Consumption of Tree Nuts in the Prevention of Coronary Heart and Cardiovascular Disease

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Abstract: Emerging research from epidemiologic studies and clinical trials is demonstrating that tree nuts promote satiety and weight maintenance. Moreover, tree nuts contain a plethora of nutrients, natural phenolic antioxidants, and other bioactive compounds (*e.g.*, phytosterols), which are now being recognized for bestowing health benefits. As will be discussed in this review, tree nuts have been linked to improving heart health, lowering low-density lipoprotein cholesterol levels, and reducing inflammation. The strongest evidence that tree nuts are cardio-protective foodstuffs comes from epidemiological observations indicating a consistent and well-defined inverse association between the frequency of nut consumption and development of coronary heart disease, and several short-term clinical trials demonstrating the beneficial effects of nut intake on lipid profiles as well as other intermediate markers of heart disease. In this review research findings from the existing literature published within the last 15 years have been compiled and summarised. Three bases: SCOPUS, Web Science, and PubMed were used for search.

Keywords: Tree nuts, Fatty acids, Phytosterols, Phenolic compounds, Cardiovascular disease.

INTRODUCTION

Cardiovascular disease is a public health problem worldwide with high costs for the management of patients who suffer, so that any strategy for prevention, such as eating foods such as nuts, could be relevant to improving the quality of life of those suffering from these pathologies.

In human nutrition tree nuts are a rich source of healthful lipids, plant protein, minerals, and vitamins, and bioactive phytocompounds. The combination of these beneficial nutrients is most likely responsible for their proposed health benefits. According to O'Neil *et al.* [1] tree nut consumers comprised a lower percentage ($p < 0.0001$) of the population below the estimated average requirement (EAR) for vitamins A, E, and C, folate, calcium, iron, magnesium, and zinc and thus possessed better nutrient adequacy than non-consumers.

Tree nuts are considered as an excellent energy source. With triacylglycerols being the predominate component, the lipid contents in tree nuts vary from 53.5% in almonds to 75.1% in pine nuts [2]. Nuts are generally low in available carbohydrate and glycemic index, ranging from 27.5 g/100 g in pistachios to 12.3 g/100 g in Brazil nuts.

Tree nuts are characterized by a high content of protein [3]. Most tree nuts proteins are rich in arginine. This amino acid can be metabolized by endothelial NO synthase to nitric oxide, an important signaling molecule and a potent vasodilator [4]. A ratio of lysine to arginine in nut proteins generally is lower than that of animal proteins. This ratio is associated with a significantly lower risk of developing hypercholesterolemia and atherosclerosis, which also decreases the risk of cardiovascular diseases [4].

To the most commercially-important tree nuts belong:

- almonds (*Prunus dulcis*, Rosaceae),
- Brazil nuts (*Bertholletia excelsa*, Lecythisaceae),
- cashew (*Anacardium occidentale*, Anacardiaceae),
- hazelnuts (*Corylus avellana* L., Betulaceae),
- macadamia nuts (*Macadamia interfolia*, Proteaceae),
- pecans (*Carya illinoinensis*, Juglandaceae),
- pine nuts (*Pinus spp*., Pineaceae),
- pistachios (*Pistacia vera* L., Anacardiaceae),
- walnuts (*Julans regia*, Juglandaceae).

The aim of this article is to review the role of tree nuts in prevention of cardiovascular disease

1. TREE NUTS AS A SOURCE OF MONO- AND POLYUNSATURATED FAATTY ACIDS

The lipids of tree nuts are generally high in unsaturated fats, with the exception being Brazil and

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E-ISSN: 2410-2822/16

cashew nut oils (Table **1**). Although tree nut oils differed considerably in their levels of individual fatty acids, oleic acid (C18:1 ω-9) and linoleic acid (C18:2 ω-6) are considered as the two predominant ones. The oleic/linoleic (O/L) ratio is greatest in hazelnuts, while the lowest ratios were reported for pine nut and walnut oils. Of particular note is that walnuts are the only tree nut containing a significant amount of α-linolenic acid (C18:3 ω-3).

There is epidemiological evidence that dietary monounsaturated fatty acids (MUFAs) have a beneficial effect on the risk of CHD. Moreover, evidence from controlled clinical studies has shown that MUFAs favorably affect a number of risk factors for CHD, including plasma lipids and lipoproteins, and *in vitro* LDL oxidative susceptibility [11]. MUFAs may decrease platelet aggregation, increase bleeding time, and increase fibrinolysis, thereby protecting against thrombogenesis [12-14].

Several observational and experimental studies show the beneficial effects of omega-3 poly-unsaturated fatty acids (PUFAs) in cardiovascular disease. The results from such studies justify supplementation of omega-3 PUFA in primary and secondary prevention of several clinical conditions, including coronary heart disease, sudden cardiac death and heart failure. [15, 16]. Omega-3 PUFAs may protect against CVD through several mechanisms: acting as an antiatherogenic agent, lowering serum triacylglicerols, lowering blood pressure, improving endothelial function, reducing inflammation, inhibiting platelet aggregation and thrombosis, and decreasing the incidence of arrhythmias [17-19].

2. TREE NUTS AS A SOURCE OF PHYTOSTEROLS

According to literature data, beta-sitosterol is the most abundant sterol in all tree nut types, followed by stigmasterol and campesterol (Table **2**). Phytosterols reduce cholesterol absorption from the gut, due to their structural similarity with cholesterol (Figure **1**). In the last decades, purified plant sterols or stanols have been added to various foods items to obtain functional foods with remarkable hypocholesterolemic activity. A

Table 1: Content of Unsaturated Fatty Acids in Edible Tree Nuts Lipid (g/100 g oil) [5-10]

Nut type	C16:1 ω7	C18:1 ω9	C20:1 ω9	C18:2 ω6	C18:3 ω3
Almond	0.40-0.43	65.70-67.62	-	24.03-24.80	trace
Brazil nut	0.29	29.76-38.36	-	36.84-45.17	0.074
Cashew	0.34	56.87-60.57	0.19	17.03-22.22	0.21
Hazelnut	0.16-0.19	79.57-79.64	0.15-0.16	11.78-12.72	0.08
Macadamia	17.95-20.8	54.1-60.08	2.62-2.53	2.32-3.74	-
Pecan	-	62.36	-	27.69	1.25
Pine nut	0.08	24.82-27.67	1.32-1.38	45.02-46.41	19.28
Pistachio	1.07	55.11-56.75	-	28.56-29.45	0.33-0.37
Walnut	0.07	14.80-16.96	0.19	58.64-63.10	11.67-13.43

Table 2: Content of the Main Phytosterols in Edible Tree Nuts Lipid (mg/100 g oil) [5, 8, 9, 20, 21]

Nut Type	Campesterol	Stigmasterol	β-Sitosterol	Δ5-Avenasterol
Almond	5.50-10.6	5.17-6.59	207-322	43.9
Brazil nut	1.75	8.02	91.4	32.1
Cashew	19.3	1.57	250	16.7
Hazelnut	10.1-11.4	1.85-2.43	155-203	6.16-12.2
Macadamia	7.33-12.3	3.83	151-197	20.8
Pecan	8.20	3.28	167	10.0
Pine nut	32.1	2.75	198	66.2
Pistachio	10.8	1.9	219.6	22.2
Walnut	7.76-8.28	0.60-1.34	143-154	8.60-13.7

daily intake of plant sterols or stanols of 1.6-2g/day is able to reduce cholesterol absorption from the gut by about 30%, and plasma LDL cholesterol levels by 8-10%. Since the action of plant sterols or stanols on plasma LDL cholesterol is additive to that of statins, the former can be used to increase the latter's hypocholesterolemic action in patients needing a marked reduction in plasma LDL cholesterol levels [22-24].

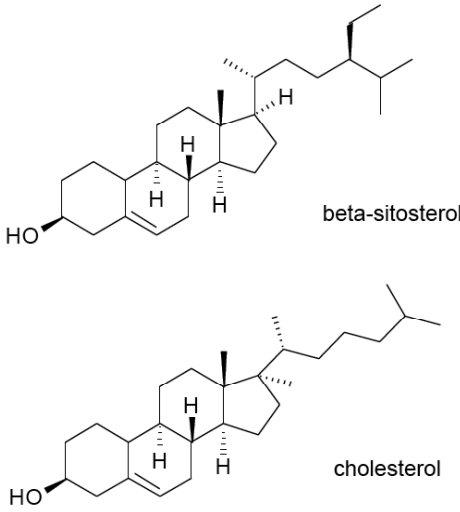
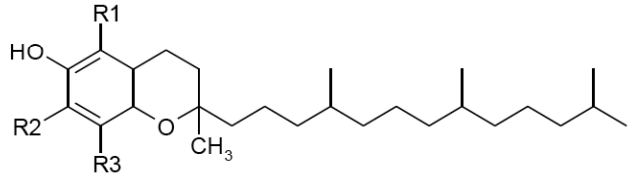


Figure 1: Chemical structure of beta-sitosterol and cholesterol.

3. TREE NUTS AS A SOURCE OF NATURAL ANTIOXIDANTS

The LDL oxidation plays a key role in atherogenesis [25]. In this way modified LDLs are the pathogenesis of atherosclerotic lesions via the formation of foam cells. Oxidized LDLs have been detected in atherosclerotic vessels. They can decrease the bioactivity of nitrogen oxide in endothelial cells, which causes dilation in response to increased blood flow. A large number of epidemiological, case-control, and prospective or prospective cohort studies on the link of dietary antioxidant intake to the reduction/prevention of cardiovascular diseases exist. The impact of antioxidants pertaining to LDL oxidation, which plays an important role in the early atherogenic process, has been confirmed in several studies.

In tree nuts a role of natural antioxidants play tocopherols (lipophilic compounds, Figure **2**) and polyphenols (lipophobic compounds, Figure **3**).



R1	R2	R3	
CH_3	CH_3	CH_3	α-tocopherol
CH_3	H	CH_3	β-tocopherol
H	CH_3	CH_3	γ-tocopherol
H	H	CH_3	δ-tokopherol

Figure 2: Chemical structure of tocopherols.

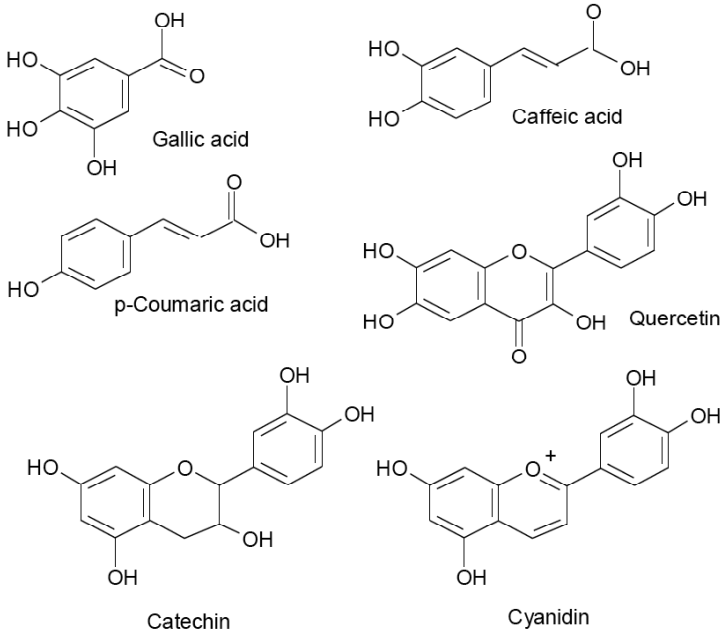


Figure 3: Chemical structure of natural phenolic antioxidants present in tree nuts.

The tocopherol contents of major nut types are summarized in Table **3**. Four tocopherol isomers were reported in all tree nuts at various levels. The predominant tocopherol isomer in tree nut oils is γ-tocopherol, with the exception being almond and hazelnut lipids, which are high in α-tocopherol. The levels of both the α- and γ-isomers are similar in pine nut oil. Worth to be emphasized is information, that one of γ-CEHC, the metabolite of γ-tocopherol [2,7,8-trimethyl-2-(beta-carboxyethyl)-6-hydroxychroman (γ-CEHC)]) may have an anti-inflammatory effect as demonstrated by its down-regulating capacity of cycloxygenase-2 and 5-lipoxygenase [27-29].

The antioxidant properties of tree nut polyphenols were confirmed *in vitro* studies using several chemical methods (Table **4**). The same properties were also observed *in vivo* studies. In human studies consumption of hazelnuts (1 g/day/kg body weight) improved oxidative stress markers [36]. The research of Hudthagosol *et al.* [37] (a randomized, placebo-controlled, crossover trial) with pecan consumption indicated that the bioactive constituents from pecan are absorbable and contribute to the postprandial antioxidant defenses in the human body.

Table 3: Content of Tocopherols in Edible Tree Nuts (g/100 g Nutmeat, Fresh Weight) According to USDA National Nutrient Database for Standard Reference [26]

Nut type	α-Tocopherol	β-Tocopherol	γ-Tocopherol	δ-Tocopherol
Almond	25.63	0.23	0.64	0.07
Brazil nut	5.65	0.01	9.56	0.63
Cashew	0.90	0.03	5.31	0.36
Hazelnut	15.03	0.33	0.00	0.00
Macadamia	0.54	0.00	0.00	0.00
Pecan	1.40	0.39	24.44	0.47
Pine nut	9.33	0.00	11.15	0.00
Pistachio	12.30	0.00	11.15	0.00
Walnut	12.30	0.00	22.0	0.80

Table 4: Antioxidant Potential of the Tree Nuts Confirmed *in vitro* Studies

Nut Type	Conclusions	Reference
Almond	Extracts prepared from whole almond seeds and their brown skins showed antioxidant activity evaluated using a cooked comminuted pork model, a β-carotene-linoleate model, and a bulk stripped-corn oil system. RP-HPLC analysis revealed the presence of caffeic, ferulic, *p*-coumaric, and sinapic acids as the major phenolic acids in the extracts examined.	[30]
Peanut, hazelnut, almond	Roasted skins obtained from the industrial processing of peanuts, hazelnuts, and almonds as well as fractions containing low- and high-molecular-weight bioactives exhibited high total antioxidant capacity, $ORAC_{FL}$, antiradical activity against DPPH radical, and reducing power.	[31]
Almond	Phenolic compounds present in a crude extract of almonds and its fractions, after separation on a lipophilic Sephadex LH-20 column, showed antioxidant and antiradical properties, as revealed following studies using a β-carotene-linoleate model system, the total antioxidant activity method, DPPH radical-scavenging assay, and reducing power evaluation. Results of these assays showed the highest values of antioxidant activity for the tannins fraction. RP-HPLC analysis of a crude extract from almond seeds revealed the presence of vanillic, caffeic, *p*-coumaric, and ferulic acids (after basic hydrolysis), as well as quercetin, kaempferol, and isorhamnetin (after acidic hydrolysis), delphinidin and cyanidin (after *n*-butanol-HCl hydrolysis), and procyanidin B_2 and B_3.	[32]
Hazelnut	The antioxidant activity of a crude hazelnut extract and its fractions was confirmed by the ABTS radical cation and DPPH radical-scavenging assays, reducing power, and β-carotene-linoleate model system. In the extract, five phenolic acids, namely gallic acid, caffeic acid, *p*-coumaric acid, ferulic acid, and sinapic acid, were tentatively identified and quantified, among which gallic acid was the most abundant in both free and esterified forms.	[33]
Walnut	Copper-mediated LDL oxidation was inhibited by 84% in the presence of a walnut extract. Plasma TBARS formation was significantly inhibited by the walnut extracts.	[34]
Almond	Almond-pellicle flavonoids increased the resistance of copper-mediated LDL oxidation *in vitro* and *ex vitro* and acted synergistically with vitamins C and E.	[35]

4. NUTS CONSUMPTION AND CORONARY HEART AND CARDIOVASCULAR DISEASE

Results of numerous investigations suggested that nut consumption might reduce the risk of coronary heart and cardiovascular disease. by improving serum blood lipids [38, 39]. Subjects who consumed tree nuts more than four times per week experienced substantially fewer definite fatal CHD events and definite nonfatal myocardial infarctions, when compared with those who consumed nuts less than once per week [40]. Substitution of energy from carbohydrates by the fat from one ounce was is associated with a 30% reduction in CHD risk [41].

In a prospective cohort study, the inverse association between nut consumption and the risk of CVD mortality among all subjects was observed [42]. In a randomized cross-over clinical trial almond consumption favorably altered the serum fatty acid by increasing total MUFA content. These changes in the fatty acid profile are likely associated with lowered CHD risk [43]. Supplementation of diet of 20 mildly hypercholesterolemic subjects with baru almonds (20 g/day) reduced total cholesterol by 2.4%, LDL-cholesterol by 9.2%TC, and HDL-cholesterol by 8.4% [44]. Brazil nuts intake improved the lipid profile and microvascular function in obese adolescents [45].

The hazelnut-enrich diet after 12 week significantly improved flow-mediated dilation (FMD) in 21 hypercholesterolemic adults participated in a double control sandwich model intervention [46]. In experiment of Li *et al*. [47] increased nut consumption was significantly associated with lower LDL cholesterol, non-HDL cholesterol, total cholesterol, and apolipoprotein-B-100 concentrations. Serum triacylglycerol concentration was reduced by 24% during three-week addition of peanuts to the diet of fifteen normolipidemic adults participated in a crossover intervention [48]. Two servings/day of a pistachio diet, decreased total cholesterol, LDL cholesterol, non-HDL cholesterol, and plasma of stearoyl-CoA desaturase activity [49]. The diet containing whole pecans prevented hyperleptinemia and decreased the content of total cholesterol in blood. Addition of pecan oils to the diet with reduced the level of triacylglycerol in blood [50]. The regular consumption for 5 weeks of walnut-enriched meat decreasd total cholesterol in blood of by 12.8%. and increased concentration of gamma-tocopherol (16.8%) [51]. In overweight adults with visceral adiposity consumption of 56 g of walnuts per day improved endothelial function [52]. The Adventist Health Study found that the greater the consumption of nuts (more than five times a week) decreased the risk fatal heart attack in track six years [53].

The study of Nishi *et al.* [43] revealed that almond consumption altered the serum fatty acids by increasing their total MUFA content. These changes in the fatty acid profile were postulated as being associated with a lower CHD risk.

In the etiology and development of atherosclerosis plaque important role play a chronic inflammation. The activation of the vascular endothelium is an early inflammatory event in the development of atherosclerosis loading to endothelium dysfunction and its consequences [54]. The bioactive compounds present in nuts (ω-3 polyunsaturated fatty acids, dietary fiber, magnesium, L-arginine, and some antioxidants) can protect human against inflammation [55]. According to Jiang *et al.* [56] frequent nut and consumption is associated with lower levels of inflammatory markers.

CONCLUSIONS

In summary, well-designed human intervention studies are steel needed to further validate the health effects of various nuts. Some limitations from previous studies need to be addressed to demonstrate more results about activity of individual bioactive compounds of nuts. It has been suggested that future human studies should address subject characteristics, their health status, and other confounding factors before making any reliable conclusions for the health effects of nuts.

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Received on 29-09-2016 Accepted on 10-10-2016 Published on 18-10-2016

http://dx.doi.org/10.15379/2410-2822.2016.03.02.03