but due to irregular consumption (50 μg of catechin per day), as reported by Hayek *et al.*[14].

Pomegranate (*Punica granatum*, Family- Punicaceae):

The pomegranate tree has been extensively used as folk medicine in many cultures. Bennasr *et al.*[15] reported that edible parts of fruit (about 50 percent of total fruit weight) comprise 80 percent juice and 20 percent seeds. Fresh juice contains 85 percent moisture, 10 percent total sugars, 15 percent pectin, ascorbic acid, polyphenols and flavonoids. Pomegranate juice was shown to possess an antioxidant activity that was three times higher than the antioxidant activity of the red wine or of green tea as reported by Gil *et al.*[16]. The antioxidant activity was higher in juice extracted from whole pomegranate than in juice obtained from arils only.

Aviram *et al.*[17] has shown that the mechanism for the antioxidant effect of pomegranate juice against lipoprotein oxidation could be related to its capacity to scavenge free radicals. The water soluble fraction of the pomegranate's inner and outer peels but not that of the seeds, where even stronger antioxidants against LDL oxidation than the juice. Pomegranate juice contained a higher concentration of total polyphenols than red wine of other fruit juices. In parallel, pomegranate juice exhibited a very low IC_{50} (the concentration needed to inhibit LDL oxidation by 50 percent) in protection of LDL against oxidation compared with other examined beverages.

Pomegranate juice is the most potent antioxidant against LDL oxidation and this effect could be related to its high polyphenolic flavonoid content as well as to the specific potent flavonoid present in pomegranate juice such as tannins and anthocyanins that include pedunculagin, casuarinin, tellmagradin, gallgyldilacone and punicalin.

Pomegranate juice not only inhibit LDL oxidation but also reduce other related modification of the lipoproteins; that is, its relation to proteoglycan (as analyzed by LDL binding to chondroitin sulfate), and its susceptibility to aggregation (induced by LDL vortexing) as reported by Aviram *et al.*[18]. Inhibition of lipid peroxidation by nutritional antioxidants such as pomegranate juice contributes to the attenuation of macrophage cholesterol accumulation, foam cell formation and atherosclerosis.

Sinzinger[19] reported that platelet activation, additional risk factors for atherosclerosis that is also associated with oxidative stress, was also inhibited by pomegranate juice consumption. According to Aviram[20] this effect may be related to an interaction of pomegranate juice constituents with the platelet surface binding sites for collagen or by their ability to scavenge free radicals and hence to attenuate platelet activation induced by oxidative stress. The potent antioxidative capacity of pomegranate juice against lipid peroxidation may be the central link for the antiatherogenic effects of pomegranate juice on lipoproteins, macrophages and platelets.

Apple (*Malus pumila,* Family- Rosaceae):

Apple has long been used as a symbol of prevention and good health. Apples are widely consumed and are rich source of phytochemicals. Epidemiological studies have linked the consumption of apples with reduced risk of some cancers, cardiovascular disease, asthma and diabetes. In the laboratory, apples have been found to have very strong antioxidant activity, inhibit cancer, cell proliferation, and decrease lipid oxidation and lower cholesterol. Boyer and Liu[21] reported that apples contain a variety of phytochemicals, including quercetin (4.42 mg/100 g), catechin (0.95 mg/100g) and epicatechin (8.14 mg/100g) all of which are strong antioxidants.

According to Arts *et al.*[22] reduced risk of cardiovascular diseases has been associated with apple consumption. The intake of catechin and epicatechin, both constituents of apples were inversely associated with coronary heart disease. Apple catechins may be bioavailable than the catechin and epicatechin gallates commonly found in teas. Mayer *et al.*[23] has shown that apple ingestion led to a decrease in diphenylhexatriene labeled phosphatidylcholine (DPHPC) oxidation (indicator of oxidation), reflecting the apple antioxidant activity *in vivo.*

Breinholt *et al.*[24] reported that quercetin, a major flavonoid in apples, had no effect on lipid oxidation when ingested by rats, suggesting that quercetin alone is not responsible for the apples ability to inhibit lipid oxidation. Other antioxidants including quercetin may contribute to the antioxidant activity of apples. Pearson *et al.*[25] has reported that the addition of various apple juices to an *in vitro* LDL oxidation system reduced LDL oxidation by 9-34 percent.

The observed reduction in LDL oxidation was achieved with only a moderate consumption of daily juice, (375 ml) compared to the amount used in studies with grape juice approximately 2-4 times this amount. Daily consumption of moderate amounts of unsupplemented apple juice reduces *ex vivo* oxidative susceptibility of LDL cholesterol in health, normo-lipedemic men and women. Hyson *et al.*[26] suggested that apple juice constitutes by their *in vivo* effects on LDL properties, may reduce the risk of coronary artery disease.

Citrus fruits (C*itrus spp.* L., Family- *Rutaceae*):

Citrus fruits and juices have long been considered a valuable part of a healthy and nutritious diet and it is well established that some of the nutrients in citrus promote health and provide protection against chronic diseases. Citrus fruits including grapefruit, orange, lemon and lime are consumed not only for its vitamin C content but also for other important nutrients and phytochemicals. Citrus fruits are also rich in flavonoids such as hisperidin, naringenin, quercetin, and myrecetin. In orange fruits, at least 170 phytochemicals have been identified. More than sixty flavonoids in citrus fruit possess a wide range of properties including anti-inflammatory, antitumor and antioxidant activity as reported by Middleston and Kandaswami[27].

Citrus bioflavonoids are bitter tasting flavonoid glucosides including neohesperdin and naringenin; flavanone such as naringin and taxifolin; non bitter tasting flavonoids such as hesperdin, rutoside, sinersetin, nobitetin, tangeretin, poly metholylate flavones, numerous hydroxy cinnamates and atleast 44 different flavone glycosides. Other common flavonoids include catecin, epicatecin, myricetin and kaempferol(www.florahealth.com/flora/home/usa/healthinformation/encyclopedias/citrusbioflavonoids.asp.) Baghurst reported the antioxidant (free radical scaveng-ing) ability of fruits such as citrus is generally high protective against free radical damage to proteins, lipids and DNA, which is an integral part of the body's defence mechanism(http://www.austcitrus.org.au/home/files/Exec Summary -The Health Benefits of Citrus Fruits.pdf). It is possible that at least some of the antioxidants in fruits such as citrus may contribute to enhancing this endogenous antioxidant defence. Vinson *et al.*[28] stated that citrus extract contains flavonoids and ascorbic acid, which are used as synergic inhibitor of *in vitro* cupric ion induced LDL, and VLDL oxidation compared with ascorbic acid or the flavonoids alone.

Naringenin belongs to the class of flavonoids called flavonones and is abundant in citrus fruits as reported by Montanari *et al.*[29]. The role of naringenin and the related citrus flavone hesperedin in the prevention and treatment of disease, with particular interest in the use of these flavonones as antiatherogenic compounds have been reported by Samman *et al.*[30].

Wikox *et al.*[31] stated that flavonoids can be incorporated into lipoproteins within the liver or intestine and subsequently be transported within the lipoprotein particle. Naringenin has also been shown to associate with and penetrate lipid membrane. Therefore flavonoid including naringenin may be ideally located for protecting LDL from oxidation. Naringenin and other citrus flavonoids may be potentially useful as pharmacological agents in the treatment or prevention of atherosclerosis.

Berries (*Rubus spp.*, Family- Rosaceae):

Brightly colored berries are edible fruits that may protect against certain cancers, heart disease and aging (http:/www.driscolls.com/healthDriscollsBerryNutrition ForConsumers.pdf). Redberry fruits such as eiderberry, chokeberry and bilberry have been used in folk medicine in Europe and North America for centuries. Heinonen *et al.*[32] reported that anthocyanins constitute the main group of phenolic compounds in berries. Generally the content of flavonols (quercetin) is higher than flavon-3-ols (catecin and epicatecin) in all types of berries. However in gooseberry, red raspberry and strawberry, the content of flavon-3-ols has been reported to be higher than that of flavonols. Myricetin was detected in cranberry, blackcurrant, cowberry, blueberries and bilberry. Kaempferol was detected only in gooseberry and strawberry as reported by Karenlempi *et al.*[33].

Epidemiological studies prove that drinking tea lowers the risk of heart disease; blueberries may have an equal or greater effect since they have higher flavonoid content than tea. Wilson *et al.*[34] stated that Blackberries, raspberries and strawberries are all good source of antioxidants and potent free radical scavengers. Antioxidant compounds found in blueberries, sweetcherries, strawberries and blackberries may fight arterial diseases by preventing the oxidation of LDL (bad cholesterol). Cranberry extract containing 1,548 mg-galicacid equivalents/liter (initial pH 2.5) affected LDL oxidation induced by 10 μm cupric sulphate as reported by Reed[35].

To conclude, flavonoids, essentially polyphenolic compounds found in fruits play an important role in the prevention of atherosclerosis. Flavonoids show their antiatherosclerosis property through its antioxidant nature of LDL oxidation. The consumption of fruits rich in flavonoids is indispensable to fight LDL oxidation as the intake of fruits may play pivotal role in fighting coronary artery diseases. The fruits of interest studied orient to well known temperate and tropical regions and are highly seasonal. The possibility of dietary flavonoids from rare fruits places challenge in fighting atherosclerosis. So consumption of these fruits keeps healthy heart away from atherosclerosis.

The study of flavonoids is complex because of the heterogeneity of the different molecular structure and the scarcity of data on bioavailability. Further more, insufficient methods are available to measure oxidative damage *in vivo* and the measurement of objective and end points remains difficult. There is a need to improve analytical techniques to allow collection of more data on absorption and extraction. Nevertheless, flavonoids in fruits and vegetables serve as biological agents in preventing atherosclerosis *in vivo* and *in vitro*.

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