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Chapter

Nuts as Dietary Source of Fatty Acids and Micro Nutrients in Human Health

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Abstract

In recent times, the Mediterranean diet plans are very popular because it has a lot of advantage in protecting from chronic health problems. Nuts are the integral part of the Mediterranean diet and advised to be incorporated in diet for health benefits. Both tree nuts and pea nut are good source of unsaturated fatty acids, soluble and insoluble fibers, good quantity of vitamins, minerals and phytochemicals with recognized benefits to human health. Due to life style disorders many chronic diseases are increasing in human beings. There are many epidemiological studies and research conducted on the relationship between consumption of nuts and chronic disease risks. This book chapter elaborately discusses about the nutritional composition of the nuts and their effect on cardiovascular disease, obesity, diabetes and cancer.

Keywords: nuts, chemical composition, cardiovascular disease, obesity, diabetes, cancer

1. Introduction

Nuts are excellent source of nutrients and bio active compounds. It is consumed by majority of the populations of the world in some form or other depending upon the availability in the geographical area. Nuts can be divided in to two types such as tree nuts and legumes. The important tree nuts are viz., almonds, walnuts, pistachios, cashew nuts, Brazil nuts, hazelnuts, macadamia, and pine nut. Peanut is a legume commonly consumed as roasted or as pea nut butter. Pea nut is more economical than other nuts and popularly called as 'poor man's almond'. These nuts due to their unique nutritional properties are very much appreciated in vegan diets, gluten free diets and paleo diets [1]. Nut consumption and associated health benefits gained much interest in recent times and even considered as alternative to milk and meat [2, 3]. Nuts are the part of traditional Mediterranean diet and now the nutrition research community advocates its consumption in a regular basis [4].

There is a gradual increase in non-communicable diseases (NCDs) such as cardiovascular, obesity, diabetes and cancer in the population. The major reason for the NCDs are basically due to life style disorders, poor feeding habit, work related stress, and less physical activity. Cardiovascular diseases (CVDs) are a leading cause of mortality globally and in 2010 around 13 million people died due to heart related diseases [5]. Obesity constitutes a worldwide epidemic and is the major cause of type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease,

non-alcoholic fatty liver disease, reproductive dysfunction, respiratory abnormalities and psychiatric conditions [6]. According to the International Diabetes Federation (IDF) data there are 382 million diabetic people worldwide in 2013, and by 2035 the number will grow to 592 million. Diabetes brings huge economic burden to the individuals, family as well as the health care system of a country. Similarly, as per WHO reports the global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. These diseases are the serious concerns in the society for future developments and progress.

Nut consumption has proven role in reducing cardiovascular diseases [7], obesity [8], hypertension [9], diabetes mellitus [10], and cancer [11]. Dietary nuts reduces the mediators of chronic diseases such as oxidative stress, inflammation, visceral adiposity, hyperglycemia, insulin resistance, endothelial dysfunction, and metabolic syndrome with the unique bioactive compounds what they possess [12].

This chapter will review the nutritional composition of tree nuts and pea nut. The consumption of nut and health aspects related to cardiovascular disease, obesity, diabetes and cancer are also the major highlights of this chapter.

2. Nutrient composition of nuts

Nuts are good source of nutrients such as fats with good quantity of mono unsaturated fatty acids (MUFA) and poly unsaturated fatty acids (PUFA), soluble and insoluble fibers, vitamins E and K, folate, thiamine and minerals such as magnesium, copper, potassium, and selenium [13]. The phytochemicals such as phenolic compounds, zanthophyll carotenoids, alkaloids, and phytosterols compounds, with recognized benefits to human health are also the major constituents of nuts.

Nuts are very good source of fats after vegetable oil seeds and are calorie-dense (∼500–700 kcal/100 g edible portion). The lipid quantity in the nuts varies in a range of 40 to 75% (**Table 1**). Typically, walnut, macadamia, pine nut, Brazil nut and pecans contain higher lipid (∼70%) as compared to cashew, almond, pistachio and hazelnut which contains lipid between 45 and 62%. The lipid content of all the nuts varies according to the agro-climatic condition, maturity of kernels and varieties. Barreca et al. [14] observed lipid content 42.4–56% in 19 varieties of almond grown in different agro-climatic conditions. Similarly, Venkatachalam et al. [15] indicated a range in the lipid content 67–78.1% for 27 pecan cultivars grown in different regions of the United States. The availability of phytosterols and sphingolipids are also common in tree nuts. The sterol content in tree nuts ranges from 0.16 (pine nut) to 0.28 g/100 g (pecans) of the oil content. In the phospholipid fraction, all most all the tree nuts contain more amount of phosphotidylcholine in a range of 0.37 g/100 g oil (pine nut) to 0.78 g/100 g oil (Brazil nut) followed by phosphotididylserine in range of 0.32 g/100 g oil (almond and Brazil nut) to 0.59 g/100 g oil (pistachio) and phosphatidylinositol in a range of 0.08 g/100 g oil (hazel nut) to 0.31 g/100 g/100 g oil (walnut).

All most all the edible nuts contain good amount mono unsaturated fatty acids (MUFA) followed by poly unsaturated fatty acids (PUFAs) (**Table 2**). The MUFA content of nuts are basically in the form of oleic acid (18:1 n-9). The oleic acid content of almond varies in a range of 50 to 80% of the total MUFA content. Similarly, the oleic acid is 76 to 86% of the total MUFA content of hazelnut [16]. The PUFA content of almond is in the form of linoleic acid (LA, 18:2 n-6) which is around 24% of the total fat content. Nuts basically contain LA and alpha linolenic acid (ALA, 18:3 n-3) as PUFAs. However, LA is the dominant PUFA in nuts.

Micronutrients such as vitamins and minerals are the major groups of nutrients that the body needs for several physiological functions. Nuts such as almond,

Nuts	Oil content	TG	Sterol	Sterol ester	PS	PI	PC	PA	SL	Energy kcal
Almonds	53	98	0.25	0.05	0.32	0.17	0.56	ND	0.63	581
Walnuts	72.5	97.1	0.28	0.09	0.46	0.31	0.52	ND	0.68	618
Pistachio	54.1	95.8	0.21	0.03	0.59	0.28	0.68	ND	0.82	557
Cashew	45	96	—	—	—	—	0.54	—	—	553
Brazil nuts	68.9	96.6	0.19	0.05	0.32	0.10	0.78	ND	0.91	656
Pine nut	75.1	97.1	0.16	0.05	0.33	0.19	0.37	ND	0.57	629
Pecans	73.4	96.3	0.28	0.07	0.47	0.18	0.52	ND	0.55	691
Macadamia nuts	71.0	—	—	—	—	—	—	—	—	718
Hazelnuts	61.9	97.6	0.22	0.04	0.36	0.08	0.48	0.05	0.32	629

TG, triacylglycerol.
Source: Miraliakbari and Shahidi [17]; US Department of Agriculture Nutrient Data Base at http://www.nal.usda.gov/fnic/cgi-bin/nut_search.pl
Note: The oils of tree nuts were extracted using chloroform/methanol system; ND, Not Detected.

Table 1.
Lipid Classes (g/100 g oil) and energy content of nuts.

Nuts	Total fat	SFA	MUFA	PUFA	18:2n-6	18:3n-3
Almonds	50.6	3.9	32.2	12.2	12.2	0.00
Walnuts	65.2	6.1	8.9	47.2	38.1	9.08
Pistachio	44.4	5.4	23.3	13.5	13.2	0.25
Cashew	46.4	9.2	27.3	7.8	7.7	0.15
Brazil nuts	66.4	15.1	24.5	20.6	20.5	0.05
Pine nut	68.4	4.9	18.8	34.1	33.2	0.16
Pecans	72.0	6.2	40.8	21.6	20.6	1.00
Macadamia nuts	75.8	12.1	58.9	1.5	1.3	0.21
Hazelnuts	60.8	4.5	45.7	7.9	7.8	0.09
Peanuts	49.2	6.8	24.4	15.6	15.6	0.00

Source: Kim et al. [18], modified.

Table 2.
Fatty acid profile of nuts (g/100 g).

cashew nuts, pistachios, walnut and peanuts are very good source of B-vitamins, folate and vitamin E (**Table 3**). Nuts are also rich source of minerals such as magnesium and potassium (**Table 4**). Selenium is found particularly in Brazil nuts in greater concentrations.

There are varieties of phytochemicals present in nuts (**Table 5**) and they are well known in health and disease of humans [20]. Tree nut phytochemicals such as total phenols, flavonoids, proantocyanidins (PAC), stilbenes, phytosterols, carotenoids have been associated with many bioactivities such as antioxidant, antiviral, antiproliferative, hypocholesterolemic, and anti-inflammatory actions [21, 22]. The poly phenolic compounds are the major phytochemical class. All most all the tree nut are very good source of total phenolic compounds. However, walnuts and pecans are considered as the richest source of the total phenolic compounds

Nuts (mg/100 g)		Riboflavin (B_2) (mg/100 g)	Niacin (B_3) (mg/100 g)	Pantothenic acid (B_5) (mg/100 g)	Pyridoxine (B_6) (mg/100 g)	Cobalamin (B_{12}) (mg/100 g)	Folate (mg/100 g)	Vitamin C (total ascorbic acid) (mg/100 g)	Vitamin E (α-tocopherol) (mg/100 g)	Vitamin A (retinol activity equivalents) (mg/100 g)	Vitamin K (phylloquinone) (mg/100 g)
Almond	0.2	0.8	3.9	0.3	0.1	0.0001	0.05	0.0	25.9	0.0	0.0
Walnut	0.3	0.2	1.1	0.6	0.5	0.0005	0.098	1.3	13.0	0.001	0.0003
Pistachio	0.9	0.2	1.3	0.5	1.7	0.0017	0.051	5.0	2.3	0.028	0.0
Cashew nut	0.4	0.1	1.1	0.9	0.4	0.0004	0.025	0.5	0.9	0.0	0.0341
Brazil nut	0.1	0.04	0.3	0.2	0.1	0.0001	0.022	0.7	5.7	0.0	0.0
Hazelnuts	0.6	0.1	1.8	0.9	0.6	0.0006	0.133	6.3	15.0	0.001	0.0142
Pine nut	0.4	0.2	4.4	0.3	0.1	0.0001	0.034	0.8	9.3	0.0	0.0539
Pecan	0.7	0.1	1.2	0.9	0.2	0.0002	0.022	1.1	1.4	0.0	0.0035
Macademia	1.2	0.2	2.5	0.8	0.3	0.0003	0.011	1.2	0.5	0.0	0.0
Peanuts	0.18	0.04	5.75	0.59	0.11	-	0.062	0	0	0	0.00295

Source: Sathe et al. [19], modified.

Table 3.
Vitamin content of tree nuts and pea nut.

Nuts (mg/100 g)	Calcium	Magnesium	Sodium	Potassium	Copper	Iron	Zinc	Selenium
Almonds	248	275	1	728	1.03	3.71	3.12	0.004
Walnuts	98	158	2	441	1585	2.91	3.09	0.005
Pistachio	107	121	1	1025	1.3	3.92	2.2	0.007
Cashew	37	292	12	660	2195	6.68	5.78	0.019
Brazil nut	160	376	3	659	1.74	2.43	4.06	1.917
Hazelnut	114	163	0	680	1725	4.7	2.45	0.002
Pine nut	16	251	2	597	1.32	5.53	6.45	0.0007
Pecans	70	121	0	410	1.2	2.53	4.53	0.004
Macadamia	85	130	5	368	0.75	3.69	1.3	0.004
Peanut	92	168	18	705	1.14	4.58	3.27	0.007

Source: United States Department of Agriculture Nutrient Database for Standard Reference.

Table 4.
Mineral composition of nuts.

containing around 1600 mg GAE/100 g. Almond, Brazil nuts, cashews, macadamias and pine nuts contains almost similar amount of total phenol between 200 to 300 mg GAE/100 g. Flavonoids are a subclass of phenolics and mainly are available in three forms such as flavan-3-ols, flavonols and anthocyanins. In tree nut, the flavonoid content varies from 0.03 mg/100 g in pine nuts to 2700 mg/100 g in pecans. Hazel nuts and pecans are the major source of Proanthocyanidins (PAC) and contains around 500 mg/100 g. Stilbenes are the plant secondary metabolites derived from the phenylpropanoid pathway [23]. Among nuts, pistachio (803.22 μg/100 g) is the only nut has been reported to contain stilbenes. The sterol content in tree nuts ranges between 105 to 233 mg/100 g. Carotenoids are the color pigments which is ubiquitous in the plant kingdom. There are more than 750 carotenoids have been reported in nature, out of which 500 have been properly characterized. Brazil nut and Macadamias are reported to have no carotenoids however; pistachios are very rich in carotenoid content (22,832 μg/100 g). Cashew nut kernel contains carotenoids such asβ carotene (9.57 μg/100 g), lutein (30.29 μg/100 g) and zeaxanthin (0.56 μg/100 g) [24]. Hazel nut contains appreciable level of carotenoids (106 μg/100 g). Carotenoid content in the hazelnut oil was estimated as 5.51 mg/kg oil while lutein and zeaxanthin were determined as main carotenoids with the concentration of 0.19 and 0.85 mg/kg oil, respectively [25]. Alkaloids are widely distributed and occurring in approximately 20% of plant species. Alkaloids are not common in nuts only negligible amount was detected in walnuts. Tree nuts contain a significant amount of phytates from 100 to 2500 mg/100 g. Almonds have the highest reported phytate content, while pine nuts and Brazil nuts having the lowest content.

3. Nut consumption and relationship between disease conditions

3.1 Almond

Almonds are rich in macro and micro nutrients and upon consumption in adequate quantity impart a lot of health benefits. Traditionally, the ancient Greeks, Persians, Chinese and Indians use almonds for medical purposes as a health-promoting food [26]. There are also several epidemiological studies and clinical trials

Tree nut	Total phenols (mg GAE/100 g)	Flavonoids (mg/100 g)	Proanthocyanidins (mg/100 g)	Stilbenes (mg/100 g)	Sterol (mg/100 g)	Carotenoids (mg/100 g)	Alkaloids (mg/100 g)	Phytates (mg/100 g)
Almond	261	25.01	184.10	ND	192.37	0.002	ND	2542.11
Walnuts	1602	0.54	67.25	ND	197.89	0.021	0.0004	2070.00
Pistachios	703	136.45	252.71	0.803	189.43	22.83	ND	1562.50
Cashews	242	1.12	8.70	ND	154.00	0.031	ND	697.73
Brazil nuts	197	0.85	0–10	ND	160.19	—	ND	190.00
Hazelnuts	447	13.21	500.66	ND	132.47	0.106	ND	1285.00
Macadamias	233	137.9	0–10	ND	105.70	ND	ND	470.85
Pecans	1588	2713.49	494.05	ND	233.52	0.055	ND	851.60
Pine nuts	206	0.03	0–1	ND	190.75	0.026	ND	200.00

Source: Kim et al. [18].

Table 5.
The phytochemical content of the nuts.

which reports positive effects of nut consumption against a different diseases conditions like cardiovascular conditions, inflammation and oxidative stress, obesity, hypertension, diabetes mellitus and metabolic syndrome [14]. The consumption of almond and relationship between different disease conditions is presented in **Table 6**.

3.1.1 Almond and cardiovascular disease

The role of dietary almonds against cardiovascular disease (CVD) has been shown in several studies. The high carbohydrate or saturated fatty acid diet is often associated with impaired glucose and lipid homeostasis which alters blood lipid profile in terms of elevated low density lipoprotein cholesterol (LDL-C), total cholesterol, apolipoprotein B (Apo B), and increases body weight which leads to cardiovascular risks. A recent study conducted by Wang et al. [27] reported that 42.5 g almond consumption per day changes LDL-C which is also cost effective to prevent cardiovascular disease in the short term and potentially in the long term. Furthermore, studies conducted by Gulati et al.[28] and Jalali-Khanabadi [29] reported that dietary almond can improve blood lipid profile by lowering total cholesterol (TC) and triglyceride, respectively in cardiovascular patients. In addition to their cholesterol-lowering effects, the ability of almonds to minimize the risk of heart disease may also be attributed to the antioxidant activity of vitamin E found in them. A meta-analysis of randomized controlled trial conducted by Lee-Bravatti et al. [30] also found that >42.5 g daily consumption of almond reduced TC, LDL cholesterol, and also significantly decreased other CVD risk factors such as body weight. Almond consumption, other than cholesterol reduction also associated with control of hyperlipidemia, inflammation, blood pressure, blood glucose and insulin concentrations, metabolic syndrome, and body weight/fat/composition which also plays key roles in managing cardiovascular risk factors [31]. The lower blood HDL-C is the marker of cardiovascular risk [32]. Drug therapies to increase the HDL-C level are not very much successful. Some combination of medicine such as high doses of niacin, fibric acid or bile acid sequestrants can improve HDL-C minimally [33]. According to the Indian Heart Association 2015, risk of heart disease comes to half with every 10 fold increase in HDL-C [34].

The phytochemicals such as phytates and phenolics compounds in almonds confers antioxidant, anti-inflammatory and lipid-lowering properties [35]. Almond also contains good quantity of magnesium and potassium. Magnesium deficiency is not only associated with heart disease, but also the lack of adequate magnesium causes free radical damage to the heart [36]. Potassium is an effective electrolyte necessary to maintain normal blood pressure.

3.1.2 Almond and obesity

Obesity is a very serious problem in the affluent nations which is also the basic reason of type 2 diabetes (T2D). There are studies which demonstrate the role of almond consumption on overweight and obesity in humans. A 24 week clinical trial was conducted with 65 overweight and obese (body mass index (BMI): 27–55 kg/m^2) adults of age group between 27 to 79 y [37]. In the weight reduction program, the subjects were received almond enriched and complex carbohydrate enriched low calorie diet (LCD) with similar protein and calories. The main outcome of the study was based on the anthropometric, body composition and metabolic parameters which showed that almond-LCD group experienced a sustained and greater weight reduction than the complex carbohydrate fed group. The authors concluded that the results could be due to high MUFA content in almonds which have high oxidation rate than get stored as fat. In another 12 week clinical trial with 86 healthy subjects with a BMI

Design and study population	Intervention	Duration	Main outcomes	Reference
Cardiovascular disease				
US adults of mean age approximately 30 years (150 participants)	42.5 g almond/day	12 months	42.5 g almond/day is a cost-effective approach to prevent CVD. Decrease in LDL-C	[27]
Asian Indians	Raw almonds (20% of energy intake)	24 weeks	Lowered waist circumference, waist-to-height ratio, TC, serum triglycerides and LDL-C	[28]
Thirty healthy volunteer men (age 45.57 ± 7.14 years and body-mass index 24.29 ± 2.15 kg/m^2)	60 g almond/day	4 weeks	Decreased LDL-C, total cholesterol (TC), and apolipoprotein B100 (apo-B100)	[29]
Meta-analysis (534 subjects)	>42.5 g almond/day	15 eligible trials	Decreased TC and LDL cholesterol, and body weight.	[30]
Obesity				
A randomized trial (65 overweight and obese adults)	A formula-based low calorie diet enriched with 84 g/day of almonds	24 weeks	Weight reduction	[37]
A randomized controlled clinical trial 86 healthy adults [body mass index (in kg/m^2): 25–40]	Almond-enriched diet (AED) (15% energy from almonds)	12 weeks	Reduced truncal and total body fat. Reduced diastolic blood pressure	[38]
A randomized study (Overweight and obese individuals [n = 123; age = 46.8 y, BMI (in kg/m^2) = 34.0])	Hypocaloric almond-enriched diet	18 months	Reduced weight. Improved lipid profile	[39]
Diabetes				
Asian Indians	Raw almonds (20% of energy intake)	24 weeks	Lowered glycosylated hemoglobin and improvements in sensitivity C-reactive protein (hs-CRP)	[28]
A randomized, 5-arm, crossover design study (14 impaired glucose tolerant (IGT) adults)	Whole almonds (WA), almond butter (AB), defatted almond flour (AF), almond oil (AO) or no almonds (vehicle - V) were incorporated into a 75 g available carbohydrate-matched breakfast meal		Reduced blood glucose	[41]

Design and study population	Intervention	Duration	Main outcomes	Reference
Randomized, crossover and controlled feeding trial (33 Chinese patients)	60 d almond/day	12 weeks	Decreased post-interventional fasting serum glucose	[42]
15 healthy subjects	Almond co consumed with bread	4 hours	Decreased glycemic excursion. Increased Serum protein thiol	[43]
A randomized crossover trial [19 adults (including 7 adults with type 2 diabetes mellitus)]	28 g/day	12 weeks	Reduced hemoglobin A (1c). Reduced postprandial glycemia	[40]
Cancer				
A case control study (923 colorectal cancer patients and 1846 controls, Korea)	Nut consumption was categorized as none, < 1 serving per week, 1–3 servings per week, and ≥ 3 servings per week	Dietary intake information collected using a semi-quantitative food frequency questionnaire	≥3 servings per week reduced risk of colorectal cancer	[45]
Six-week-old male F344 rats (Treated with azoxymethane)	Whole almond, almond meal or almond oil containing diet	26 weeks	Reduced colon cancer risk	[51]

Table 6.
Effect of almond consumption on different disease conditions.

25 to 40 kg/m^2 when treated in two diet intervention groups: an almond-enriched hypocaloric diet (AED, 15% of total kcal from almonds) and a nut-free hypocaloric diet (NFD) for 12 weeks showed AED followed group had significant weight loss with reduced truncal fat mass. Similarly, the authors concluded that the results might be due to the unsaturated fatty content in almonds which is more oxidation prone than storage [38]. A study conducted by Foster et al. [39] on 123 overweight and obese adults found that a daily dose of 56 g almond for 6 months is effective in body weight loss. Taking the above results in to consideration it is understood that the MUFA, fiber and protein of almond have a satiating effect and benefit individuals during weight loss program.

3.1.3 Almond and diabetes

The role of almond supplementation in glucose homeostasis has been studied by several researchers [28, 40]. In 2017, Gulati and colleagues [28] reported the health benefits of almond in terms of measures of glycemia through the assessment of glycosylated hemoglobin (HbA1c) in the type 2 diabetic (T2D) patients when provided 20% of the total energy intake for 24 weeks along with diet and physical activity counseling. The HbA1c levels in subjects after almond supplementation declined significantly compared with their levels on the control diet which is clinically accepted as the indicator of reduction in the diabetic complications. Overall, the study suggested that dietary almond controls glycemic condition through insulin management rather than in reduction of glucose absorption or increased clearance. Similarly, Mori and colleagues [41] reported that almond consumption

improved the metabolic profile by decreasing blood glucose concentrations when included in the breakfast meal of 14 impaired glucose tolerant (IGT) adults. It is suggested that the high content of fiber, high unsaturated fatty acid and low carbohydrate which makes almond as low glycemic index food played a role in the reduction of glucose. Under nutrition therapy Chen et al. [42] made 40 T2D patients receive almond for 12 weeks after a 2 weeks run in period among 27 of 33 patients with the baseline HbA1c ≤8, almond receiving groups decreased post-interventional fasting serum glucose and HbA1c by 5.9% and 3.0% as compared to that of control, respectively. It is concluded from the study that almonds incorporated into healthful diets can improve glycemic status in diabetic patients with a better glycemic control. Many clinical interventions suggested that dietary almond through multiple mechanisms of actions, i.e., reducing glycemic index value of co-consumed food, increasing insulin secretion, and alleviating insulin resistance controls diabetes [40, 43]. It is also suggested that the polyphenols mainly flavonoids present in almond also controls blood glucose levels by the action of inhibiting amylase which is a carbohydrate digestive enzyme [40, 44].

3.1.4 Almond and cancer

In 2018, Lee and colleagues [45] conducted a case study among 923 colorectal cancer patients and 1846 controls recruited from the National Cancer Center in Korea. They collected the dietary intake information of food items including nuts such as peanuts, pine nuts, and almonds (as 1 food item). The results of the study showed that high consumption of nuts (>45 g/week, in three servings) was strongly associated with reduced risk of colorectal cancer. Authors concluded that the relationship between nut consumption and reduction of colorectal cancer risk could be due to the presence of fiber, resveratrol, selenium, flavonoids (quercetin), polyphenols (ellagic acid), and folic acid. These bioactive compounds have strong antioxidant properties which regulate cell proliferation, reduce DNA damage, inflammatory response and immunological activity as indicated by Gonzalez and Salas-Salvado [46]. The triterpenoids present in almond, including betulinic, oleanolic, and ursolic acids, have also been reported earlier as antitumor agents [47, 48]. There are studies which depicts about the link between the consumption of roasted almond and development human cancer because of the presence of acrylamide in it. Almonds contain free asparagine and reducing sugars and acrylamide is formed when undergo roasting above 154°C temperature [49]. Acrylamide can be found in roasted almonds, but is not found in raw almonds. As per National Health and Nutrition Examination Survey (NHANES) (2001–2010), daily almond consumption for a habitual American consumer is 29.5 g [50]. A consumer of body weight of 65 kg the daily acrylamide exposure from almonds would be 0.08 μg/kg body weight. The unroasted almond consumption is more a common practice therefore; the actual acrylamide exposure from almonds would be lower. Anticancer property of almond and its extracts has been also been reported. Davis and Iwahashi [51] reported that whole almond and almond fractions can reduce aberrant crypt foci (ACF) in a rat model of colon carcinogenesis. According to Heasman and Mellentin [52] the anticancer properties of almond is mainly attributed to the phytochemicals such as, quercetin and kaempferol, which suppresses lung and prostate tumor cell growth. Almond consumption and the overall health benefits are presented in **Figure 1**.

3.2 Walnuts

Walnut is one of the world's most popular temperate grown nuts. Walnut kernel is a rich source of proteins, fats, minerals, vitamins, and polyphenols that render the

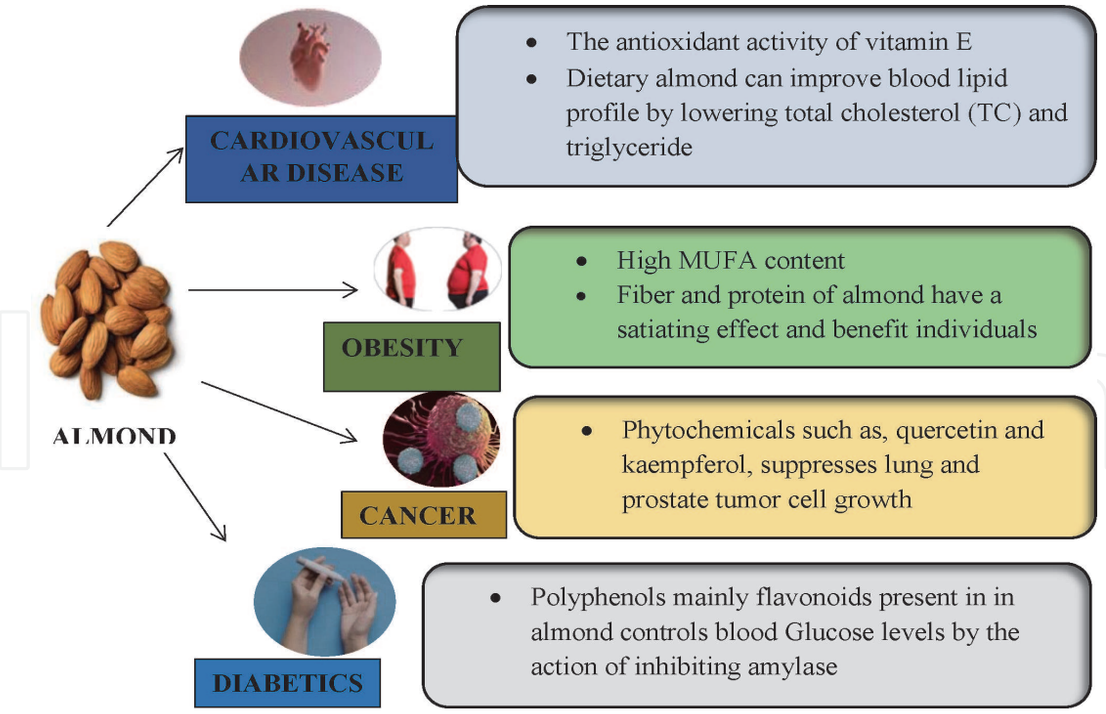


Figure 1.
Almond consumption and health benefits.

fruit indispensable for human nutrition. These also have a good source of flavonoids, sterols, pectic compounds and phenolic acids. Worldwide 3.7 tonnes of walnut is produced per year and china contributes approximately 50 per cent of the total world walnut production (atlasbig.com/en-in/countries-by-walnut-production). The consumption of walnut and relationship between different disease conditions is presented in **Table 7**.

3.2.1 Walnut and cardiovascular disease

Walnuts differ from other nuts in terms high LA and ALA content which has known anti atherogenic properties [53]. It is also recommended that 84 g of walnut on a daily basis for four weeks has a potential to decrease serum levels of total cholesterol by 12% [54]. The beneficial effect of walnut consumption in reducing the risk of CVD is not limited to reducing blood cholesterol level only but also attributed to the lowering LDL-C, vascular inflammation, improving endothelial dysfunction and enhancing antioxidant activity [55–57]. The cholesterol lowering effect of walnut could be due to the presence of phytosterols in it. According to Gylling et al. [58] intake of phytosterols (2 g/day) is associated with a significant reduction (8–10%) in LDL-cholesterol because phytosterol mostly interfere in the intestinal absorption of cholesterol. In 2014, Wu and colleagues [59] assessed the effect of walnuts on lipid and glucose metabolism, adipokines, inflammation and endothelial function in 40 healthy subjects, 10 men and 30 postmenopausal women ≥50 years old with BMI 24.9 ± 0.6 kg/m^2. The subjects first received a walnut enriched (43 g/d) and then a Western-type (control) diet or vice-versa, with each lasting 8 weeks and separated by a 2-week wash-out. The study reported that walnut diet significantly reduced non-HDL cholesterol (walnut vs. control: −10 ± 3 vs. −3 ± 2 mg/dL; p = 0.025) and apolipoprotein-B (−5.0 ± 1.3 vs. −0.2 ± 1.1 mg/dL; p = 0.009) in comparison to control diet after adjusting for age, gender, BMI and diet sequence. Total cholesterol showed a trend toward reduction. However, fasting adipokines, C-reactive protein, biomarkers of endothelial dysfunction, postprandial

Design and study population	Intervention	Duration	Main outcomes	Reference
Cardiovascular disease				
A randomized trial (18 healthy men)	20% calorie from walnut	4 weeks	Reduced total cholesterol, lowered LDL-C/HDL-C ratio	[54]
Five controlled clinical trial (200 subjects)	Walnut consumption varied from 28 g/day to 78 g/day	3–6 weeks	Reduced the TC, LDL-C, and HDL-C values. Decreased ratios of TC:HDL-C and LDL-C:HDL-C. Reduced apo B levels	[55]
A randomized 2-period, crossover and controlled intervention study (27 overweight volunteers)	23.1% energy from walnut	2–6 weeks	Improved flow mediated dilation and biochemically by sVCAM (soluble vascular cell adhesion molecules)	[57]
A randomized cross over study (40 subjects)	43 g/day	8 weeks	Reduced total cholesterol, non-HDL-cholesterol and apolipoprotein-B	[59]
Obesity				
Overweight and obese subjects (n = 100)	walnut-enriched (15% of energy) reduced-energy diet	3–6 months	Weight loss, favorable effects on LDL-C and systolic blood pressure	[61]
A randomized, controlled, crossover trial (46 overweight adults)	Walnut enriched *ad libitum* diet	8 weeks	Improved flow-mediated vasodilation (FMD), no weight gain	[62]
A double-blinded, randomized, placebo-controlled study (15 obese subjects)	48 g/day	4 days	Increases apolipoprotein A concentrations	[65]
Diabetes				
Dietary interventions and cohort studies	Walnut consumption from dietary recall	Over a period of 15 years	Reduced risk of diabetes, reduced blood glucose and HbA1c	[66]
A randomized control clinical trial (100 patients)	Walnut oil 15 g/day	3 months	Decreased HbA1c level, reduced fasting blood sugar	[69]
Diabetic male rats (200 g)	Walnut oil gavage with β-sitosterol0.5 ml/kg	4 weeks	Decreased inflammation of lymphocytes, improved blood parameters	[71]
Cancer				
Human esophageal adenocarcinoma cell line	20 mg/mL walnut oil		Induced necrosis and accumulation of cells in G0/G1 phase. Down regulated NFkB expression	[78]
Effect of walnut methanolic extracts on human renal cancer cell lines A-498 and 769-P and the colon cancer cell line Caco-2	0.226 and 0.291 mg/mL walnut extract		Inhibited growth of human kidney and colon cancer cells	[79]
Human cancer cell line	Chloroform and ethyl acetate extract of walnut		Reduced proliferation of HepG-2, liver cancer cell line	[80]
Cancer stem cells (CSCs)	Walnut phenolic extract (WPE)		Inhibited cell differentiation, down regulated CSCs markers	[81]

Table 7.
Effect of walnut consumption on different disease conditions.

lipid and glucose metabolism and endothelial function were unaffected. It was concluded from the study that daily consumption of 43 g of walnuts for 8 weeks could be beneficial for the reduction of non-HDL-cholesterol and apolipoprotein-B, beneficial in lowering CHD risk. It is suggested that the increased PUFA intake through walnut could be responsible for the lowered cholesterol in the subjects. Walnut not only a good source of PUFA but also contains a lower ratio n6/n3 ratio. It is suggested that the lower n-6/n-3 ratio is desirable in reducing the risk of many of the chronic diseases including lowering blood cholesterol, reducing vascular inflammation and improving endothelial function [60].

3.2.2 Walnut and obesity

Better weight management and less adiposity can be maintained with regular nut consumption. Rock and colleagues [61] conducted a study where overweight and obese men and women (n = 100) were randomly assigned to a standard reduced energy- density diet or a walnut-enriched (15% of energy) reduced-energy diet in the context of a behavioral weight loss intervention. Both study groups reduced weight, body mass index and waist circumference. Change in weight was $9.4 \pm 0.9\%$ vs. $8.9 \pm 0.7\%$ for the standard vs. walnut-enriched diet groups, respectively. The results of the study demonstrated that a walnut-enriched reduced-energy diet can promote weight loss that is comparable to a standard reduced-energy-density diet in the context of a behavioral weight loss intervention. It is suggested that despite walnut is very high in energy density, but when consumed as a component of a reduced-energy diet the total energy intake get reduced and also give a satiety response. The study conducted by Katz et al. [62] on effects of walnuts on endothelial function in overweight adults with visceral obesity found that daily ingestion of 56 g of walnuts with *ad libitum* diet in comparison ad libitum diet without walnut did not lead to weight gain however, improved endothelial function. Adiponectin is a peptide secreted from adipocytes, whose low concentration is an indicator of overweight, visceral fat accumulations and related diseases such as insulin resistance/T2D and cardiovascular disease [63]. The production of adiponectin and its role is presented in **Figure 2**. Cardona-Alvarado et al. [64] found that adiponectin concentration increased by 30% in obese subjects supplemented with a daily intake of approximately 15 g of walnuts. Similarly, Aronis et al. [65] reported that after short-term (four days) consumption of 48 g/d walnut, 6.4% adiponectin increased in the circulation. The results suggested that the improvement observed in the metabolic state may be due to the activation of peroxisome proliferator-activated receptor alpha (PPARγ) and adiponectin expression, promoted by the increase in circulating lipocalin2 (Lcn2) concentrations which is a novel regulator of brown adipose tissue.

3.2.3 Walnut and diabetes

Arab and colleagues [66] examined the associations between walnut consumption and diabetes risk using data from the National Health and Nutrition Examination Survey. Diabetes status or risk was assessed on self-report, medication use, fasting plasma glucose levels, and haemoglobinA1c (HbA1c) levels. The results demonstrated that walnut consumers had lower risk for diabetes compared with non-nut consumers and prevalence of diabetes dropped 47%. It is suggested from the study that walnut possibly impact hunger. The decreased feelings of hunger and appetite and increased activation of the right insula indirectly reduces risk of diabetes. In the diet of diabetic patients, carbohydrate is replaced with MUFAs and PUFAs under therapeutic strategy [67]. The intake of MUFAs by diabetic patients

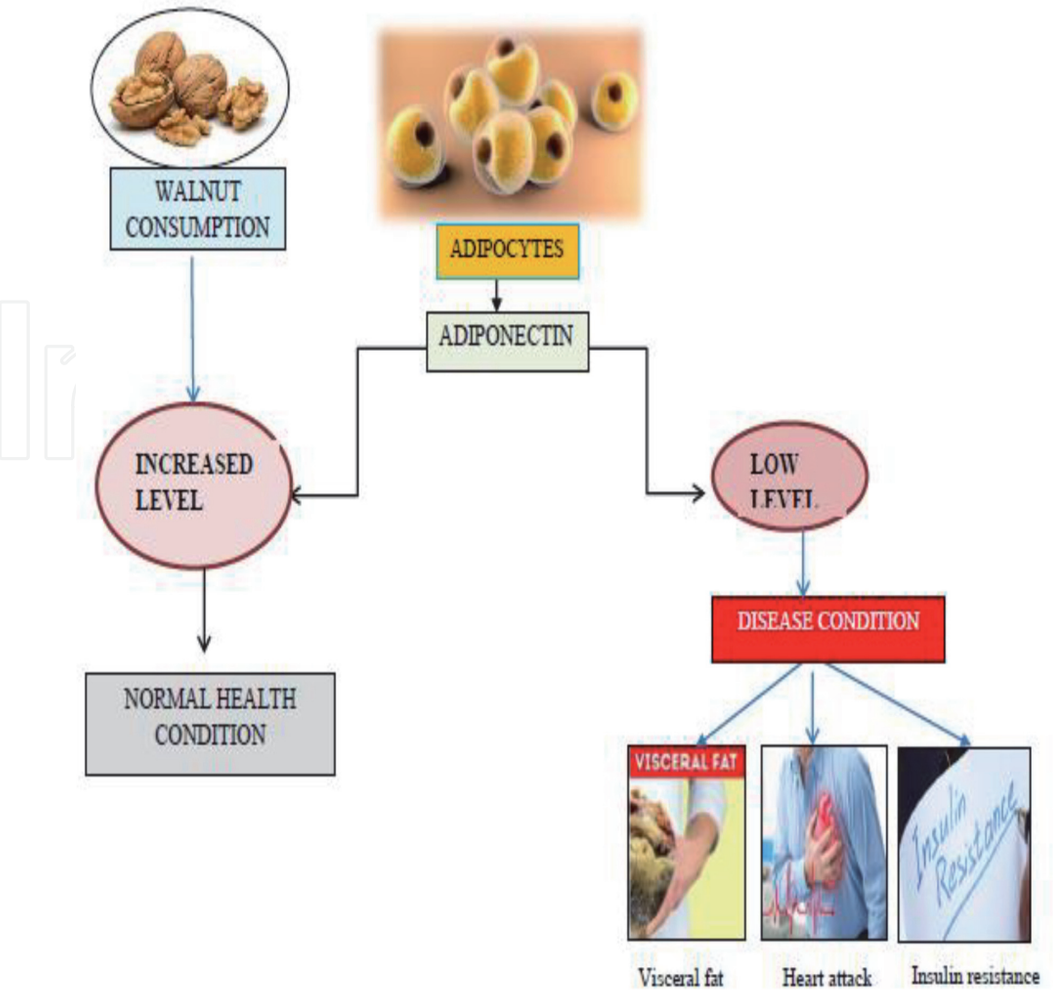


Figure 2.
Walnut intake increases circulating adiponectin levels.

has also been seen with elevated high density lipoprotein (HDL)-cholesterol levels and improved blood sugar changes [68]. In this regard, Nezhad et al. [69] reported that consumption of walnut oil (15 g/day for three months) can improve blood glucose level. It is also suggested that oils containing PUFA could exert their antidiabetic effect by reducing resistance and enhancing sensitivity to insulin via the mechanism of over expression of glucose transporter GLUT4 and insulin receptors on the adipocyte membrane [70]. A study conducted by Ghorbani et al. [71] found that walnut oil led to reduction in blood glucose, cholesterol, triglyceride, ASP, ALT, ALP, and bilirubin in diabetic rat. It is suggested that the better blood profile was primary because of the β-sitosterol in the walnut oil. β-Sitosterol is considered as an important potential factor in diabetes mellitus due to its effect on regulation of glucose adsorption, adipogenesis, and lipolysis in adipocytes. It is also presumed that like insulin, β-sitosterol down regulates GLUT4 expression however, not fully confirmed yet [72]. Recent studies have reported that the composition and the balance of gut microbiota are involved in the obesity and obesity-related complications such as nonalcoholic fatty liver disease (NAFLD), insulin resistance and T2D [73]. In this regard, Li et al. [74] observed that polyphenol rich walnut meal (WMP) impeded the changes of intestinal flora in feces of rats, the gut microbiota mainly included Firmicutes, Bacteroidetes, and Proteobacteria, the symbol of healthy gut micro biota composition. This is the indication of promising effects of WMP on T2DM through the change in gut microbiota composition. Authors of the study highlighted that WMP decreased the levels of TNF-α and IL-6 in serum. TNF-

α is the first pro-inflammatory cytokine recognized for its involvement in pathogenesis of insulin resistance and T2DM. TNF-α reduces the expression of insulin-regulated glucose transporter type 4 (GLUT4) and increases the diabetic risk [75].

3.2.4 Walnut and cancer

There are several studies which highlights the anticancer properties of walnuts in mice. Hardman [76] summarized the potential of walnut in cancer prevention and treatment in mice. The points what he put forth was as follows: (1) the walnut-containing diet inhibited the growth rate of human breast cancers implanted in nude mice by 80%, (2) the walnut-containing diet reduced the number of mammary gland tumors by 60% in a transgenic mouse model, (3) the reduction in mammary gland tumors was greater with whole walnuts than with a diet containing the same amount of n-3 fatty acids, supporting the idea that multiple components in walnuts additively or synergistically contribute to cancer suppression and (4) walnuts slowed the growth of prostate, colon, and renal cancers by anti-proliferative and antiangiogenic mechanisms. The author explained that the n-3 fatty acids, tocopherols, b-sitosterol, and pedunculagin, present in walnuts all have cancer-prevention properties. Induja et al. [77] reported the cytotoxic effects of walnut oil on oral cancer cell line by DNA fragmentation. They suggested that other than perfect balance of n-6 and n-3 fatty acids, the walnut residue is rich in protein with anticancer peptides. In 2018, Batirel and colleagues [78] investigated the effect of walnut oil on tumor growth and metastatic potential in esophageal cancer cells. The results of the study confirmed that 20 mg/mL walnut oil reduced cell viability of esophageal cancer cells by ~50% when compared with control. Walnut oil exhibited anti-carcinogenic effect by inducing necrosis and cell cycle arrest at the G0/G1 phase. It down regulated the NFkB pathway. It is suggested from the study that walnut oil, and walnut consumption, may have beneficial effects in esophageal cancer in humans. Similarly, the anti-carcinogenic effect of walnut extract has been seen due to the antioxidant and anti-proliferative activity in many different cell lines such as MCF-7 (estrogen receptor positive breast adenocarcinoma), HepG-2 (liver), WRL-68 (liver), A-498 (renal), 769-P (renal), KB (oral and mouth), and Caco2 (colon) [79, 80]. In another study, walnut phenolic extract (WPE) and its bioactive compounds suppressed colon cancer cell growth by regulating colon cancer stem cells (CSC) [81]. This study evaluated the anti-CSCs potential of walnut phenolic extract (WPE) and its bioactive compounds, including (+)-catechin, chlorogenic acid, ellagic acid, and gallic acid. WPE and its bioactive compounds to mediate an inhibition of colon CSCs by inducing cell differentiation, down-regulation in the expression of the CSC markers, CD133, CD44, DLK1, Notch1, and β-catenin/p-GSK3 signaling pathways and suppress CSC self-renewal capacity. These results suggest that WPE has the potential to prevent and treat human malignant colorectal cancer by regulating CSCs. In another study, it was found that telomere length in WPE-treated cells were significantly decreased in a dose dependent manner which could be a mechanistic link to the effect of walnuts on the viability of colon CSCs. Telomere maintenance is a prerequisite for indefinite proliferation in cancer. Therefore, inhibiting the maintenance of telomeres may prove to be a useful strategy for cancer therapy [82]. Walnut consumption and the overall health benefits are presented in **Figure 3**.

3.3 Pistachio

The Islamic Republic of Iran and United States of America are the world leaders in pistachio production and cultivation followed by Turkey and China. Pistachio is

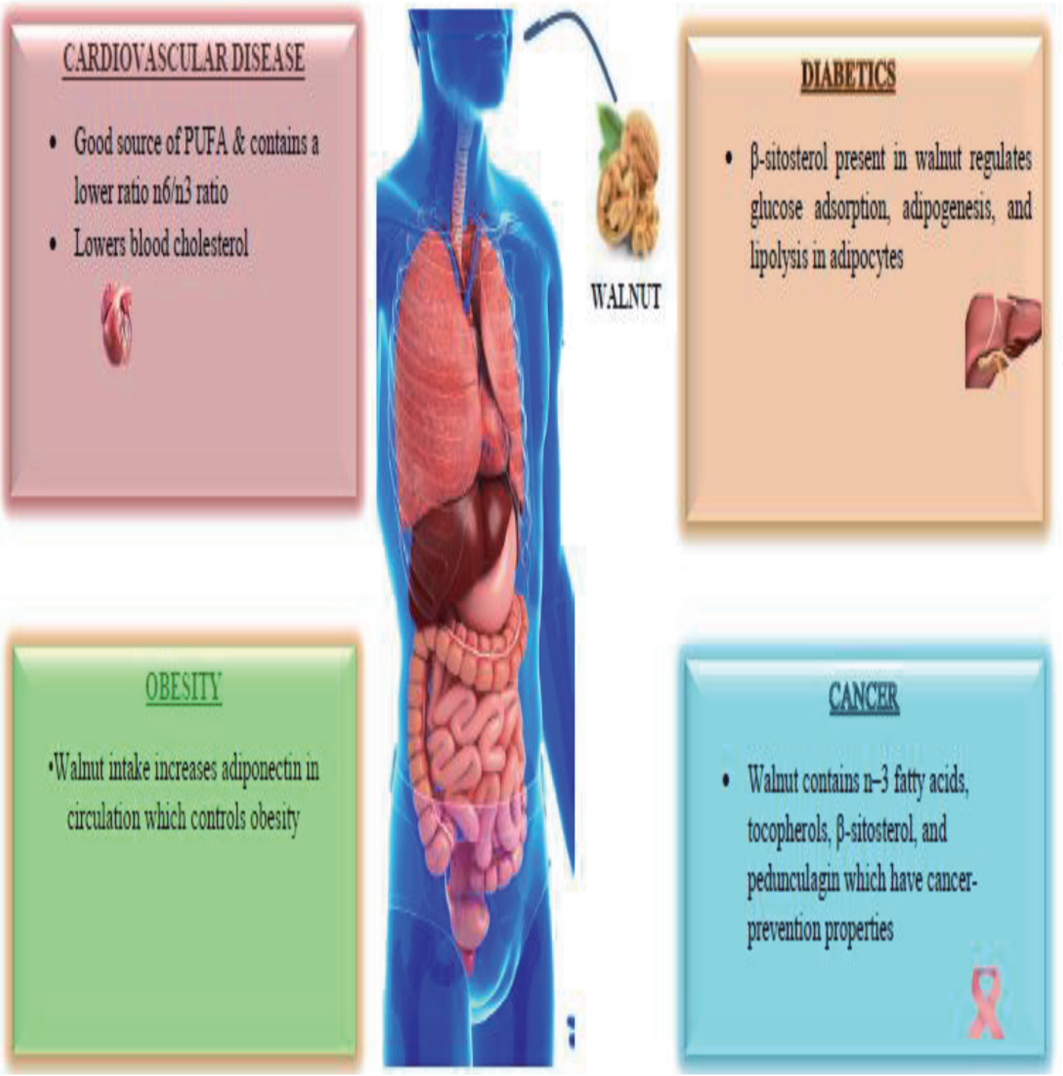


Figure 3.
Walnut consumption and health benefits.

known as the "green nut" and has been associated with human activities since centuries [83]. Pistachios are good source of unsaturated fatty acids (linoleic acid, linolenic acid, and oleic acid). They also contain a high amount of monounsaturated fatty acids (MUFA) (>55%) [84]. Pistachios contain the highest levels of potassium, g-tocopherol, vitamin K, phytosterols, folate, and xanthophyll carotenoids in comparison to other nuts. The diverse set up of nutrients makes pistachio a very good health promoting food. The consumption of pistachio and relationship between different disease conditions is presented in **Table 8**.

3.3.1 Pistachio and cardiovascular disease

Pistachios are rich source of numerous antioxidants, including tocopherols, carotenes, lutein, selenium, flavonoids, and phytoestrogens. The high rate of tocopherol in pistachio prevents heart disease, LDL oxidation, diabetes, and cancer and promotes the immune system. Pistachios can enhance blood lipid profiles in subjects with moderate hypercholesterolemia, and can in turn, reduce the risk of Chronic Vascular Diseases [85]. The beneficial effect of pistachios on lipid profiles may be due to essential fatty acids (EFAs) in its composition. In a study, when pistachios were given to healthy young men for 4 weeks, significant decreases in

blood glucose, total cholesterol, and serum interleukin-6 were observed with improved endothelium vasodilation and total antioxidant status [86]. The intake of pistachios has been shown to significantly decrease oxidative stress as it contains the highest amount of antioxidants. In another study, when twenty-eight hypercholesterolaemic adults were intervened with a diet containing 10 and 20% of energy from pistachios (32–63 and 63–126 g/d, respectively) showed increased antioxidant concentrations in serum, such as g-tocopherol, lutein and b-carotene, whereas it decreased oxidized LDL concentrations comparison to a control diet without pistachios [87]. In 2007, Sheridan and colleagues [88] conducted a randomized cross over trial where 15 patients with moderate hypercholesterolemia intervened with 4 weeks of dietary modification with 15% caloric intake (about 2–3 ounces per day), from pistachio nuts. Results of the study showed significant changes in some blood parameters such as 12% increase HDL-C and 9% decrease in TC/HDL-C, 14% decrease in LDL-C/HDL-C, 13% decrease in B-100/A-1 and 9% decrease in LDL-C. The results elucidate the effect of pistachio in reducing risk of coronary disease by improvement of the lipid profiles. It has been reported that TC/HDL-C and LDL-C/HDL-C are better predictors of CHD risk reduction than changes in levels [89]. London et al. [90] in a rat model found the health benefits of dietary pistachio in terms of lowered total cholesterol, LDL-C fractions, a beneficial change in TC/HDL-C and LDL-C/HDL-C. Regarding the ideal doses, 40 g or 1.5 oz./day of pistachio intake found suitable for reduced fasting glucose and LDL-C concentrations and increased HDL-C with improvements in vascular function in a clinical trial with mild dyslipidemic adults [91]. The pistachio (42 and 84 g/day) nut intervention during three weeks also lowered LDL-c concentrations (6%) in healthy volunteers [92]. Pistachio is a magnesium rich nut (121 mg/100 g). Magnesium is associated with lower the risk of abnormal cardiac excitation, atherosclerosis, ischemic heart disease, and congestive heart failure [93]. Considering all these studies, the beneficial effects of pistachios on lowering the risk of CVD could be through lipid-lowering, imparting many antioxidant properties and magnesium content in it.

3.3.2 Pistachio and obesity

Obesity is associated with chronic low-grade inflammation which eventually leads to abnormal metabolisms. A recent study conducted on mice demonstrated that chronic intake of pistachio exerts beneficial effects in obese mice by alleviating inflammation in adipose tissues and liver, and impacting the gut microbiome composition [94]. Nuts are very energy dense food item and there are reports of weight gain with increased consumption of nuts without energy balance. However, the daily ingestion of either 42 g or 70 g/day of pistachios for 12 weeks did not contribute to change in BMI or waist-to-hip ratio in Chinese subjects with metabolic syndrome [95]. In a recent randomized controlled intervention, sixty healthy premenopausal women in a group of 30 each consumed 44 g (250 kcal) pistachios midmorning while controls (n = 30) maintained their current eating habits for 12 weeks. Pre- and post-intervention tests showed that *ad libitum* intake adjusted to the pistachio portion, mostly via reduced intakes of carbohydrates and starch, in parallel with decreased hunger and increased satiety following the morning snack. It was concluded from the study that daily intake of 44 g pistachios improved nutrient intake without affecting body weight or composition in healthy women. It was also found that Intakes of MUFA, PUFA, linoleic acid, thiamin, pyridoxine, copper, manganese, and zinc were significantly higher among women consuming the pistachio snack, in spite of compensatory adjustments in intake [96]. Similarly, in another study, in healthy French women, in which a daily portion of pistachios was compared to an isoenergetic load of a comparator food (cheese biscuits) ingested in

Design and study population	Intervention	Duration	Main outcomes	Reference
Cardiovascular disease				
A randomized, crossover controlled-feeding study	Pistachio amounts ranged from 32 to 63 g/d for the 1 PD and 63 to 126 g/d for the 2 PD, depending on energy level	4 weeks	Increased plasma leutin, α-carotene, and β-carotene. Lowered serum oxidized-LDL concentrations, lowered cholesterol	[87]
Randomized crossover trial (15 subjects)	15% caloric intake from pistachio nuts	4 weeks	Reduced TC/HDL-C, LDL-C/HDL-C andB-100/A-1. Increased HDL-C	[88]
Open label, randomized parallel-group study (60 adults with mild dyslipidemia)	40 g/day	3 months	Increased HDL-C, reduced LDL-C, total cholesterol and fasting blood sugar. Improved brachial artery flow-mediated vasodilation (BAFMD)	[91]
Obesity				
90 subjects with metabolic syndrome	42 g/day normal dose 70 g/day high dose	12 weeks	No change in body weight, lowered serum triglyceride level in normal dose	[95]
A randomized, controlled intervention (n = 30)	44 g/day	12 weeks	No change in body weight and composition. Improved nutrient (MUFA, PUFA, linoleic acid, thiamin, pyridoxine, copper, manganese, and zinc) intake	[96]
A randomized controlled pilot study (n = 30, French women)	56 g/day	1 month	No change in body weight. Improved nutrient (thiamin, vitamin B6, copper, and potassium) intake	[97]
31 obese subjects	53 g/day	12 weeks	Lowered weight and serum triglyceride	[98]
Diabetes				
A randomized crossover study (20 subjects with metabolic syndrome)	Carbohydrate meal with pistachio	5–10 weeks	Reduced postprandial glycemia, increased glucagon-like-peptide levels	[104]
A randomized control trial (60 Asian Indian)	Pistachio (20% of energy)	24 weeks	Reduced waste circumference, fasting blood sugar, total cholesterol, LDL-C, high-sensitivity C-reactive protein. Improvement in mean values of free fatty acids, TNFα, TBARS	[105]
A randomized, controlled, crossover Study (gestational diabetes mellitus (GDM) Chinese women patients)	42 g/day	90 and 120 min after intake	Improve postprandial glucose, insulin, and glucagon-like peptide-1response	[106]

Design and study population	Intervention	Duration	Main outcomes	Reference
Cancer				
MCF-7 Human Breast Cancer Cells	Pistachio (*Pistaciavera* L.) hulls extract		Induced apoptosis and inhibited angiogenesis	[112]
A549, MCF-7, and HeLa human cancer cells	Extracts of red hulls, kernels and oleo-gum resins of Pistachio	100 to 1000 μg mL^{-1} concentrations	Showed neuro-protective potentials, inhibited AChE and BChE enzymes	[113]

Table 8.
Effect of pistachio consumption on different disease conditions.

the afternoon, reported no change in body weight after four weeks but it did improve micronutrient intake [97]. It had also been seen that pistachio did not contribute to weight gain in patients with obesity, prediabetic or diabetic conditions [98–100]. It is suggested that the main mode of weight control of pistachio is through increased satiation, satiety signals and lower metabolizable energy [92, 101, 102].

3.3.3 Pistachio and diabetes

Studies have shown that pistachios promote a healthier metabolic profile by lowering glucose level [92, 103]. Among all nuts, pistachios have a low glycemic index. In a randomized cross-over study conducted on 20 subjects with the metabolic syndrome, 85.04 g of pistachios consumed along with bread reduced postprandial glycaemia levels and increased glucagon-like peptide levels compared with bread alone therefore, contribute to reducing the T2DM risk [104]. Jenkins et al. [68] reported the reduction of HbA1c in T2DM subjects consumed mixed nuts (including pistachios) for 3 months in a randomized controlled study as a replacement for carbohydrate-containing foods compared with a half-nut and control-muffin doses. In 2014, Gulati and colleagues [105] conducted a 24-wk randomized control trial, 60 individuals with the metabolic syndrome were randomized to either pistachio (20% energy) (intervention group) or control group. At the end of the study, statistically significant improvement was seen in levels of fasting blood sugar (FBG) however, no significant effect was seen on HbA1c and insulin levels. In a recent study conducted to evaluate the acute effects of two isocaloric test meals, 42 g pistachios and 100 g whole-wheat bread (WWB) on postprandial glucose, insulin, and gut derived incretin levels in Chinese women with gestational impaired glucose tolerance (GIGT) or gestational diabetes mellitus (GDM) suggested that pistachios are effective alternative to a low-fat, high-carbohydrate food to improve postprandial glucose, insulin, and GLP-1 response in women with GDM and GIGT [106]. The fiber, healthy fats, low available carbohydrate and carotenoid content of pistachios are the important nutrients involved in glucose metabolism as suggested by Bullo et al. [107]. Akbaraly et al. [108] reported that the higher plasma carotenoid level was associated with 58% lower risk of T2DM mellitus. Similarly, other phytonutrients in pistachios, such as ellagitannins, can also possibly affect gastrointestinal sugar absorption and thus influence postprandial blood glucose levels [109]. Pistachio consumption and effects on insulin resistance, secretion or diabetes control are less so, more studies are required to clarify the long term effects.

3.3.4 Pistachio and cancer

Pistachios are rich sources of phenolic compounds such as epicatechin, quercetin, kaempferol, cyaniding-3-O-galactoside, cyanindin-3-O-glucoside, among other polyphenol [110]. These poly phenolic compounds have strong antioxidant properties for which pistachio is ranked among 50 highest antioxidant food products [111]. Phenolic compounds play protective roles against free radical production and controls disease like CVD and cancer. Seifaddinipour et al. [112] assessed the cytotoxic effects of hexane, ethyl acetate, methanol, and water extract of pistachio hull against human colon cancer (HT-29 and HCT-116), breast adenocarcinoma (MCF-7), lung adenocarcinoma (H23), liver hepatocellular carcinoma (HepG2), cervical cancer (Ca Ski), and normal fibroblast (BJ-5ta) cells using a MTT cell viability assay and reported that pistachio hull extract has anti-tumor and anti-angiogenic potentials. It is also suggested that the apoptosis induction and angiogenesis potential of pistachio hull extract makes it a suitable product for further cancer research. In a similar kind of study, pistachio extracts exhibited noteworthy cytotoxic potentials against adenocarcinomic human alveolar basal epithelial cells (A-549), MCF-7, and HeLa human cancer cells, compared to HUVEC control cells [113]. It is also reported that the parts of pistachio known as waste parts such as hulls and oleo-gum resins were found to possess higher cancer prevention potentials, compared to those of the part consumed as food such kernels. The antioxidant properties of pistachio on reduction of precancerous colon cancer lesion in rats were evaluated and it was found that pistachio enhanced activities endogenous antioxidants such as glutathione-s-transferase (GST), glutathione (GSH), glutathione peroxidase (GPx) super oxide dismutase (SOD) and catalase. Glutathione is a very important non enzymatic antioxidant which offers protection against reactive oxygen species (ROS) as well as exogenous carcinogens [114]. This study also showed reduced incidence of Aberrant Crypt Foci (ACF) and crypt multiplicity which are the earliest identifiable neoplastic lesions in the colon carcinogenetic model. There are several studies on the anticancer properties of pistachio products and they all indicate toward the presence of phytochemicals such as flavonoids, quercetin and kaempferol and their antioxidant, antimicrobial, enzyme inhibitory and radical scavenging effects to control cancer [115–117]. Pistachio consumption and the overall health benefits are presented in **Figure 4**.

3.4 Cashew nuts

Cashew (*Anacardium occidentale*) is an evergreen tree native to Central and South America. However, now a days, cultivated widely in Africa, India, Vietnam and Sri Lanka. India is a major producer, processor, consumer and exporter of cashew in the world. Nutritional composition of cashew nuts includes good quantity of MUFA, squalenes, phytosterols, β-carotene, lutein, zeaxanthin, α-tocopherol, γ-tocopherol and thiamin [24, 118]. Cashews nut is also very good source of copper and zinc. The consumption of cashew nut and relationship between different disease conditions is presented in **Table 9**.

3.4.1 Cashew nut and cardiovascular disease

The micronutrients such as folate and tocopherols what found in cashew nut are very important in terms of protecting against atherosclerosis and other chronic non-communicable diseases (CNCD) [119]. Various epidemiological studies have drawn a link between folate status and atherosclerotic vascular disease. The relationship between low serum folate levels and increased cardiovascular disease risk has also

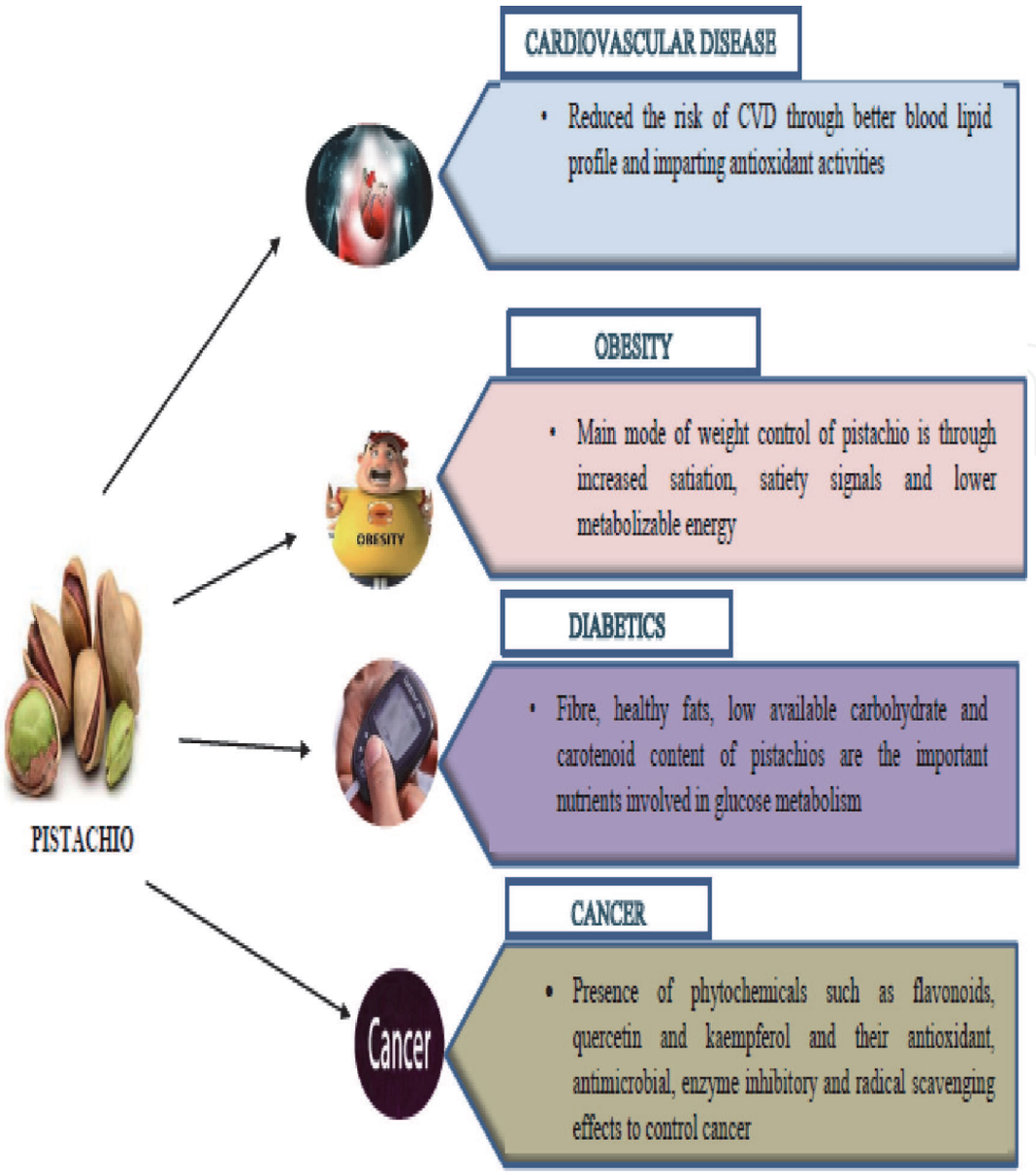


Figure 4.
Pistachio consumption and health benefits.

been seen in many studies [120, 121]. Dietary factors such as single high fat meal, oral fat load, animal protein and less fruit and vegetable consumption causes temporary endothelial dysfunction and increases cardiovascular disease risk [122, 123]. Reports claim that the supplementation of folic acid completely prevented the observed diet-induced impairment in endothelial function [124]. The mechanistic principle behind the action of folic acid is that, it reduces the plasma homocysteine levels which happen to be a causal factor in cardiovascular disease [125]. Tocopherols are strong antioxidants which exert cardiovascular (CV) benefit, including inhibition of oxidation of low-density lipoprotein (LDL) cholesterol in plasma [126]. Cashew nuts because of their high saturated fat content were exempted from "heart healthy" health claim by Federal Drug Administration in the year 2003. However, many recent studies claim the ability of cashew nuts to lower total and LDL-C [127]. In 2018, a 12-week randomized controlled study conducted by Mohan V and colleagues [128] reported that cashew nut supplementation reduced systolic blood pressure and increased HDL-C in Asian Indians with type-2 diabetes mellitus with no deleterious effects on body weight, glycemia, or other lipid variables.

Design and study population	Intervention	Duration	Main outcomes	Reference
Cardiovascular disease				
A randomized controlled trial (300 Asian Indians with T2DM)	30 g/day	12 weeks	Decreased systolic blood pressure and increased plasma HDL-C	[128]
Meta-analysis (five studies with 246 participants)	Increased cashew nut intake		Improved TG levels as well as systolic and diastolic blood pressure	[129]
Obesity				
Male Swiss albino mice (25–30 g) and Female Sprague Dawley rats (150–200 g)	200 mg/kg/day	40 days	Decreased body weight, LDL, VLDL, TG, TC and increased HDL level. Decreased fat-pad weights like Kidney fat, Mesenteric fat and Uterine fat	[130]
Diet-induced obesity (DIO) mouse model	Cashew apple extract 200 mg/kg	8 weeks	Reduced body-weight gain and fat storage. Lowered glycaemia, insulinaemia and insulin resistance	[131]
A randomized controlled trial (300 Asian Indians with T2DM)	30 g/day	12 weeks	No weight gain	[128]
Diabetes				
A randomized, controlled-feeding trial (50 patients with type 2 diabetes mellitus)	10% of total calorie from cashews	8 weeks	Decreased serum insulin and LDL-C/HDL-C ratio. Decreased HOMA-IR (homeostatic model assessment of insulin resistance). No change in body weight, BMI and waist circumference (WC)	[132]
Fructose-fed (diabetic) rats	Cashew plant stem-bark methanol extract 200.0 mg/kg body weight	21 days	Prevented changes in plasma glucose, triglyceride, total cholesterol/HDL-cholesterol ratio, malonyldialdehyde, urea, and creatinine	[133]
Cancer				
Six- to eight-week-old male BALB/c mice (20–25g)	50 mg/kg Anacardic acids from cashew nut shell liquid	30 days	Decreased levels of neutrophils and tumor necrosis factor in the lungs	[135]
HeLa cells	Cashew nut shell liquid (CNSL)		Inhibited cell proliferation and growth of *Bacillus subtilis*	[140]

Table 9.
Effect of Cashew nut consumption on different disease conditions.

According to the authors the MUFA content of cashew nut increased the level of apolipoprotein A-I (apoA-I) which is capable to increase the endogenous synthesis of functional HDL particles. However, the meta-analysis data of Mahboobi [129] showed that cashew can improve triglyceride levels as well as maintain systolic and diastolic blood pressure with no significant effects on other cardiometabolic factors such as total cholesterol, HDL-C, and LDL-C.

3.4.2 Cashew nut and obesity

Cashew nuts are rich in energy and dietary fiber which exerts beneficial effect on weight management. Dietary fiber can produce a feeling of fullness in the stomach, controls appetite suggested as an aid in weight loss diets. A study conducted by Asdaq and Malsawmtluangi [130] on the anti-obesity effect of cashew nut in rats fed on cafeteria and atherogenic diet reported that cashew high dose (200 mg/kg) is effective in decreasing body weight, lipid parameters like LDL, VLDL, TG, TC and increased HDL level. They also observed from the study that there was decreased fat-pad weights like Kidney fat, Mesenteric fat, and Uterine fat which showed the anti-obesity potential of cashew nut. The authors suggested the anti-obesity activity of cashew nut might be due to the presence of soluble fibers and flavonoids, namely, catechin, epicatechin, and epigallocatechin, which inhibit lipoxygenase. In another study, Beejmohun et al. [131] evaluated the effect of cashew nut apple extract on obesity and diabetes using the diet-induced obesity (DIO) mouse model. Two different designs: a 'prevention' design and curative design was adopted to evaluate the ability of the extract to prevent the development of obesity, hyperglycaemia and insulin resistance, and capacity to reverse an established disease state, respectively. In both the designs, cashew apple extract of 200 mg/kg body weight significantly reduced body-weight gain, fat storage, hyperglycaemia, hyperinsulinaemia and insulin resistance in DIO mice. It was suggested from the study that reduction in body-weight gain was at least partly due to a decrease in the peri-epididymal (perivisceral) adipose tissue mass. It has been seen that cashew nut supplementation in Asian Indians with type-2 diabetes had no deleterious effects on body weight [128].

3.4.3 Cashew nut and diabetes

An eight-week, randomized, isocaloric, controlled-feeding study was conducted by Darvish Damavandi et al. [132] on 50 patients with type 2 diabetes mellitus (T2DM) randomly assigned to either the control or intervention group with 10% of total calorie from cashews. The results demonstrated that replacing 10% of daily total energy intake with unsalted cashews reduced serum insulin and LDL-C/HDL-C ratio (as an atherogenic index) in patients with T2D. Authors suggested that the decrease could be due to the bioactive compounds, as well as unsaturated fatty acids (MUFAs and PUFAs) present in cashews, which may play an important role in insulin and lipid profile control. Also, fiber and polyphenols may have anti-diabetic effects by regulating microbiome and lipid profile ratio. In an animal model study, the cashew plant bark extract showed a potential antidiabetic activity. Methanol extract of cashew plant stem-bark at a dose of 200.0 mg/kg body weight improved plasma glucose and lipids in fructose-induced diabetic rats, which was associated with a reduced lipid peroxidation [133]. Viguiliouk et al. [10] through a meta-analysis reported that diet supplemented with tree nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios and walnuts) at a median dose of 56 g/day improved glycemic control in subjects with T2DM, showing significantly decreased HbA1c levels and fasting glucose with no effect on fasting insulin or homeostasis model assessment of insulin resistance index (HOMA-IR).

3.4.4 Cashew nut and cancer

The cashew nuts contain phenolic compounds which are strong antioxidants and capable of scavenging free super oxide radicals, reducing the risk of cancer [134].

However, there are many reports on the use of cashew nut shell liquid (CNSL) from cashew nut as a potent anti- cancer agent. Anacardic acids are the main constituents of natural CNSL. In a study, 50 mg/kg of anacardic acids ameliorated tumor necrosis factor in lungs induced by exposure to diesel exhaust particles in mice [135]. Anacardic acid was the first natural product inhibitor of histone acetyltransferase (HAT) activities reported [136]. HATs are the critical regulators of cell development and carcinogenesis [137]. It is also reported that anacardic acid presents anti-inflammatory and anti-invasive properties by suppressing tumor necrosis factor (TNF)-α-induced overexpression of anti-apoptotic proteins (e.g., Bcl-2, Bcl-xl, and survivin) and UV-induced tumorigenesis [138, 139]. In a study conducted by Ashraf and Rathinasamy [140] to check the antibacterial and anticancer activity of the purified CNSL, it inhibited the proliferation of HeLa cells with an IC50 of 0.004% (v/v) and inhibited the growth of *Bacillus subtilis* with an IC50 of 0.35% (v/v). It induced apoptosis in HeLa cells and accelerated wound closure in L929 cells. Authors concluded that CNSL have the potential to be used as anticancer and antibacterial drug development. These data suggests the anticancer role of anacardic acid. Anacardic acids (AAs) are alkyl phenols. Higher amounts of AAs have been detected in CNSL (353.6 g/kg) followed by cashew fiber (6.1 g/kg), while the lowest (0.65 g/kg) amounts were found in roasted cashew nut [141]. Cashew nut consumption and the overall health benefits are presented in **Figure 5**.

3.5 Other nuts

The tree nuts such as Brazil nut, hazel nut, macadamia nut, pine nut, pecans and legume, pea nut possess good quantity of protein, unsaturated fatty acids, dietary fibers, vitamins, minerals and different bioactive compounds, such as phytosterols, phenolic

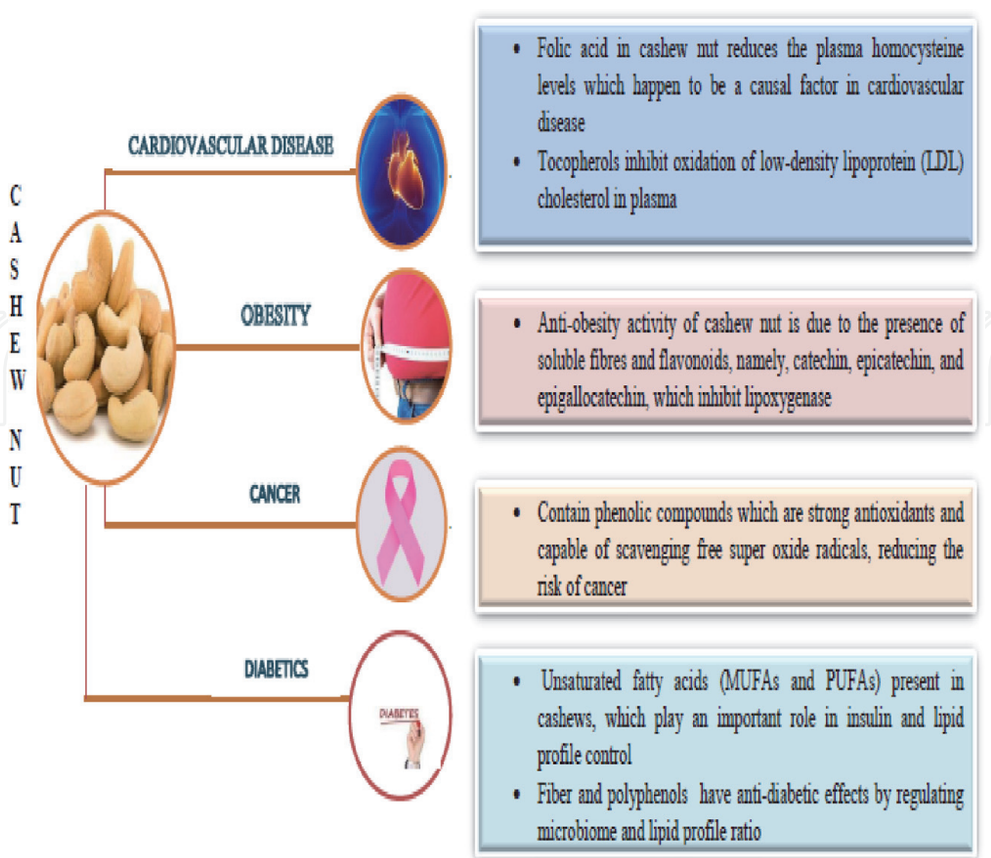


Figure 5.
Cashew nut consumption and health benefits.

compounds and carotenoids. These compounds are able to reduce cholesterol levels and promote antioxidant and anti-inflammatory effects. The consumption of some other nuts and relationship between different disease conditions is presented in **Table 10**.

3.5.1 Cardiovascular diseases

In a study, it was observed that 9 hours after the ingestion of 20 or 50 g of Brazil nut serum LDL-c level significantly reduced and HDL-c significantly improved. Interestingly, significant increase of the plasma selenium levels was observed at 6 hours within the groups receiving the nuts [142]. It was suggested from the study

Design and study population	Intervention	Duration	Main outcomes	Reference
Cardiovascular disease				
10 healthy subjects	20 or 50 g Brazil nut	9 hrs	Decreased LDL-C and increased HDL-C. Increased plasma selenium	[142]
A randomized crossover trial (30 volunteers aged 18 to 53 years)	Macadamia nut-based monounsaturated fat diet (37% energy from fat)	30 days	Decreased cholesterol and LDL-C	[146]
Obesity				
Obese female adolescents (n = 17)	15–25 g/day Brazil nut	16 weeks	Reduced total cholesterol and LDL-C. Improved microvascular function	[150]
A randomized, controlled trial (107 overweight and obese individuals)	60 g/day hazelnut	12 weeks	Improved blood cholesterol and no weight gain	[153]
A pilot clinical trial (24 healthy volunteers)	40 g/day hazelnut	6 weeks	No weight gain, improved antioxidant capacity. Up regulated of genes implied in oxidant reactions and inflammation	[154]
Cross-over, intervention study (15 healthy individuals)	66% of the energy provided by the peanuts	30 weeks	No change in body weight. No decline in pleasantness or hunger ratings	[155]
Diabetes				
Sixty type 2 diabetic patients (aged 43–81 years)	1 Brazil nut/day	6 months	Reduced oxidative DNA damage	[157]
A randomized, parallel-group (50 patients with metabolic syndrome)	30 g/day of raw nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts)	12 weeks	Decreased lipid responsiveness but improved insulin sensitivity	[160]
Cancer				
A375 and HeLa cells	A methanol hazelnut shells extract (526 μg/mL)		A pro-apoptotic effect	[165]

Table 10.
Effect of some other nuts on different disease conditions.

that the change in lipid level could be due to the presence of selenium which mediates selenoproteins. Some selenoproteins such as glutathione peroxidase (GPx) and thioredoxinreductase (TrxR) are important antioxidant enzymes and can provide cardiovascular benefits [143]. Similarly, it was observed that hazelnut-enriched diets exerted antiatherogenic effect by improving endothelial function, preventing LDL oxidation, and inflammatory markers beyond only lipid lowering effect [144]. However, after 4 weeks on a hazel nut free diet, the beneficial effects got changed. Hazel nut is a good source of vitamin E, which protects low-density lipoprotein (LDL) against oxidation and a high level of L-arginine, which is precursor of nitric oxide and other bioactives, could be the reason of antiatherogenic effect. It is suggested from the study that hazelnut may be incorporated into daily diet without change in total caloric intake for sustained health benefit. It has also been seen in women with type 2 diabetes that frequent nut and peanut butter consumption (serving size, 28 g (1 ounce) for nuts and 16 g (1 tablespoon) for pea nut butter) was associated with a significantly lower CVD risk [145]. Macadamia nuts are good source of MUFA and have been tried in the diets to reduce the TC and LDL-cholesterol with positive results [146, 147]. Improvements of vascular function reduce CVD risk. It is indicated from many epidemiological studies that nuts have positive effects on vascular endothelial function [148, 149].

3.5.2 Obesity

Obesity is one of the reasons of morpho-functional microvascular damage. The intake of 15–25 g/day Brazil nuts improved the microvascular function in obese female adolescents BMI of 35.6 ± 3.3 kg/m^2. It is suggested that the bioactive substances of Brazil nut like selenium, α- e γ- tocopherol, folate and polyunsaturated fatty acids improved the microcirculation with their antioxidant capacity [150]. It is also observed that a high intake of Se from Brazil nut for long periods by obese women was harmful to health which was associated with the gene expression of some inflammatory markers [151]. The tolerable upper intake level (UL) of Se is around 400 mg/day, for both males and females [152] could be the reason with high intake of Brazil nut and associated health problems. Experimental evidences suggest that consumption of hazel nut up to 60 g per day did not affect weight and improve blood cholesterol levels [153]. Renzo et al. [154] observed that when 24 healthy volunteers consumed 40 g of hazelnuts (261.99 kcal/1096.17 kJ) daily as a snack for six weeks, did not gain weight but a significant up regulation was detected for SOD1, CAT, macrophage migration inhibitory factor (MIF), PPARγ, vitamin D receptor (VDR), methyl enetetra hydrofolate reductase (MTHFR) and angiotensin I-converting enzyme (ACE) which was an indication of modulation in oxidative stress and inflammation gene expression. Alper and Mattes [155] reported that peanut consumption has little effect on energy balance when peanuts are added to, or incorporated into, an energy-controlled diet. Little change in body weight over 3 weeks with peanuts added to habitual diets. In a study when obese mice were supplemented with macadamia nut oil, hypertrophy of adipocytes, inflammation in the adipose tissue and macrophages were attenuated [156]. It is suggested from the study that the reduced/controlled growth of adipocytes brings more cellular homeostasis and decreases leptin production and secretion. Otherwise, leptin is associated with an elevation in low grade inflammation.

3.5.3 Diabetes

Diabetes elicits oxidative stress and causes DNA damage. Prevention of DNA oxidation is extremely important and through dietary interventions, T2D-related

complications and DNA damage can be prevented. In this regard, Mecan et al. [157] investigated the correlation of Brazil nut supplementation and DNA damage in T2D patients and found significant increase in fasting blood glucose after six months of consuming Brazil nuts; however, no significant effect was observed on the levels of HbA1c level. The cells were more resistant to H_2O_2-induced DNA damage after six months of supplementation with Brazil nut. It was concluded from the study that consumption of Brazil nuts could decrease oxidative DNA damage in T2D patients, probably through the antioxidative effects of Se. An 8-week controlled randomized parallel study in patients with T2D indicated that incorporation of hazelnuts into diet (10% of total daily calorie intake was replaced with hazelnuts) in intervention group can prevent reduction of HDL-C concentrations in patients with type 2 diabetes, but had no effect on FBS or other lipid profile indices [158]. However, it is suggested from the studies that the Mediterranean-style diet with 30 g of mixed nuts (15 g/d walnuts, 7.5 g/d hazelnuts and 7.5 g/d almonds) could improve FBS concentration after 3 months in patients at high-risk for CVD [159]. In contrast, Casas-Agustench et al. [160] demonstrated that incorporating 30 g of mixed nuts (15 g/d walnuts, 7.5 g/d hazelnuts, and 7.5 g/d almonds) into a healthy diet for 12 weeks did not affect FBS. Study conducted by Jiang et al. [161] very elaborately discussed about the nut and pea nut butter consumption on the diabetes outcomes. The authors reported that nut and peanut butter consumption was inversely associated with risk of type 2 diabetes. Diabetes reduced 27% in those who ate nuts 5 or more times per week compared with those who rarely or never ate nuts.

3.5.4 Cancer

Ip and Lisk [162] reported the relationship between Brazil nut and prevention of mammary cancer. They compared the selenium in Brazil nut with selenite selenium and found both were equally bioactive. Their study demonstrated a dose-dependent inhibitory response at dietary Se concentrations of 1–3 mg/g in dimethylbenz[a] anthracene-treated rat model. The anti-carcinogenic activity of Se has also been tried in other animal models with positive response. Selenium is an important component of antioxidant enzymes and the beneficial effects in terms of inhibition of cell proliferation, triggering apoptosis and repairing DNA activating p53 is mainly because of the antioxidant properties [163]. Antimutagenecity and anticancer activities has also been reported from fresh hazelnuts whereas dried hazelnut shows moderate activity [164]. Hazenut shell extract contains phenolic compounds, including neolignans, and a diarylheptanoid which has strong antioxidant properties. It is a potent anticancer agent and showed an inhibitory effect on the growth of human cancer cell lines A375, SK-Mel-28 and HeLa [165]. Macadamia nut is a good source of tocopherols, tocotrienols, and squalene which can confer antioxidant and anticancer properties to consumers. Nieuwenhuisa and Brandt [166] conducted a large prospective cohort study and reported that total nut, tree nut, and peanut intake reduced the risk of small cell carcinoma in men.

4. Conclusion

All nuts contain good quantity of MUFAs, PUFAs, fibers, vitamins, minerals and bioactive compounds with antioxidant potential which makes them a good candidate in human diets. Almond consumption reduces serum triglyceride, total cholesterol and LDL-C in the subjects mainly due to the presence of vitamin E and phenolic compounds in it. Similarly, almond consumption also helps in weight loss, lowered glycosylated hemoglobin, and reduced blood glucose when tried in patients

with obesity and diabetes. The benefit of almond for cancer prevention is mainly due to the phytochemicals such as quercentin and kampferol which is known for reducing prostrate and lungs cancer cell growth. Walnut consumption is also very useful for reducing cardiovascular disease risk. Walnut intake not only improves blood lipid profile by reducing triglyceride and total cholesterol but also improves flow mediated dialation, HDL-C level and apolipoproten B status which is very useful for heart health. Despite an energy dese nut, walnut did not contribute to weight gain in any of the trials with obese patients but helped in controlling systolic blood pressure. In diabetic patients walnut intake reduces fasting blood sugar and HBA1C. Walnut contains tocopherol, βsitosterol, and peduncalgin which have anti-cancer properties. In human cell line studies for role of walnut in cancer prevention found walnut oil is capable of inducing necrosis and down regulated NFkB. Pistachio intake increases serum antioxidants and reduces oxidized LDL-C through which imparted beneficial effect on cardiovascular health status. It also controls obesity and diabetes through increasing satiation and regulating glucose metabolism. The hull extract of pistachio shows anticancer properties and radical scavenging activities. Almond, walnut and pistachio consumption in a range of 42 to 85 g/day was found to be beneficial for human health. Cashew nut is very common and popular among nuts. The intake of 30 g/day cashew nut is beneficial for heart health and also does not contribute to weight gain. In an animal model study, the cashew plant bark extract showed a potential antidiabetic activity. Cashew nut shell liquid (CNSL) from cashew nut is a potent anti- cancer agent. The phenolic compounds present in cashew nut are also strong antioxidants and capable of scavenging free super oxide radicals, reducing the risk of cancer. Similarly, intake of Brazil nut and hazel nut in a range of 25–50 g/day imparted beneficial effects on antioxidant status and reduced risk of diabetes and cancer. Moreover, daily nut intake of tree nut or pea nut has demonstrated an active role in controlling inflammation, dyslipidemia and oxidative stress.

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