Lead Article

Nuts and legume seeds for cardiovascular risk reduction: scientific evidence and mechanisms of action

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Consumption of tree nuts and legume seeds is associated with a reduction in cardiovascular risk. The reduction in blood lipids and in inflammatory and oxidative processes exhibited by bioactive compounds such as monounsaturated and polyunsaturated fatty acids, fibers, phenolic compounds, tocopherols, phospholipids, carotenoids, some minerals, and arginine, has stimulated research on the mechanisms of action of these substances through distinct experimental approaches. It is, therefore, important to know the metabolic effect of each nut and legume seed or the mixture of them to choose the most suitable nutritional interventions in clinical practice. The aim of this narrative bibliographic review was to investigate the effects of tree nuts and legume seeds on biomarkers of cardiovascular risk, as well as their mechanisms of action with regard to lipid profiles, insulin resistance, arterial pressure, oxidative stress, and inflammation. The findings indicate that a mixture of nuts and legume seeds optimizes the protective effect against cardiovascular risk.

INTRODUCTION

Various factors contribute to the increase in the risk of developing cardiovascular diseases. Obesity is an independent risk factor for coronary artery disease and one of the main risk factors for the development of metabolic syndrome.[1,2] Fat tissue is metabolically active and can trigger a cascade of metabolic reactions that result in insulin resistance, arterial hypertension, dyslipidemia, cancer, osteoarthritis, and microvascular and macrovascular damage.[3–5]

Risk markers are important indicators of subclinical disease and a valuable tool for cardiovascular disease monitoring and prevention.[6] Metabolic markers indicate an increase in cardiovascular risk, particularly in the presence of obesity, because the active metabolism of adipose tissue induces metabolic changes, leading to type 2 diabetes, arterial hypertension, and dyslipidemia. These diseases are characterized by changes in biological markers such as blood glucose levels, insulin resistance, sodium retention, and serum lipoprotein levels.[4,5] Fat tissues induce a significant release of inflammatory cytokines and an increase in the production of reactive oxygen species,[7] which are inflammatory and oxidative stress markers.[8–10] In turn, the chronic oxidative state causes damage to membrane lipids, proteins, enzymes, carbohydrates, and DNA.[11]

A reduction in inflammatory and oxidative processes using bioactive compounds such as monounsaturated and polyunsaturated fatty acids (MUFAs and PUFAs, respectively), dietary fibers, phenolic compounds, tocopherols, phospholipids, carotenoids, some minerals, and arginine has stimulated research on the mechanisms of action of these substances through distinct experimental approaches.[12–16] It has been shown that the consumption of tree nuts such as almonds,

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Brazil nuts, pistachios, and walnuts, as well as legume seeds such as peanuts and baru, is associated with a reduction in cardiovascular risk.[15–17]

However, the metabolic effect of nuts and legume seeds depends on the quantity and which type is consumed, according to the nutritional composition. Therefore, it is important to know the effects of each tree nut and legume seed in order to define the specific nutritional intervention in clinical practice. In this context, the aim of this narrative bibliographic review was to investigate the effects of tree nuts and legume seeds, as well as to show their mechanisms of action on lipid profile, insulin resistance, arterial pressure, oxidative stress, and inflammatory state, to illustrate how the mixture of nuts and legume seeds optimizes the protective effect of cardiovascular risk.

LITERATURE SEARCH METHODS

A literature review was performed using the electronic database Medline (via PubMed) and the following selection criteria: cohort studies, research on animal models, and clinical trials published in the last 10 years in journals with an impact factor (according to the *Journal of Citation Reports*) of $\geq$1.0. The search terms were selected by consulting the medical subject headings and were as follows: almond, baru, blood pressure, Brazil nut, cardiovascular disease, cashew nut, glucose, hazelnut, lipid profile, macadamia, nuts, peanut, pistachio, and walnut. Because of the small number of experimental studies investigating some nuts such as pecans, chestnuts, and pine nuts, those nuts were not included in the search terms. The Boolean operators "and," "or," and "and not" were used to combine the search terms. As a result of the search, 4 cohort studies,[18–21] 5 *in vitro* studies,[15,22–25] 8 studies with animal models,[22,26–32] and 33 clinical trials[33–65] were selected. In addition to these studies, the present review includes the citation of 31 articles that were used to define the scientific terms and discuss the results.

Nuts and legume seeds

True nuts (almonds, hazelnuts, cashew nuts, Brazil nuts, macadamia nuts, walnuts, and pistachios) and legume seeds (peanuts and baru) are foods with high energy density.[15,22,23] This is due to their nutritional composition, which is characterized by a high percentage of total lipids, ranging from 42 to 76 g/100 g. However, the fatty acid content of these foods is beneficial for health because such foods are low in saturated fatty acids (SFAs) and high in unsaturated fatty acids, particularly MUFAs.[15] In addition, tree nuts and legume seeds are high in other nutrients and bioactive compounds such as antioxidant nutrients, fibers, and phenolic compounds (Table 1).[23–25,66–68]

Differences in the nutritional composition of tree nuts and legume seeds may determine their effect on cardiovascular risk markers. As noted in Table 1, baru, a seed of the Baruzeiro tree (*Dipteryx alata* Vog.), which is a common plant growing on the Brazilian savanna with a flavor similar to that of a peanut, exhibits the lowest lipid content (41.95%), whereas macadamia nuts exhibits the highest (75.77%). Regarding the types of lipids, almonds and hazelnuts stand out because they have a high MUFA-to-SFA ratio and α-tocopherol. On the other hand, Brazil nuts exhibit the lowest MUFA-to-SFA ratio and macadamia nuts exhibit the highest MUFA-to-PUFA ratio. Legume seeds have a higher protein content than tree nuts. Tree nuts and legume seeds are high in fiber; almonds have the highest percentage of fiber, whereas cashew nuts have the lowest. Walnuts have the highest amount of phenolic compounds, although all other nuts also exhibit a significant amount. Regarding the mineral content, the highest magnesium concentration is found in Brazil nuts, almonds, and cashew nuts. Macadamia nuts and baru stand out for having a high zinc concentration. Brazil nuts have an exceptionally high content of selenium, while hazelnuts also have an appreciable amount of this mineral. Pistachios have the highest concentrations of potassium and carotenoids. Pistachios and peanuts show the highest phytosterol concentrations. In addition, tree nuts and legume seeds have a low lysine-to-arginine ratio, with walnuts exhibiting the lowest ratio and pistachios the highest.

EFFECT OF TREE NUTS AND LEGUME SEEDS ON CARDIOVASCULAR DISEASE RISK: EVIDENCE AND MECHANISMS OF ACTION

Lipid profile

A diet rich in nuts and legume seeds improves the serum lipid profile because it is high in MUFAs, PUFAs, and bioactive substances.[1] This effect has been confirmed in different types of research, including epidemiological studies, studies with animal models, and clinical trials (Tables 2–5). A cohort study with 6309 women with type 2 diabetes showed that the usual intake of peanut butter (16 g) or at least five portions of nuts (28 g each) per week reduced cardiovascular disease risk by 44%, as well as levels of some inflammatory biomarkers such as total cholesterol, low-density lipoprotein (LDL), and apolipoprotein B (apo B). However, no significant change was observed in high-density lipoprotein (HDL) levels.[20]

Regarding evidence from studies with animal models, hamsters on a diet supplemented with peanuts or its

Table 1 **Nutrients and bioactive compounds of tree nuts and legume seeds**

Nut/seed[a]	Energy (kcal)	Lipid (g/100 g)	Fatty acid (g/100 g)					Protein (g/100 g)	Carbohydrate (g/100 g)	Fiber (g/100 g)	Tocopherol (mg/100 g)[b]		Total Phenolics (mg/100 g)	Minerals (mg/100 g, Se µg/100 g)				Phytosterols (mg/100 g)[c]	Carotenoids (µg/100 g)[c]		Lysine/ arginine
			S	M	P	M:S	M:P				α	β	γ	Mg	Zn	Se	K		A	β
Almonds	579	49.93	3.73	31.55	12.32	8.3:1	2.5:1	21.15	51.55	12.5	25.22	0.29	0.65	239	270	3.12	4.1	733	141	0	1	0.24
Peanuts	567	49.24	6.83	24.43	15.56	3.6:1	1.6:1	25.80	16.13	8.5	8.33	–	–	420	168	3.27	7.2	705	220	0	0	0.30
Hazelnuts	628	60.75	4.46	45.65	7.92	10:1	5.8:1	14.95	16.70	9.7	15.03	0.33	0.00	291	163	2.42	90.0	680	96	3	11	0.23
Baru	546	41.95[d]	18.77[d]	51.07[d]	32.35[d]	2.7:1	1.58:1	29.92[e]	18.92	9.21	–	–	–	–	165	4.29	0.4	–	–	–	–	0.44
Brazil nuts	656	66.43	15.14	24.55	20.58	1.6:1	1.2:1	14.32	12.27	7.5	5.73	0.00	7.87	112	376	4.06	1917.0	659	–	0	0	0.23
Cashews	553	43.85	7.78	23.80	7.84	3.0:1	3.0:1	18,22	30.19	3.3	0.90	0.03	5.31	137	292	5.78	19.9	660	–	0	0	0.44
Macadamia	718	75.77	12.06	58.88	1.50	4.9:1	39.2:1	7.91	13.82	8.6	0.54	0.00	0.00	46	130	1.30	3.6	368	116	–	–	0.33[c]
Walnuts	654	65.21	6.13	8.93	47.17	1.4:1	0.2:1	15.23	13.71	6.7	0.70	0.15	20.83	1625	158	3.09	4.9	441	72	0	12	0.19
Pistachios	564	45.39	5.55	23.82	13.74	4.3:1	1.7:1	20.95	28.66	10.3	2.3	0.00	22.60	867	121	2.20	7.0	1007	214	0	156	0.55

Data from the US Department of Agriculture Nutrient Database for Standard Reference, Release 26.[66]
[a]Nuts and seeds are raw, except Brazil nuts (dried, unblanched), walnuts (walnuts, English).
[b]Kornsteiner (2006).[24]
[c]Venkatachalam and Sathe (2006).[23]
[d]Average for Togashi and Sgarbieri (1994)[67] and Vallillo et al. (1990).[68]
[e]Fernandes et al. (2010).[25]
Abbreviations: K, potassium; M, monounsaturated fatty acid; Mg, magnesium; M:P, monounsaturated fatty acid to polyunsaturated fatty acid ratio; M:S, monounsaturated fatty acid to saturated fatty acid ratio; P, polyunsaturated fatty acid; S, saturated fatty acid; Se, selenium; Zn, zinc; –,no data available.

byproducts exhibited lowered concentrations of total cholesterol and lowered risk of developing atherosclerosis.[27] In another study, rats on diets that contained pistachios as a source of lipids at concentrations ranging from 20% to 40% exhibited increased serum HDL levels and a decreased total cholesterol -to-HDL ratio (Table 3).[27]

Clinical trials with dyslipidemic adults have shown a positive effect of the consumption of different types of tree nuts and legume seeds on biochemical parameters (Table 4).[34–36,39,42,47,49,57–62] In the first phase of the American National Cholesterol Education Program, healthy, moderately hypercholesterolemic adults were given a hyperlipidic diet in which lipid content was increased every 4 weeks through supplementation with almonds. A positive effect of this intervention on the lipid profile was observed in a dose–response manner. The diet with the highest percentage of lipids (39%), which contained 68 g of almonds, yielded the following results: 8.6% reduction in total cholesterol, 8% reduction in apo B, and 4% increase in apo A.[33] In another study, replacing 15% of the total energy intake with pistachios reduced LDL (−10%) and triglyceride (−4%) concentrations and the apo B-100-to-apo A1 ratio (−20%).[34] The reduction in the total cholesterol-to-HDL and LDL-to-HDL ratios was even more remarkable in moderately hypercholesterolemic individuals who were on a diet in which 33% of the total energy intake was from macadamia nuts (42.5 g/day) compared with individuals who received an isolipidic diet without macadamia nuts.[35] Supplementation with approximately 77 g of peanuts (i.e., an addition of 20% to the usual energy intake of the individuals) for 4 weeks reduced total cholesterol and LDL concentrations, the plasma atherogenic index, and arterial pressure. Furthermore, it increased HDL levels and the total serum antioxidant capacity.[36] Similarly, supplementation with almonds or walnuts (40–75 g/day) at approximately 22% of the total energy intake for 4 weeks reduced LDL levels and the LDL-to-HDL ratio in hypercholesterolemic individuals. It is worth noting that the positive effect on the lipid profile was not observed in the group treated with virgin olive oil.[37] On the other hand, the consumption of only 30 g of hazelnuts per day for 12 weeks caused a similar effect on lipid fractions in hypercholesterolemic individuals and reduced triglycerides and apo B concentrations.[38] It is worth mentioning that, in general, an increase in body mass has not been observed with an increased consumption of tree nuts and legume seeds.[18,38,39] In fact, supplementation with only 30 g of walnuts per day for 12 weeks reduced central obesity by 16% in individuals with metabolic syndrome.[40]

Several mechanisms have been suggested to explain the benefits that consumption of tree nuts and legume

Table 2 **Summary of cohort studies investigating tree nut and legume seed consumption relative to risk of coronary heart disease**

Reference	No. of participants	Study design	Results		
			Nut or legume seed consumption	Relative risk or OR (95% CI)	*P* value[a]
Bes-Rastrollo et al. (2009)[18]	51 188 healthy women (Nurses' Health Study II); age range, 20–45 y	Dietary intake of nuts and weight changes from 1991 to 1999	2 times per week or never/almost never consumption of nuts	Slightly lower risk of obesity: OR, 0.77 (0.57–1.02)	0.001
Djoussé et al. (2009)[19]	15 966 participants from the Physicians' Health Study	Nut consumption (self-reported using a simple abbreviated semiquantitative food-frequency questionnaire) and hypertension at 12 mo post-randomization of the trial study	4 groups (rarely/never, 1–3/month, 1/week, 2–6/week or daily)	Inverse relation between nut intake and hypertension in lean participants: 1–3/month: OR, 0.97 (0.91–1.03); 1/week: OR, 0.98 (0.92–1.05); 2–6/week: OR, 0.96 (0.89–1.03); ≥7/week: OR, 0.82 (0.71–0.94)	0.014
Li et al. (2009)[20]	6309 women with diabetes	Nut consumption (food-frequency questionnaire every 2–4 y) and incident cardiovascular disease from 1980 to 2002	At least five serving (28 g nuts or 16 g peanut butter) per week	Consumption of nuts or peanut butter was significantly associated with a lower risk of: CVD: RR, 0.56 (0.36–0.89) Myocardial infarction: RR, 0.40 (0.24–0.67)	 <0.05 <0.05
O'Neil et al. (2012)[21]	24 385 individuals from the National Health and Nutrition Examination Survey 1999–2000, 2001–2002, and 2003–2004	Nut consumption and the prevalence of risk factors for cardiovascular disease and metabolic syndrome of three groups (2–11 y, 12–18 y, and 19+ y)	≥1/4 oz (7 g) of nuts and peanuts or more per d/nonconsumer	Adults 19 y and older: HBP: OR, 0.81 (0.67–0.98) LDL: OR, 0.91 (0.69–1.20) HDL: OR, 0.79 (0.64–0.97) TG: OR, 0.88 (0.69–1.13)	<0.05

[a]*P* value considered statistically significant.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HBP, high blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; RR, relative risk; TG, triglycerides.

seeds has been shown to have on the lipid profile, including reducing apo B and increasing apo A1; increasing the activity of enzymes involved in reducing lipid oxidation; and increasing plasma adiponectin (a hormone that favors fatty acid metabolism and oxidative stress reduction).[41,69] Therefore, the nutritional composition of tree nuts and legume seeds is a key factor for the activation of these mechanisms because PUFAs reduce the levels of apo B and MUFAs increase the levels of apo A1, which mediates the efflux of cholesterol associated with HDL particles.[70] This is important because not only the amount of cholesterol carried by LDL particles but also its apo B content increases cardiovascular risk.[71] This was confirmed in one study that found a 25% reduction in the incidence of coronary disease caused by a 10% reduction in total cholesterol over 5 years and a 20% reduction in the risk of ischemic heart diseases per millimole per liter LDL reduction.[72] The consumption of pistachios as a source of lipids in a proportion of 20% of the diet led to increases of 35% and 65%, respectively, in the activity of paraoxonase and arylesterase.[27] These enzymes are responsible for reducing LDL oxidation. However, the same effect was not observed among rats given pistachios in a proportion of 40% of the total caloric diet.[27] Moreover, another study confirmed the relationship between the daily intake of 1 (63 g) or 2 (126 g) portions of pistachios in a hyperlipidic diet and the reduction in total cholesterol, LDL, and apo B concentrations, which probably occurred due to the decreased activity of steaoryl-CoA desaturase, a key enzyme for the synthesis of triglycerides, which are directly associated with weight loss.[59] This protective effect has also been associated with an increased MUFA-to-SFA ratio in a macadamia nut–rich diet.[35]

Although scientific evidence of the cardioprotective effects of eating peanuts and walnuts has been found, studies with baru remain scarce; nevertheless, baru's nutritional composition makes it important to investigate the effect of this legume seed on human health.

Glycemia and insulin resistance

Lifestyle is a key factor for the development of type 2 diabetes. In addition, diet plays an important role in the prevention and control of this disease. The inclusion of tree

Table 3 **Summary of experimental studies (animal models) investigating tree nut and legume seed consumption relative to biomarkers of coronary heart disease**

Reference	No. of animal subjects	Study design	Results	*P* value[a]
Peanut				
Emekli-Alturfan and Kasikci (2007)[26]	32 diabetic rats	12 weeks, 4 groups: control; control + 0.63 g/100 g peanut; diabetic; diabetic + 0.63 g/100 g peanut	Peanut consumption: ↑ GSH and HDL levels; ↓ TBARS	<0.01
Emekli-Alturfan et al. (2008)[28]	32 Wistar albino rats	12 weeks, 4 groups: control; control + 0.63 g/100 g peanut; hyperlipidemic; hyperlipidemic + 0.63 g/100 g peanut	Peanut consumption: ↑ GSH and HDL levels ↓ TBARS	<0.01
Jacques et al. (2010)[29]	32 male adult rats	28 days, 4 groups: casein; cod protein; PP; casein + PP (50:50) mixture	PP group: ↓ plasma triglycerides ↓ hepatic cholesterol	0.016 0.031
Stephens et al. (2010)[30]	82 male Syrian golden hamsters	24 weeks, 4 groups: high-fat and high-cholesterol diets (control); control diet plus whole peanut flour; control diet plus peanut oil; control diet plus fat-free peanut flour	Whole peanut flour, peanut oil, and fat-free peanut flour groups: ↓ total plasma cholesterol	<0.05
Pistachio				
Aksoy et al. (2007)[27]	36 rats	10 weeks, 3 groups: control diet, control diet plus pistachios of energy intake 20% (2.5 g/d), control diet plus pistachios of energy intake 40% (5 g/d) of energy intake	Pistachio groups: ↑ HDL, ↓ TC/HDL ↑ serum paraoxonase activity ↑ arylesterase activity	<0.05
Marinou et al. (2010)[32]	24 New Zealand white rabbits	3 mo, 3 groups: atherogenic diet (control), control diet plus ME of the *Pistacia vera* nut, control diet plus CHE of the *Pistacia vera* nut	ME and CHE groups: ↑ HDL ME group: ↓ MDA and aortic surface lesions CHE group: ↑ ALT and AST	<0.05 <0.05 <0.05

[a]*P* value considered statistically significant.
Abbreviations: ↓, decrease; ↑, increase; ALT, alanine aminotransferase; AST, aspartate aminotranferase; CHE, cyclohexane extract; GSH, blood glutathione; HDL, high-density lipoprotein; MDA, malondialdehyde; ME, methanolic extract; *P*, value of difference between nuts and control diet; PP, peanut protein; TBARS, thiobarbituric acid reactive substances; TC/HDL, relationship between total cholesterol and high-density lipoprotein.

nuts and legume seeds in the diet can promote a reduction in the glucose and insulin peaks[43,73] because these foods are high in lipids and fibers and low in carbohydrates.[15]

In prediabetic adults, the introduction of almonds in a proportion of 20% of the total energy intake (~56 g/day) for 16 weeks led to a reduction in insulin concentration and peripheral resistance, with an improvement in the response of pancreatic beta cells.[42] In a study with diabetic individuals, replacing 2 portions of carbohydrates with a mixture of nuts (average, 73 g/day) for 12 weeks resulted in a 20% reduction in glycated hemoglobin.[44] In another study with diabetic individuals, supplementation with 60 g of almonds/day (20% of the total energy intake) for only 4 weeks was sufficient to reduce serum insulin concentrations in 4.1% of participants and the insulin resistance index (homeostatic model assessment insulin resistance) in 9.2% compared with the baseline.[45] The beneficial effect of tree nuts and legume seeds was also observed in individuals with metabolic syndrome who were treated with 42–70 g of pistachios for 4 weeks. This treatment promoted the reduction in postprandial glucose and serum triglycerides levels.[39]

Some mechanisms are suggested in the literature for the beneficial effect of nut and seed consumption on serum glucose levels. Unsaturated fatty acids, which are present in high concentrations in these foods (Table 1), increase cell membrane permeability to insulin and reduce the gene expression of enzymes involved in inflammation.[73] In addition, the high content of lipids, fibers, and phenolic compounds delays digestion and absorption, thus contributing to the reduction in glucose peaks and postprandial glucose.[46] An additional potential mechanism underlying the relationship between the consumption of tree nuts and legume seeds and glycemia is the inhibition of enzymes that participate in carbohydrate digestion and absorption.[74] For example, the concentrated extract of chestnut peel delayed the absorption of carbohydrates and the reduction in postprandial glucose and inhibited the action of α-amylase.[43] Another suggested mechanism is the reduction in levels of aspartate aminotransferase, which is associated with insulin resistance in obese individuals.[39]

Furthermore, the low lysine-to-arginine ratio found in almonds,[40] hazelnuts, Brazil nuts, and walnuts may contribute to the increase in glucagon levels by reducing the gene expression of sterol regulatory element-binding protein 1 in the liver, a protein involved in lipogenic and insulin transcription.[75,76]

Table 4 **Summary of clinical trials with no healthy participants investigating tree nut and peanut (legume seed) consumption relative to biomarkers of coronary heart disease**

Reference	No. of participants	Study design	Results (intervention group versus control)	*P* value[a]
Almond				
Jenkins et al. (2008)[57]	27 hyperlipidemic participants	Randomized crossover study; 1 mo. for each isoenergetic diet supplement provided 22.2% of daily energy (423 kcal/d)	Full-dose almonds group:	
			↓ 24-h creatinine output (mmol/d): −8.6 ± 0.7 versus −7.1 ± 0.5	<0.05
			↓ Creatinine-corrected 24-h C-peptide output (μmol/mmol): 2578 ± 60 versus 3801 ± 76	<0.01
		Full-dose almonds (73 ± 3 g/d)		
		Half-dose almonds plus half-dose muffins		
		Full-dose whole-wheat muffins (147 ± 6 g/d)		
Wien et al. (2010)[42]	65 prediabetic adults	Randomized parallel-group trial; 16 weeks	↓ Insulin: −23.3% versus +19.2%	0.002
		Control group: nut-free diet recommended by American Dietetic Association (ADA diet)	↓ Insulin resistance: −24.9% versus +15.5%	0.007
			↓ Beta-cell function: −17.8% versus +30.0%	0.001
		Intervention group: ADA diet plus almonds (20% of energy; ≅2 oz/d)	↓ LDL (mg/dL): −10.6% versus −0.4%	0.052
Foster et al. (2012)[58]	132 overweight and obese individuals	Randomized controlled-feeding study; 18 mo.	↓ TC (mg/dL): −8.7 ± 2.8 versus −0.1 ± 2.8	0.030
		Control group: hypocaloric nut-free diet	↓ TG (mg/dL): −12.1 ± 4.6 versus −1.0 ± 4.6	0.048
		Intervention group: hypocaloric, almond-enriched diet (56 g/d)		
Pistachio				
Sheridan et al. (2007)[34]	15 participants with moderate hypercholesterolemia	Randomized crossover study; 4 weeks for each group	Difference and confidence interval:	
			↓ TC/HDL (mg/dL): −0.38 (−0.57, −0.19)	0.001
		Control group: regular diet	↓ LDL/HDL (mg/dL): −0.40 (−0.66, −0.15)	0.004
		Intervention group: 15% energy intake from pistachios (≅2–3 oz/d)	↓ Apo B/A-1 (mg/dL): −0.11 (−0.19, −0.03)	0.009
			↑ HDL (mg/dL): +2.3 (0.48, 4.0)	0.020
Gebauer et al. (2008)[59]	28 participants with elevated LDL cholesterol	Randomized, crossover, controlled-feeding study; 4 weeks for each group (3 isoenergetic diets)	Intervention group 1:	<0.001
			↓ TC: −7.2%	
			↓ LDL: −9%	
		Control group: 25% of diet energy from total fat (8% SFAs, 9% MUFAs, and 5% PUFAs) without pistachios	↓ non-HDL: −8.2%	
			Intervention group 2:	
			↓ TC: −8%	<0.001
			↓ LDL: −12%	<0.001
		Intervention group 1: 10% of energy from pistachios (63 g); 30% total fat (8% SFAs, 12% MUFAs, and 6% PUFAs)	↓ non-HDL: −11%	<0.001
			↓ Apo B: −4%	<0.01
			↓ Apo B/Apo A-I: −4%	<0.01
			↓ Stearoyl-CoA desaturase activity: −1%	<0.05
		Intervention group 2: 20% of energy from pistachios (126 g); 34% total fat (8% SFAs, 15% MUFAs, and 8% PUFAs)		

(continued)

Table 4 **Continued**

Reference	No. of participants	Study design	Results (intervention group versus control)	*P* value[a]
Wang et al. (2012)[39]	90 participants with metabolic syndrome	Randomized controlled-feeding study; 12 weeks All participants received dietary counseling according to the guidelines of the American Heart Association Step I diet for 4 weeks before treatments Control group: no pistachios Intervention groups: 42 g/d pistachios or 70 g/d pistachios	42 -g pistachio group: ↓ TG (−0.38 ± 0.79 mmol/L) compared with baseline 70-g pistachio group: ↓ glucose values 2 h after 75 g glucose (−1.13 ± 2.58 mmol/L) compared with baseline	 0.018 0.020
Hazelnut				
Mercanligil et al. (2007)[60]	15 hypercholesterolemic adults	Randomized, controlled-feeding study; 8 weeks Control group: low-fat, low-cholesterol, and high-carbohydrate diet Intervention group: control diet supplemented with hazelnuts (40 g/d)	↓ VLDL: −29.5% ↓ TG: −31.8% ↓ Apo B: −9.2% ↑ HDL: −12.6%	<0.05 <0.05 <0.05 <0.05
Tey et al. (2011)[38]	48 mildly hypercholesterolemic participants	Randomized crossover study; 3 mo 30 g of hazelnuts (5 days/week), raw, ground, and sliced during 4 weeks for each	Difference and confidence interval ↓ TC (mmol/L): −0.19 (−0.30, −0.09) ↓ LDL (mmol/L): −0.22 (−0.31, −0.13) ↑ HDL (mmol/L): +0.03 (0.00, +0.06) ↓ TC/HDL (mmol/L): −0.29 (−0.41, −0.18) ↓ Apo B (mmol/L): −0.04 (−0.07, −0.02) ↓ Apo B/Apo A1 (mmol/L): −0.03 (−0.04, −0.01) ↑ α-Tocopherol (mmol/l): +1.32 (0.41, 2.23)	 <0.001 <0.001 0.023 <0.001 0.002 <0.001 0.005
Walnut				
Tapsell et al. (2004)[61]	58 participants with type 2 diabetes	Randomized controlled-feeding study; 6 mo Control group: low fat, <30% energy as fat Intervention groups: modified low fat (using exchange lists inclusive of fatty acid considerations) and low fat including 30 g of walnuts/d	↓ TC/HDL: −22% ↑ HDL: +18.18% ↓ LDL: −10%	0.049 0.046 0.032
Macadamia				
Griel et al. (2008)[35]	25 mildly hypercholesterolemic participants	Randomized, crossover, controlled–feeding study; 5 weeks each diet Control group: average American diet (33% total fat; 13% SFA, 11% MUFA, 5% PUFA) Intervention group: macadamia nut–rich diet (42.5 g/d)	↓ TC/HDL (mmol/L): 4.94 ± 0.17 versus 5.45 ± 0.17 ↓ LDL (mmol/L): 3.14 ± 0.14 versus 3.44 ± 0.14	<0.05 <0.05

(continued)

Table 4 **Continued**

Reference	No. of participants	Study design	Results (intervention group versus control)	*P* value[a]
Mixed nuts				
López-Uriarte et al. (2010)[49]	50 participants with metabolic syndrome	Randomized, controlled, parallel-feeding study; 12 weeks	↓ DNA damage	<0.001
		Control group: healthy diet	Urine 8-isoprostanes (nmol/mmol creatinine): −138.01 versus −121.06	0.000
		Intervention group: healthy diet supplemented with 30 g/d of mixed nuts (walnuts, 15 g; almonds, 7.5 g; and hazelnuts, 7.5 g)	Urine 8-oxo-dG (nmol/mmol creatinine): −6.35 versus −3.93	0.000
			ICAM-1 (mg/L): −91.98 versus −11.35	0.038
Casas-Agustench et al. (2011)[47]	50 participants with metabolic syndrome	Randomized, controlled, parallel-feeding study; 12 weeks	↓ Insulin (mU/mL): −2.07 versus +0.53	0.013
		Control group: healthy diet	↓ HOMA-IR: −0.58 versus +0.14	0.013
		Intervention group: healthy diet supplemented with 30 g/d of mixed nuts (walnuts, 15 g; almonds, 7.5 g; and hazelnuts, 7.5 g)		
Peanuts				
Nouran et al. (2009)[36]	54 hypercholesterolemic men	Randomized, crossover clinical study; 4 weeks each diet	↓ TC/HDL (mg/dL): −0.7 ± 0.2 versus +0.3 ± 0.2	0.001
		Control group: habitual diet	↓ LDL/HDL (mg/dL): −0.4 ± 0.1 versus +0.3 ± 0.1	0.001
		Intervention group: habitual diet plus peanut supplement (≅77 g/d; 20% of total energy intake)	↑ HDL (mg/dL): +4.7 ± 0.9 versus −1.4 ± 0.8	0.001
			↑ TAC (U/mL): +0.3 ± 0.5 versus −1.0 ± 0.4	0.040
			↓ AIP: −0.09 ± 0.03 versus +0.002 ± 0.03	0.010
			↓ CHD estimated risk over 10 y based on systolic (−1.2 ± 0.4 versus 0.4 ± 0.4 mmHg) and diastolic blood pressures (−1.4 ± 0.4 versus 0.9 ± 0.4 mmHg)	<0.01
Reis et al. (2012)[62]	15 obese women	Randomized, crossover clinical trial	↓ second-meal glycemic response IAUC	0.03
		Control group: breakfast (75 g carbohydrate-matched breakfast meal) without peanut	↓ glucose concentration at 45 min after meal	0.05
		Intervention group: 42.5 g of whole peanuts without skins or peanut butter		

[a]*P* value of difference between intervention group and control diet. [a]*P* value considered statistically significant.
Abbreviations: ↓, decrease; ↑, increase; 8-oxo-dG, 8-hydroxy-2′-deoxyguanosine; AIP, athrogenic index of plasma; Apo A, apolipoprotein A; Apo B, apolipoprotein B; Apo B/Apo A, relationship between apolipoprotein B and Apo A; CHD, coronary heart disease; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance; IAUC, incremental area under the blood glucose response curve; ICAM-1, intracellular adhesion molecule-1; LDL, low-density lipoprotein; LDL/HDL, relationship between low-density lipoprotein and high-density lipoprotein; MUFAs, monounsaturated fatty acids; non-HDL, total cholesterol minus high-density lipoprotein; PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids; TAC, total antioxidant capacity; TC, total cholesterol; TC/HDL, relationship between total cholesterol and high-density lipoprotein; TG, triglycerides; VLDL, very-low-density lipoprotein.

Arterial pressure

Arterial hypertension is considered a major risk factor for cardiovascular diseases, and the consumption of some tree nuts and legume seeds is associated with reduction of this risk. In a cohort study conducted over 26 years with a healthy population, a lower risk for stroke was observed among individuals who ate nuts two to four times per week.[19]

Table 5 **Summary of clinical trials with healthy participants investigating tree nut and legume seed consumption relative to biomarkers of coronary heart disease**

Reference	No. of participants	Study design	Results (intervention group versus control)	*P* value[a]
Alper and Mattes (2003)[48]	15	Randomized crossover clinical study; 30 weeks. Intervention groups: FF: 50% of dietary fat energy was provided by nuts –FF; peanut ADD: 50% of dietary fat energy was added to a prescribed diet isocaloric (41 lipids after addition); SUB: reduced fat intake by 50%, and this was replaced with an equivalent amount of fat from peanuts (17% lipids of diet + 17% lipids of peanuts)	↓TG: 24% during ADD, 17% during SUB, and 14% during FF	<0.05
Sabaté et al. (2003)[33]	25	Randomized crossover design; 4 weeks each diet	High almonds versus control group:	
		Control group: isocaloric diet with 0% almonds	↓ TC (mmol/L): 5.17 ± 0.19 versus 5.41 ± 0.19	0.001
		Intervention groups: isocaloric diets with 10% (low) or 20% (high) almonds	↓ LDL (mmol/L): 3.48 ± 0.21 versus 3.74 ± 0.21	<0.001
			↓ Apo B (mg/dL): 93.7 ± 5.6 versus 100.3 ± 5.6	<0.001
			↓ LDL/HDL: 3.10 ± 0.28 versus 3.40 ± 0.28	<0.001
Jambazian et al. (2005)[63]	16	Randomized crossover design; 4 weeks each diet	Low almond:	
		Control group: isocaloric diet with 0% almonds	↑ α-tocopherol/TC (mmol/L:mol/L): 54.20 ± 1.95 versus 48.21 ± 1.94	<0.01
		Intervention groups: isocaloric diets with 10% (low) or 20% (high) almond	High almond:	
			↑ α-tocopherol/TC (mmol/L:mol/L): 56.39 ± 1.98 versus 48.21 ± 1.94	<0.01
Josse et al. (2007)[64]	9	Randomized crossover trial; 1 day each meal	↓ glycemic index of the meal in a dose-dependent manner for 30 g (105.8 ± 23.3), 60 g (63.0 ± 9.0), and 90 g (45.2 ± 5.8) doses of almonds, respectively	0.001
		Control group: meal contained 50 g carbohydrate from white bread + 0 g almonds		
		Intervention groups: meal contained 50 g carbohydrate from white bread + 30, 60, or 90 g almonds		
Kocyigit et al. (2006)[65]	44	Randomized controlled study; 3 weeks for each	Differences between before and after:	
		Control group: habitual diet	↑ AOP (mmol/L): −0.85 ± 0.72 versus +0.48 ± 0.16	<0.05
		Intervention group: 20% of daily energy intake replaced pistachios	↓ MDA (mmol/L): −0.43 ± 0.33 versus −0.07 ± 0.06	<0.05
			↓ TC (mmol/L): −0.47 ± 0.09 versus −0.02 ± 0.03	<0.05
			↑ HDL (mmol/L): +0.27 ± 0.01 versus −0.03 ± 0.01	0.005
			↑ AOP/MDA(mmol/L): +0.66 ± 0.25 versus +0.41 ± 0.11	<0.05
			↓ TC/HDL(mmol/L): −0.81 ± 0.37 versus +0.07 ± 0.15	<0.001
			↓ LDL/HDL(mmol/L): −0.24 ± 0.04 versus +0.01 ± 0.05	<0.001

[a]*P* value considered statistically significant.
Abbreviations: ↓, decrease; ↑, increase; ADD, addition; AOP, antioxidant potential; AOP/MDA, relationship between antioxidant potential and malondialdehyde; Apo B, apolipoprotein B; FF, free feeding; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDL/HDL, relationship between low-density lipoprotein and high-density lipoprotein; MDA, malondialdehyde; *P*, value of difference between intervention group and control diet; TC, total cholesterol; TC/HDL, relationship between total cholesterol and high-density lipoprotein; TG, triglycerides; SUB, substitution.

Clinical evidence regarding the relationship between consumption of tree nuts and reduction in arterial pressure remains scarce. A clinical trial with symptomatic individuals with high cardiovascular risk showed that supplementation with a mixture of 15 g of walnuts, 7.5 g of almonds, and 7.5 g of hazelnuts was associated with a 7.1-mmHg reduction in systolic arterial pressure and a 2.6-mmHg reduction in diastolic pressure after 3 months of intervention.[77] In another clinical trial with 54 hypercholesterolemic men, the addition

of 77 g of peanuts to the usual diet caused a significant reduction in the total cholesterol-to-HDL and LDL-to-HDL ratios as well as cardiovascular risk, which was assessed on the basis of systolic and diastolic pressures.[36]

A diet low in sodium and rich in foods that are sources of unsaturated fats, minerals such as potassium, magnesium, and calcium,[47] as well as arginine reduces peripheral vascular resistance because it increases nitric oxide production and reduces angiotensin II levels.[78] Tree nuts and legume seeds, which exhibit the above-mentioned nutritional characteristics (Table 1),[23–25,66–68] may contribute to the reduction in arterial pressure. Magnesium and arginine favor the production of nitric oxide and vasodilator prostacyclins.[48] Potassium participates in the modulation of the volume of extracellular fluid and thus helps in the regulation of arterial pressure.[49] In a study with healthy individuals, the effect of adding and replacing 500 kcal of the diet with peanuts was assessed, and a significant increase in serum magnesium levels was observed in the test group.[48]

Oxidative stress and inflammatory state

Oxidative stress, which is an imbalance between reactive oxygen species and antioxidant factors, is involved in the development of cardiovascular diseases. Reactive oxygen species cause an increase in the expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and a reduction in antioxidant enzymes, which results in the reduction in adipocytokine production.[79] Moreover, adipose tissue induces the release of inflammatory cytokines such as tumor necrosis factor-α and interleukin-6, increasing reactive oxygen species production and, thus, inducing oxidative stress.[80]

An SFA-rich diet induces lipid peroxidation via oxidation of LDL particles, which results in endothelial aggregation and atheroma plaque formation.[31,32] On the other hand, the high concentrations of MUFAs, PUFAs, and bioactive compounds present in nuts and legume seeds may contribute to reduction in the oxidative state and prevention of cardiovascular alterations. This effect has been observed in distinct oxidative stress models (Table 3). In rats fed a hypercholesterolemic diet and treated with pistachios for 8 weeks, a reduction in thiobarbituric acid reactive substances and an increase in the activity of glutathione peroxidase and superoxide dismutase were observed.[16] In a study in rats supplemented with iron sulfate and given a diet containing baru in a proportion of 10% of the diet, a reduction in the serum oxidative state was observed.[22] A reduction in the inflammatory state was also observed in rabbits fed a hypercholesterolemic diet and treated with hazelnut oil[31] and pistachio extract[32] for 3 months. The rabbits exhibited lowered numbers of foamy cells and inflammation in the aortic intima, with reduced thickness and a lesser extent of atherosclerotic lesions.

Studies with humans have also found a reduction in inflammatory and oxidative stress markers after the addition of nuts to the diet. One systemic inflammation marker indicated in the literature is the C-reactive protein, which is associated with the storage of body fat.[81] Healthy individuals who received almonds corresponding to 10% or 20% of the total energy intake for 4 weeks exhibited reduced serum C-reactive protein levels. However, no dose–response relationship was observed.[50] Similarly, the consumption of 40–90 g of macadamia nuts, corresponding to 15% of the total energy intake, for 4 weeks promoted a significant reduction in other inflammatory (leukotriene LTB4) and oxidative stress markers (8-isoprostane).[51] Moreover, studies with healthy adults have shown that supplementation with a mixture containing 15 g of walnuts, 7.5 g of almonds, and 7.5 g of hazelnuts for 12 weeks was sufficient to improve the levels of several oxidative stress biomarkers and reduce DNA damages, which were assessed on the basis of the biomarker 8-oxo-2′-deoxyguanosine.[49]

Other important markers of lipid oxidation are conjugated dienes, which are generated during this process. Accordingly, phenolic compounds present in tree nuts and legume seeds are capable of reducing conjugated diene biosynthesis because of their antioxidant action. This effect was observed in a study with moderately hypercholesterolemic adults who ate 60 g of almonds per day for only 4 weeks.[52] In addition to phenolic compounds, some nuts are rich in selenium. Intake of only one Brazil nut per day was sufficient to increase the serum levels of selenium, erythrocytes, and glutathione peroxidase in adults.[53,54] In obese female teenagers, supplementation with 15–25 g/day (three to five portions) of Brazil nuts increased serum selenium levels in 20.4% and reduced LDL levels in 16.18%.[55] In obese women, the intake of one Brazil nut per day for 8 weeks recovered serum selenium levels and increased HDL levels.[55] One of the suggested mechanisms for explaining the reduction in oxidative stress and the inflammatory state with the consumption of nuts and legume seeds is stimulation of the synthesis of plasma adiponectin.[41,69]

OPTIMIZED EFFECT OF MIXTURE OF TREE NUTS AND LEGUME SEEDS ON CARDIOVASCULAR DISEASE RISK: EVIDENCE AND MECHANISMS OF ACTION

Considering the nutritional attributes of tree nuts and legume seeds (Table 1),[23–25,66–68] as well as their protective effects through reduction in cardiovascular risk markers, the literature shows that this protective effect

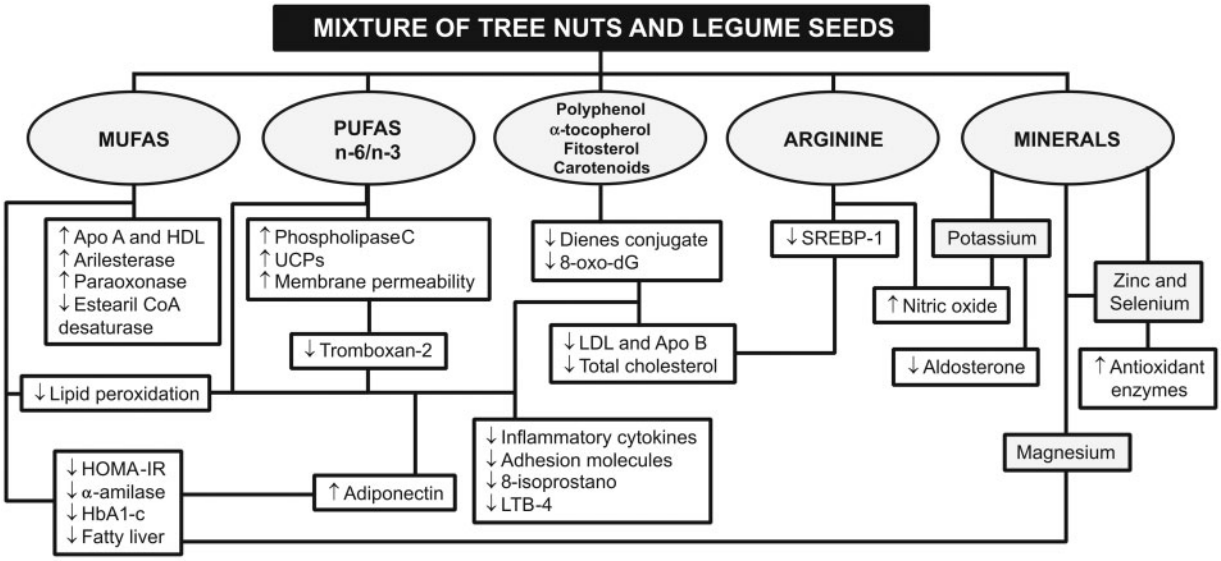

Figure 1 **Possible mechanisms of action of a mixture of tree nuts and legume seeds for cardiovascular risk reduction**
Abbreviations: 8-oxo-dG, 8-hydroxy-2′-deoxyguanosine; Apo A, apolipoprotein A; Apo B, apolipoprotein B; HbA1-c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance; LDL, low-density lipoprotein; LTB-4, leukotriene B4; MUFAs, monounsaturated fatty acids; *n*-6/*n*-3, relationship between *n*-6 fatty acids and *n*-3 fatty acids; PUFAs, polyunsaturated fatty acids; SREBP-1, sterol regulatory element-binding protein 1; UCP, uncoupling protein.

can be optimized in smaller portions with not only one type of nut but also the mixture of tree nuts and legume seeds.

To reduce the levels of a cardiovascular risk marker by supplementing with isolated tree nuts and legume seeds, the portion offered needs to reach an average of 15%–20% of the total energy intake, corresponding to 40–90 g,[33,35,36,39,45,51,52] which can be a limiting factor when considering the regular consumption of these foods.[34,42,57] However, adding a mixture of only 30 g of tree nuts (15 g of walnuts, 7.5 g of almonds, and 7.5 g of hazelnuts) to the daily diet resulted in a balanced intake of PUFAs and MUFAs, which were associated with a reduction in the fasting insulin level and homeostatic model assessment insulin resistance.[47] Furthermore, supplementation with this mixture for 12 weeks allowed the reduction in DNA oxidative damage, the inflammatory state, and arterial pressure. Thus, supplementation with the chestnut mixture was an effective strategy for individuals with metabolic syndrome, who obviously exhibit more than one cardiovascular risk marker.[47]

The hypothesis is that the mixture of nuts and legume seeds allows a balance between MUFAs, PUFAs, polyphenols, amino acids, and minerals, such that each one of these acts on the mechanism involved in the reduction of a specific risk marker. The probable mechanisms of this optimized effect of a mixture of different types of nuts and legume seeds are summarized in Figure 1.[19,23–25,31–35,38,41–44,47,49,51–53,55,57,61,66–69,78]

CONCLUSION

The results of this narrative review suggest that consumption of nuts and legume seeds reduces cardiovascular risk markers such as dyslipidemia, insulin resistance, hypertension, oxidative stress, and inflammatory state. The effects of these food items on each risk marker depend on the individual's health, the kind of nuts or legume seeds consumed, portion size, and the time of consumption. The results of cohort studies[18–21] show that consumption of small portions of nuts and legume seeds 2–6 times per week reduces the risk of obesity, hypertension, myocardial infarction, hypercholesterolemia, and lesions along the aortic surface in healthy individuals. However, the treatment of cardiovascular risk markers requires an increase in portion size and frequency of consumption of nuts and legume seeds in order to achieve significant results over a few weeks.[34–36,38,39,42,47,49,58–62] The increased consumption of nuts and legume seeds was not associated with weight gain, suggesting that these food items, which have a low glycemic index and are rich in fiber and proteins of plant origin, produce a prolonged feeling of satiety.

The beneficial effects of various nuts and legume seeds have been demonstrated. For example, peanuts[26,28–30,36,62] reduce plasma triglycerides, hepatic cholesterol, total plasma cholesterol, thiobarbituric acid reactive substances, atherogenic index of plasma,

second-meal glycemic response, and coronary heart disease, while increasing blood glutathione and HDL. Pistachios,[34,59] walnuts,[61] macadamia nuts,[35,51] and hazelnuts[38,60] are indicated for the treatment of dyslipidemia and the metabolic syndrome because they reduce LDL, total cholesterol, and apolipoprotein B, while increasing HDL. Pistachios[27,32,39] also improve triglycerides, postprandial glucose, antioxidant potential, and stearoyl-CoA desaturase activity. Almonds[42,64] are useful in the treatment of dyslipidemia and insulin resistance as they reduce the glycemic index of meals in a dose-dependent manner.

Eating a mixture of these nuts and legume seeds has been presumed to intensify their protective effects as a result of their individual nutritional specificities. Based on the evaluated studies,[47,49] potential beneficial effects of supplementation with mixed nuts and legume seeds are noted, as smaller portions appear to produce similar or even greater beneficial effects, such as reduction of DNA damage and inflammation markers.

Given that few studies have investigated the beneficial effects of consuming a mixture of nuts and legume seeds in humans, further studies are required to clarify the effects of using such mixtures to control cardiovascular risk and to elucidate the related mechanisms of the mixture effects.

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