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Potential health benefits of nuts

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Summary

Nuts play a minor role in Western dietary patterns. Although the German Nutrition Society e. V. (DGE) recommends a daily consumption of 25 g, it was shown by the National Nutrition Survey II (NVS II) that Germans only eat about 2 g a day. This is all the more incomprehensible since nuts are not only a good source for important nutrients (e. g. monounsaturated fatty acids [MUFA], polyunsaturated fatty acids [PUFA], dietary fiber, vitamins and minerals), but there is also growing evidence of positive health effects due to regular nut consumption. These relate to the support of the prevention of hyperlipidemia, hyperglycemia and atherosclerotic processes. Since previous studies also showed no adverse effects of regular nut consumption, an increased consumption should be promoted. This article gives an overview of the current state of research relating to the health potential of nuts in terms of selected metabolic diseases and cancer.

Keywords: nuts, prevention, hypertension, blood lipids, atherosclerosis, diabetes mellitus type 2, cancer

Introduction

Lifestyle diseases such as cardiovascular diseases, diabetes mellitus type 2 and cancer are among the leading causes of death worldwide. In Germany alone, around 45 % of all deaths in 2010 were due to cardiovascular diseases [1]. Since an unhealthy eating behavior contributes significantly to their formation, a deliberate choice of foods with either prophylactic effect or the ability to improve symptoms of existing diseases are of great importance.

Yet nuts are often underestimated. They are rich in dietary fiber, unsaturated fatty acids, vitamins, minerals and phytochemicals (◆Figure 1) and are increasingly associated with an overall healthy lifestyle and reduced risk of disease [2–6], such as a reduced risk of stroke [7] or a lower risk of the metabolic syndrome [8]. In this review, the term nuts is used to describe both nuts in the botanical sense (e. g. hazelnuts, walnuts) as well as legumes and drupes (e. g. peanuts, almonds, pistachios) that are commonly referred to as nuts (◆Figure 2).

The last comprehensive report on the importance of nuts in the diet was submitted in 2009 [9]. It is based on research papers from the period 2000–2009, which dealt with the effect of various types of nuts and eating patterns on diverse health parameters. The present article ties in with this report and provides an overview of the current state of research. The focus is thereby on human trials that have dealt with regular nut consumption and its impact on hypertension, hyperlipidemia, atherosclerosis and diabetes mellitus type 2 as well as animal- and *in vitro* studies on cancer.

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Nut consumption and cardiovascular risk factors

Nut consumption in hypertension

Hypertension is one of the most important cardiovascular risk factors and should therefore be avoided especially for the prevention of sequelae. Various nut ingredients have potential to reduce the risk of hypertension.

These include dietary fibers, which increase satiety and help to prevent obesity, magnesium, which mediates vasodilatory effects, or the low sodium content of nuts.

However, studies conducted up to 2009 showed no clear results in this regard. Although Djoussé et al. [10] and now Weng et al. [11] observed an inverse association between nut consumption and the risk of hypertension as well as a lower prevalence for hypertension at high nut consumption [12] in epidemiological studies, this relationship was not confirmed by the Spanish „SUN prospective Cohort"-Study [13]. Possi-

ble reasons for this are the low risk of hypertension due to the age of the participants and the preferred consumption of salted nuts in this region, because common salt may help to increase the blood pressure [14].

In recent clinical trials (◆ Table 1a) the replacement of 20 % of total calories by pistachios [15] or 40 % of the fat content by walnuts and almonds [16] showed no effect on the blood pressure in healthy individuals [15] and subjects with hypercholesterolemia [16]. However, since the subjects had a normal blood pressure at the beginning of the trial, it is questionable whether a reduction of the blood pressure was expected at all.

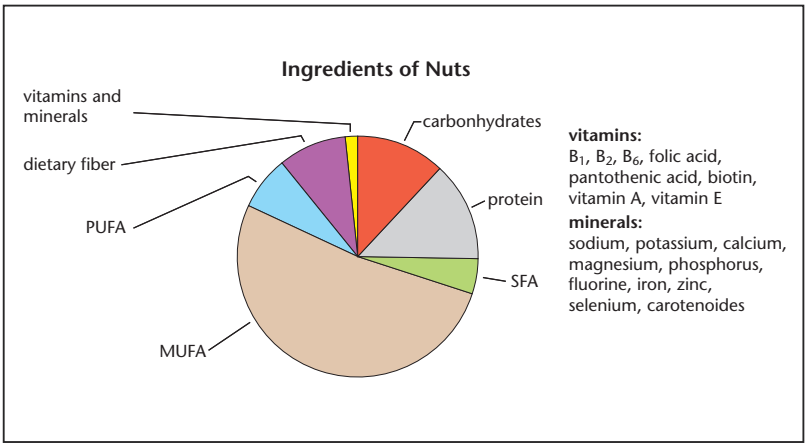

Fig. 1: **Exemplary representation of the valuably nut ingredients by the example of hazelnut** (mod. after [66])
MUFA = monounsaturated fatty acids; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids

On the other hand, there are promising results that regular nut consumption can attenuate an already *existing* hypertension, like JENKINS et al. were able to show with almonds [17]. In this one-year trial the participants lowered their blood pressure significantly (systolic: –4.2 ± 1.3 mmHg, diastolic: –2.3 ± 0,7 mmHg) through a vegetarian diet with almonds, whereby people with higher blood pressure responded more strongly to this dietary treatment. A similar reduction of the systolic blood pressure was detected after eating 42 g or 84 g pistachios respectively (–4.8 mmHg resp. –2.4 mmHg) together with a significant decrease in the peripheral resistance of the blood vessels (–62.1 dyne × s/cm^5) and the heart rate (–3 bpm) after eating 84 g [18]. Compared with a low-fat diet, a daily nut consumption couldn't only improve the diastolic blood pressure significantly (–0.65 mmHg) but also help normalize the blood pressure range, as results of the PREDIMED-trial showed [19]. In contrast, DAVIDI et al. failed to achieve a hypotensive effect through the consumption of nut and fruit bars, a result that can be explained with the composition of the bars and their relative low share of ω-3-fatty acids [20].

Decreasing blood-lipids by nuts

Clinical trials up to 2009 have already shown that regular nut consumption can have beneficial effects on cholesterol and triglyceride levels. Subsequent studies have confirmed these effects (◆ Table 1b). Several intervention studies obtained with different types of nuts (pistachios, Brazil nuts, walnuts, almonds, hazelnuts or peanuts) and consumption patterns (30–80 g/d) in healthy individuals and subjects with hyperlipidemia showed both a reduction in total cholesterol (TC) by an average of 10.1 % as well as a reduction in LDL-cholesterol (LDL-C) by an average of 8.6 % [15, 16, 21–26]. These effects were often attributed to the favorable fatty acid profile and the dietary fiber content of nuts. Some studies also showed an increase in HDL-cholesterol (HDL-C) as well as a decrease in triglycerides (TG) and apolipoprotein B (Apo B) [23, 25, 27].

Fig. 2: **Commonly, not only nuts in the botanical sense (e. g. walnut [A], hazelnut or macadamia nut) are referred to as nuts, but also certain legumes (e. g. peanut [B]) and stone fruits such as almonds [C], pistachios, pecans and coconut.**

Those results were particularly evident in people already suffering from hyperlipidemia [21, 24, 25]. Another intervention study even achieved in obese participants an improvement of blood-lipid parameters, but the level of significance for this effect was only reached in subjects with hyperlipidemia [21]. However, people with metabolic syndrome (MeS) reacted in different ways. While Aronis et al. demonstrated a significant increase of Apo A1 in subjects with MeS after four days of intervention (48 g/d walnuts) [28], another study showed no effects on cholesterol parameters in subjects with MeS after 12 weeks of intervention (30 g/d mixed nuts) [29]. It is assumed that the cholesterol absorption into the enterocytes is reduced in individuals with MeS, whereby the cholesterol-lowering effect of nut-phytosterols is outweighed [29].

Furthermore, those effects on blood-lipid levels may be dependent on the amount of consumed nuts. Din et al. weren't able to show lipid lowering effects compared to the control group after the consumption of 15 g walnuts per day [30], whereas 21 g of walnuts per day were sufficient in the study of Mckay et al. to demonstrate a significant decrease in TC, LDL and TG levels [22]. An adequate mastication appears to be required too, since cholesterol- and lipid lowering effects are limited by the bioavailability of nut-lipids [31, 32].

Author [Source]	Study type	Type of nut, amount* duration	Results
Damasceno et al. [16]	C	walnut, almond 40 % of fat content (40–75 g); 4 weeks	n. c.
Davidi et al. [20]	C	almond 22 g; 8 weeks	n. c.
Djoussé et al. [10]	E	–	inverse relation: nut consumption/risk hypertension
Djoussé et al. [12]	E	–	lower prevalence for hypertension
Jenkins et al. [17]	C	almond 22.5 g; 1 year	systolic and diastolic BP ↓
Martinez-Lapiscina et al. [13]	E	–	no association
Sari et al. [15]	C	pistachios 20 % of total calories (60–100 g); 4 weeks	n. c.
Toledo et al. [19]	C	walnut-, almond-, hazelnut-mix 30 g; 4 years	diastolic BP ↓
Weng et al. [11]	E	–	inverse relation: nut consumption/risk hypertension
West et al. [18]	C	pistachios 10 or 20 % of total calories (42–84 g); 4 weeks	systolic BP ↓ peripheral resistance ↓ heart rate ↓

Tab. 1a: **Current state of research on preventive aspects of nuts: nut consumption in hypertension**
*referring to a daily consumption
↑ = increased significantly; ↓ = decreased significantly;
↘ = non-significant decrease; ↗ = non-significant increase;
n. c. = no change; C = clinical study; E = epidemiological study
BP = blood pressure

Abbreviations

AA = arachidonic acid
Apo A1 = apolipoprotein A1
Apo B =apolipoprotein B
CRP = C-reactive protein
DHA = docosahexaenoic acid
DMT2 = diabetes mellitus type 2
EDV = endothelium dependent vasodilatation
EPA = eicosapentaenoic acid
FRAP= ferric-ion reducing antioxidant power
HbA_{1c}= hemoglobin A_{1c}
HDL-C = high density lipoprotein cholesterol
ICAM-1 = intercellular adhesion molecule-1
IL-6 = interleukin-6
LDL-C = low density lipoprotein cholesterol
MDA = malondialdehyd
MeS = metabolic syndrome
MUFA = monounsaturated fatty acids
NFκB = nuclear factor kappa-light-chain-enhancer of activated B cells
ORAC = oxygen radical absorbance capacity
PUFA = polyunsaturated fatty acids
PYY = peptide YY
RR = relative risk
TC = total cholesterol
TG = triglyceride
TNFα = tumor necrosis factor α
TNFR = tumor necrosis factor receptor
TOS = total oxidant status

Reduction of atherosclerotic process by nut consumption

The development of atherosclerosis is a multifactorial process. Therefore, the risk for atherosclerosis can be assessed by various parameters, such as the antioxidative capacity, inflammation and endothelial function.

Recent studies have shown that nut-polyphenols can display protective ef-

fects in regard to cardiovascular diseases due to their antioxidant properties. This assumption is also confirmed by current studies (◆Table 1c). A possible mechanism of action for this effect might be the binding of absorbed nut-polyphenols to lipoproteins, as VINSON et al. were able to show *in vitro* [33]. This mode of action could counteract the foam cell formation by scavenging free radicals. In addition, they found that walnuts have *in vitro* the highest proportion of polyphenols and exhibit the best antioxidative potential compared to other nuts [33].

Following the results of current clinical trials, an improvement of the antioxidative capacity was seen after regular nut consumption [15, 22, 25, 34]. For example, a daily consumption of 30 g hazelnuts led to a significant improvement of the α-tocopherol status in subjects with hypercholesterolemia [25] and after a single dose of 90 g pecans, an increase in the ORAC value (oxygen radical absorbance capacity) and the γ-tocopherol concentration as well as a postprandial decrease in lipid peroxidation (measured by malondialdehyde) were demonstrated. These effects were attributed to the high fat content of nuts, which can slow down digestion and thus increase the bioavailability of tocopherols and polyphenols [34].

In addition, there is evidence that nut consumption stimulates antioxidative enzymes. As detected by SARI et al., pistachio consumption led to both a significant decrease in TOS (total oxidant status) and a significant increase in superoxiddismutase [15]. Overweight people, who often have selenium deficiency and consequential reduced glutathione peroxidase activities, were able to eliminate these deficits by eating one Brazil nut (that contains the recommended amount of selenium) and thereby reduced their atherogenic risk [35]. Hence regular nut consumption can be useful to improve the antioxidative capacity of the organism.

Author [Source]	Study type	Type of nut, amount* duration	Results
ARONIS et al. [28]	C	walnut 48 g; 4 days	Apo A1 ↑
CASAS-AGUSTENCH et al. [29]	C	walnut-, almond-, hazelnut-mix 30 g 12 weeks	n. c.
COLPO et al. [26]	E	Brazil nut 5, 20 or 50 g once measurement at different time points	LDL ↓ HDL ↓
DAMASCENO et al. [16]	C	walnut, almond 40 % of fat content (40–75 g); 4 weeks	LDL ↓ TC ↓
DIN et al. [30]	C	walnut 15 g; 4 weeks	n. c.
LI et al. [27]	C	pistachios 53 g 12 weeks	TG ↓
MCKAY et al. [22]	C	walnut 21 or 42 g 6 weeks	TC ↓ LDL ↓ TG ↓
MCKIERNAN et al. [21]	C	peanuts 56 g 4 weeks	TC ↓ LDL ↓ TG ↓ HDL ↑
SABATÉ et al. [23]	C	almond 10 or 20 % of total calories (34–68 g) 4 weeks	TC ↓ LDL ↓ Apo B ↓ LDL/HDL ↓ HDL ↑
SARI et al. [15]	C	pistachios 20 % of total calories (60–100 g) 4 weeks	LDL ↓ TC ↓ TG ↓ HDL ↘ TC/HDL ↓ LDL/HDL ↓
TEY et al. [25]	C	hazelnut 30 g 4 weeks	TC ↓ LDL ↓ Apo B ↓ HDL ↑ TC/HDL ↓ Apo B/Apo A1 ↓
TORABIAN et al. [24]	C	walnut 12 % of total calories (28–64 g) 6 months	TC ↓ TG ↓ LDL ↘

Tab. 1b: **Current state of research on preventive aspects of nuts: decreasing blood-lipids by nuts**
*referring to a daily consumption
↑ = increased significantly; ↓ = decreased significantly;
↘ = non-significant decrease; ↗ = non-significant increase;
n. c. = no change
C = clinical study; E = epidemiological study
Apo A1 = apolipoprotein A1; Apo B = apolipoprotein B;
HDL = high density lipoprotein; LDL = low density lipoprotein;
TC = total cholesterol; TG = triglyceride

The endothelial function can also be influenced positively by nut consumption (◆ Table 1d). Therefore the European Food Safety Authority (EFSA) has approved a health claim in 2011, which states that a daily consumption of 30 g of walnuts contributes to an improved EDV (endothelium dependent vasodilatation) [36]. But even a daily consumption of 60 g pistachios could improve the EDV, what the authors constituted with the arginine content of those nuts, since arginine is the precursor of nitric oxide (NO) [15]. In contrast, a moderate daily consumption of 15 g walnuts caused no alteration in arterial stiffness [30].

A regular consumption of nuts may also affect some inflammatory markers positively (◆ Table 1d). Thus, compared to a low-fat diet, a mediterranean diet enriched with nuts led to significant reductions of inflammatory biomarkers (IL-6, TNFR, ICAM-1) that are associated with atherogenesis and an increased cardiovascular risk [37]. Likewise, a daily consumption of 60 g pistachios led to a significant decrease of IL-6 in healthy people [15]. These effects can be attributed to various ingredients of nuts. Jiang et al. justified the observed inverse relationship between nut consumption and the inflammatory markers CRP, fibrinogen and IL-6 with arginine, tocopherole and dietary fiber contained in nuts. In addition, the human body converts α-linolenic acid into EPA and DHA, which are inversely associated with CRP, fibrinogen, IL-6 and TNF-R1+2 [38]. Another study showed that the consumption of almonds caused a significant reduction in CRP [39], which can be attributed to the high magnesium content of almonds [40]. Moreover, there is evidence for the reduction of E-selectin [39, 41], an adhesion molecule activated by inflammatory cytokines, as well as reduced concentrations of prostaglandine E metabolites and thromboxane B_2, which was attributed to a better supply of γ-tocopherole [41].

Author [Source]	Study type	Type of nut, amount* duration	Results
Cominetti et al. [35]	C	Brazil nut 1 nut; 8 weeks	selenium ↑ GPx ↑
Hudthagosol et al. [34]	C	pecans 90 g 1 day	γ-Toc. ↑ ORAC ↑ MDA/TG ↓
McKay et al. [22]	C	walnut 21 or 42 g 6 weeks	ORAC ↗ FRAP ↗ MDA↘
Sari et al. [15]	C	pistachios 20 % of total calories (60–100 g) 4 weeks	TOS ↓ SOD ↑ MDA ↓
Tey et al. [25]	C	hazelnut 30 g; 4 weeks	α-tocopherol ↑

Tab. 1c: **Current state of research on preventive aspects of nuts: reduction of atherosclerotic process by nuts**
*referring to a daily consumption
↑ = increased significantly; ↓ = decreased significantly; ↘ = non-significant decrease; ↗ = non-significant increase; n. c. = no change
C = clinical study
FRAP = ferric reducing antioxidative power; GPx = glutathione peroxidase; MDA = malondialdehyd; ORAC = oral radical absorbance capacity; SOD = superoxiddismutase; TG = triglyceride, TOS = total oxidative stress; γ-Toc = γ-tocopherol

Unlike in healthy individuals, people with pre-existing conditions (MeS, hypercholesterolemia, diabetes mellitus type 2) have shown only partial improvement of inflammatory markers in previous studies [16, 28, 29, 39, 42].

Reducing the risk of type 2 diabetes mellitus by nuts

According to previous epidemiological studies (◆ Table 1e), a daily nut consumption can help women to reduce the risk of diabetes mellitus type 2 (DMT2). Thus, the Nurses´ Health Study showed in 83,818 healthy women that eating 140 g of nuts per week was related to a significant lower DMT2-risk compared to non-consumers (relative risk [RR]: 0.73) [43]. This result was inter alia attributed to the low glycemic index of nuts and their high fiber and magnesium content. In addition, recent studies with 135,956 women confirmed an association between increased walnut consumption (> 56 g/week) and a lower incidence (15 %) for DMT2 [44]. Contrary to that, Kochar et al. observed no effect of nut consumption on the DMT2-risk in 20,224 male subjects of the Physician's Health Study [45]. Although a trend for an inverse relationship was seen, it was strongly attenuated by the adaptation to confounders (i. a. age, body weight).

The responsible mechanisms mediated by nut consumption which cause a reduction of the DMT2-risk are not yet fully understood. A modulation of the adiponectine concentration appears conceivable [28]. This protein, formed by fat-laden adipocytes, is involved in the regulation of appetite and inverse associated with the DMT2-risk [46]. It is also possible that an increase in insulin sensitivity results from the arginine and zinc content of the nuts, which stimulate both insulin secretion and the receptor tyrosine kinase and thereby increase the insulin sensitivity of the cells. In addition, a reduced postprandial gly-

cemic response mediated by nut consumption and a significantly higher release of satiety hormones (PYY) may also contribute to the prevention of DMT2 [47].

Reduction of cardiovascular risk by better control of blood sugar levels by means of nut consumption

People suffering from DMT2 have an increased risk for cardiovascular diseases. Though a regular nut consumption can help to reduce this risk [48], since the consumption of nuts is associated with a reduction and better control of plasma glucose and insulin levels [15, 29, 49, 50] (◆ Table 1e).

In addition, deliberate nut consumption can reduce the glycemic response to carbohydrate foods significantly [32, 51, 52]. KENDALL et al. discovered a dose-response-relationship of this reaction in healthy subjects and DMT2 patients [51]. In the trial of BERRY et al., nut products without cell wall (muffins from almond oil and fat-free almond flour) reduced the glycemic response more significantly compared to muffins with whole almonds [32]. This effect was probably caused by a reduced bioavailability of almond lipids from structurally intact cell walls. However, a better bioavailability of non-lipid components (phenols) can contribute to a reduced glycemic response too, for example by reducing the activity of the amylase and inhibiting the glucose absorption by the sodium-glucose transporter-1 in the intestine [32].
Furthermore, nuts are probably suitable for a moderate reduction and long-term regulation of the blood glucose concentration. Thus, a regular (5 × per week) almond consumption led to a significant decrease of the HbA_{1c} (–4 %), a biomarker for glycated hemoglobin [52]. Consequently, daily nut consumption provides better glycemic control in both healthy subjects and diabetic patients.

Author [Source]	Study type	Type of nut, amount* duration	Results
ARONIS et al. [28]	C	walnut 48 g; 4 days	n. c.
CASAS-AUGUSTENCH et al. [29]	C	walnut-, almond-, hazelnut-mix 30 g; 12 weeks	IL-6 ↘
CHIANG et al. [41]	C	walnut 42.5 g 4 weeks	E-selectin ↓ PGE ↘ Tbx B2 ↘
DAMASCENO et al. [16]	C	walnut, almond 40 % of fat content (40–75 g); 4 weeks	n. c.
DIN et al. [30]	C	walnut 15 g; 4 weeks	n. c.
JIANG et al. [38]	E	–	inverse relation to CRP, IL-6 and fibrinogen
LIU et al. [42]	C	almond 56 g 4 weeks	IL-6 ↓ CRP ↓ TNFα ↓
RAJARAM et al. [39]	C	almond 10 or 20 % of total calories 4 weeks	CRP ↓ E-selectin ↓
SARI et al. [15]	C	pistachios 20 % of total calories (60–100 g) 4 weeks	EDV ↑ IL-6 ↓
URPI-SARDA et al. [37]	C	walnut-, almond-, hazelnut-mix 30 g; 1 year	IL-6 ↓ TNFR ↓ ICAM-1 ↓

Tab. 1d: **Current state of research on preventive aspects of nuts: impact of nuts on endothelial function and inflammation**
*referring to a daily consumption
↑ = increased significantly; ↓ = decreased significantly; ↘ = non-significant decrease; ↗ = non-significant increase; n. c. = no change
C = clinical study; E = epidemiological study
CRP = C-reactive protein; EDV: endothelium dependent vasodilatation; ICAM-1 = intercellular adhesion molecule-1; IL-6 = interleukin 6; PGE = prostaglandin E; Tbx B2 = thromboxan B2; TNFα = tumor necrosis factor α; TNFR = tumor necrosis factor receptor

Influence of nut consumption on colorectal and breast cancer

So far, there have been no human studies conducted that examined the direct effect of nuts on certain types of cancers. Indications for their chemo-protective potential are delivered by the EPIC study. Here, the evaluation of 478,040 participants resulted in gender differences regarding the nut effect [53]. While women with frequent nut consumption had a lower incidence of colon cancer, men showed no association.

Our current knowledge is mainly based on data from *in vitro* studies and animal experiments (◆ Table 1f). By using mouse models for colorectal cancer it was possible to demonstrate a reduction of tumor growth and weight or the number of co-

Author [Source]	Study type	Type of nut, amount* duration	Results
Aronis et al. [28]	C	walnut 48 g 4 days	adiponectine ↑
Berry et al. [32]	C	almond 50 g almond oil 1 day	glykemic response ↓
Casas-Augustench et al. [29]	C	walnut-, almond-, hazelnut-mix 30 g 12 weeks	insulin ↓
Cohen et al. [52]	C	almond 28 g 12 weeks	glykemic response ↓ HbA_{1c} ↓
Damasceno et al. [16]	C	walnut, almond 40 % of fat content (40–75 g) 4 weeks	n. c.
Pan et al. [44]	E	–	inverse relation: nut consumption/DMT2
Jiang et al. [43]	E	–	inverse relation: nut consumption /DMT2
Jenkins et al. [50]	C	almond-, macadamia-, walnut-, pistachio-, hazelnut-, peanut-cashews- and pecan-mix 75 or 37.5 g 3 weeks	HbA_{1c} ↓
Kendall et al. [51]	C	almond-, macadamia-, walnut-, pistachio-, hazelnut- and pecan-mix 30, 60 or 90 g 1 day	glykemic response ↓
Kochar et al. [45]	E	–	n. c.
Li et al. [48]	E	–	inverse relation: nut consumption/CVD
Reis et al. [47]	C	peanuts 42.5 g 1 day	glykemic response ↓ PYY ↑
Sari et al. [15]	C	pistachios 20 % of total calories (60–100 g) 4 weeks	glucose ↓
Li et al. [49]	C	almonds 60 g 12 weeks	insulin ↓ glucose ↓ insulinresistance ↓

Tab. 1e: **Current state of research on preventive aspects of nuts: reducing the risk of type 2 diabetes mellitus by nuts**
*referring to a daily consumption
↑ = increased significantly; ↓ = decreased significantly; ↘ = non-significant decrease; ↗ = non-significant increase; n. c. = no change; C = clinical study; E = epidemiological study
CVD = cardiovasculare disease; DMT2 = diabetes mellitus type 2; glykemic response = increase of blood glucose after eating carbohydrates; GPx = glutathione peroxidase; HDL = high density lipoprotein; HbA_{1c} = hemoglobin A_{1c}; PPY = peptide YY

lorectal tumors as the result of daily nut consumption [54, 55]. In vitro experiments with pre-digested and fermented nut samples showed growth-inhibitory effects on HT29 colon carcinoma cells and a clear time- and dose-dependency of this effect was observed. Furthermore, the fermented supernatants induced chemo-preventive effects, such as a reduction of the tumor-promoting secondary bile acid deoxycholic acid, an increase in short-chain fatty acids and antigenotoxic effects [56]. Rezaei et al. reported a greater impact of a pistachio extract on HT29 cells (cell cycle arrest, inhibition cell growth and increased apoptosis) compared to the common anti-cancer drug Doxorubicin [57]. Besides these molecular mechanisms, a beneficial effect on the intestinal flora may also contribute to the prevention of colorectal cancer. In this context, an increase in butyrate-producing bacteria was observed after consuming 85 g almonds or pistachios every day over a period of 19 days. This effect is considered to be beneficial for a healthy gut [58].

Regarding breast cancer, a nut-enriched diet in mouse models also led to a reduction of tumor growth and tumor size [59, 60]. On the one hand, this result might be due to the ω-3 and ω-9 fatty acids contained in nuts, as the feeding of walnut or peanut oil led to an increase of apoptosis-promoting AA in the tumor cell membranes and an inhibition of the lipoxygenase (LOX). Also the mice of the intervention group showed lower T-cell-infiltration and metastasis as well as smaller tumor volumes and a longer survival rate [59]. On the other hand, the gene expression might also be influenced by nut consumption. In this context, it was possible to observe not only a 40 % lower incidence for breast cancer and significantly lower tumor sizes and numbers in mouse models by feeding walnuts, but also an altered expression pattern of genes that are associated with the differentiation and proliferation of the breast epithelium [60].

Conclusion

The current data show that regular nut consumption is associated with a variety of health promoting effects, and to date there are no adverse effects reported even with high nut intake. This includes that regular nut consumption seems to have no negative impact on body weight neither in healthy nor in obese patients [15, 16, 21–23, 61]. Even a moderate weight loss was observed in both overweight and obese individuals by nut consumption, attributed to an increased feeling of satiety [27, 29, 62]. According to this, nuts can be easily integrated into most people's diets and also used for long-term weight loss and control [63]. Also the current data suggest promising effects of nut intake regarding the support of the prophylaxis of hyperlipidemia, hyperglycemia or particular processes of atherogenesis.

A final assessment of the importance of abundant nut consumption for the risk of developing hypertension, breast cancer and colorectal cancer is not yet possible. Yet initial indications from animal experiments and *in vitro* studies on cancer are encouraging.

Besides the prevention of diseases, there is increasing evidence that regular nut consumption can also beneficially affect biomarkers of some diseases, which is why it should be considered as a part of various therapies. For example, nuts appear to exert a hypotensive effect in hypertensive patients. Similarly, a pre-existing hyperlipidemia can be mitigated by the cholesterol- and triglyceride-lowering effects of nuts. However, further studies in these areas, especially for subjects with MeS, are necessary.

Furthermore, it was found that daily nut consumption reduces inflammatory processes and supports the antioxidant capacity of the organism. In this way, decisive processes of atherogenesis may be delayed.

Author [Source]	Study type	Type of nut, amount* duration	Results
Comba et al. [59]	A	peanut or walnut oil 6 % of total calories 35 days	AA ↑ LOX ↓ COX ↓ metastases ↓ tumor growth ↓ survival rate ↑
Davis et al. [55]	A	walnut 155 g/kg food 24 weeks	tumor numbers and -growth ↓
Hardman et al. [60]	A	walnut 18 % of total calories 145 days	tumor numbers and -growth ↓ incidence ↓
Jenab et al. [53]	E	–	inverse relation amongst women
Lux et al. [56]	An *in vitro* (HT 29)	almond, macadamia, walnut, pistachios, hazelnut 2 g *in vitro*, fermented	chemo-preventive effects
Nagel et al. [54]	A	walnut 19 % of total calories 25 days	tumor weight and -growth ↓ angiogenesis ↓
Rezaei et al. [57]	An *in vitro* (HT 29)	atlantic pistachio ethanolextract	cell cycle arrest ↑ apoptosis ↑ cell growth ↓

Tab. 1f: **Current state of research on preventive aspects of nuts: influence of nut consumption on colorectal and breast cancer**
*referring to a daily consumption
↑ = increased significantly; ↓ = decreased significantly; ↘ = non-significant decrease; ↗ = non-significant increase; n. c. = no change
A = animal study; An = analytical study; E = epidemiological study
AA = arachidonic acid; COX = cyclooxigenase; OX = lipoxygenase

Not least, daily nut consumption enables both healthy subjects and diabetic patients of a better glycemic control. Thus, nuts could not only serve for the prevention of hyperglycemia and the development of DMT2, but also contribute to a reduced risk for cardiovascular diseases.

According to current knowledge, the consumption of nuts can be fully recommended as part of a healthy diet, but a regular consumption of a sufficient portion size is necessary for both prophylactic and clinical applications of nuts. Therefore, the DGE recommends the consumption of 25 g per day [64] and the U.S. Food and Drug Administration of even 42.5 per day [65].

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Conflict of Interest
The authors declare no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

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