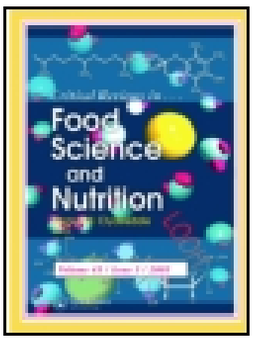

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REVIEW

Effect of chronic consumption of nuts on oxidative stress: a systematic review of clinical trials

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ABSTRACT

Nuts consumption has been associated with a protective effect against cardiovascular diseases and oxidative stress-related disorders. We aimed to perform a systematic review with clinical trials to assess the impact of chronic nuts consumption on oxidative stress and the possible mechanisms involved. Studies were identified by searching in three electronic databases: PubMed/MEDLINE, Scopus, and LILACS, and selected following PRISMA guidelines. Two authors perform searching and data extraction. A total of 16 articles were included (12 randomized clinical trials and 4 one or two-arm clinical trials). Nut doses were generally high (> 30 g/d), except for Brazil nuts (5–13 g/d). The follow-up time ranges between four weeks and six months, and the oxidized low-density lipoprotein (ox-LDL) was the most assessed biomarker. Eight articles reported improvement in oxidative stress biomarkers after nuts supplementation. Pathways regulated by selenium (e.g. glutathione peroxidase activity and nuclear factor-E2-related factor 2 (Nrf2) regulation), monounsaturated fatty acids (e.g. reduction of LDL oxidation), and bioactive compounds (e.g. antioxidant activity) were described as mechanisms involved in these beneficial effects. No studies reported harmful effects of nut consumption, even in high doses. The chronic consumption of nuts seemed to be effective to change some oxidative stress biomarkers, however, this topic remains controversial because the benefits depends on nut type, nut dose, and population characteristics.

KEYWORDS

Health; humans; antioxidants; oxidized LDL; selenium; functional foods

Introduction

Oxidative stress is involved in genesis and progression of chronic diseases, such as obesity, diabetes, and cardiovascular diseases (WHO 2018). The oxidative status is characterized by excessive reactive oxygen species (ROS) with an imbalance between oxidants and antioxidants compounds (Farzaei et al. 2018). Excessive ROS production starts harmful effects in cellular membranes, signaling proteins, and even DNA. A defense system of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), protect human cells from ROS-induced damage (Pizzino et al. 2017).

The redox balance is controlled by several defense systems. For this reason, a lot of biomarkers are used to investigate oxidative stress outcomes (Frijhoff et al. 2015; Marrocco et al. 2017). In this regard, there is no better biomarker, because each one represents a different system, which may difficult to infer about oxidative stress extent (Frijhoff et al. 2015). For example, GPx, CAT and SOD are antioxidant enzymes. The ox-LDL is produced by reaction with free radicals and plays a role in atherosclerosis triggering (Kattoor, Kanuri, and Mehta 2019). The deoxyguanosine (8-OHdG) is a biomarker of DNA damage (Stockler-Pinto et al. 2014). In summary, multiple biomarkers should be assessed to better understanding of redox balance.

In turn, foods rich in nutrients and bioactive compounds with antioxidant properties can improve defenses against oxidative stress and reduce the incidence of related diseases. Nuts, for example, are a good source of monounsaturated fatty acids (MUFA), tocopherol, minerals, polyphenols, phytosterols, and many phytochemicals that may synergically prevent an oxidative state (López-Uriarte et al. 2010). Nuts in a Mediterranean diet context are associated with a protective effect against cardiovascular diseases and oxidative stress disorders (Bulló, Lamuela-Raventos, and Salas-Salvado 2011; Sureda et al. 2016), and their consumption is recommended in dietary guidelines worldwide (López-Uriarte et al. 2010).

However, the effect of nuts intake on oxidative stress in humans is not well established, and no study has systematically reviewed this theme. Besides, the mechanisms by which nuts, and nutrients can act against oxidative stress are poorly studied. Therefore, we aimed to perform a systematic review of clinical trials to assess the effect of chronic nuts

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Table 1. Description of inclusion and exclusion criteria adopted in the systematic review.

Criteria	Inclusion criteria	Exclusion criteria
Population	Humans with at least one cardiometabolic risk factor such as overweight or obesity, diabetes mellitus, dyslipidemia, and hypertension	Healthy samples or studies with animals or cells
Study design and objective	The participants were prospectively to one or more interventions (which may include placebo or other control groups), and the effects of nuts consumption on oxidative stress were evaluated	Studies such as reviews, cohort, observational or studies who did not assessed the effect of nuts in at least one oxidative stress biomarker
Age	≥18 years	<18 years
Report of baseline and follow-up values	Baseline and follow-up values of oxidative stress biomarkers or the mean change between baseline and follow-up for each group, or the mean difference between intervention and control groups; at least one explicitly reported	Values for the difference between intervention/control groups or baseline/follow-up changes were not informed
Nut processing	Only studies with whole and raw nuts were included	Studies with powder nuts, oils, extracts or skins were excluded
Intervention	1. The intervention group were supplemented only with nuts and no other foods or dietary patterns (such Mediterranean Diet) were added, except nutritional advice 2. The chronic effect of nut intake was analyzed	1. The effect of nut could not be isolated (interventions with nuts plus other foods, exercise or Mediterranean diet) 2. The effects analyzed were acute or postprandial

consumption on oxidative stress and the possible mechanisms involved.

Methods

This systematic review followed the requirements of the PRISMA criteria guidelines (Liberati et al. 2009). The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO); registration number: CRD42020175445.

Search strategy

The articles were identified by searching three electronic databases, including PubMed, SCOPUS, and LILACS, through September 2019/March 2020, with no restriction for language or publication period. The following keywords were used in the literature research: Nut (s) OR cashew (s) OR Brazil Nut (s) OR hazelnut (s) OR almond (s) OR walnut (s) OR macadamia (s) OR pecan (s) OR pistachio (s) OR peanut (s) OR chest (s) nut OR tree nut (s). Each keyword related to nuts was combined with "oxidative stress" term to identify relevant studies. Filters for human studies were used when available. Filter for clinical trials was used at PubMed database. The search was performed independently by two investigators (BKSS and AS) who reviewed titles and abstracts, screened full texts of the papers, and selected eligible studies. Any disagreements were resolved by consensus.

Inclusion and exclusion criteria

To be included in this review, studies were required to meet the inclusion criteria, and were excluded in specific cases, according to criteria described in Table 1.

Data extraction

The following data were extracted from each study: first author, year of publication, country, sample size, health status, age and body mass index of sample, nut type, nut dose, study design and duration, details of the control arm and background diet, details of intervention groups, main results, conclusion (the article supports the protective effect of nuts against oxidative stress? – Yes or no). Studies on nuts and oxidative stress outcomes are summarized in Table 2.

Risk of bias assessment

The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials (Higgins et al. 2011) was used to evaluate the included studies. BKSS and AS appraised the risk of bias independently, and disagreements were discussed until consensus. Trials were classified as 'low risk of bias' when the information was evident in the paper, and the appraiser's judgment could deduce no bias. 'Unclear risk of bias' was attributed when insufficient information was provided to permit judgment and 'high risk of bias' when the methodological flaw was likely to have affected the exact outcome or some essential methodologic aspect was not assessed, i.e., diets and nuts composition. The blinding of participants in intervention studies with raw nuts is very difficult to achieve, so we considered this criterion as 'low risk of bias' for all studies. We highlight that the Cochranes tool was developed to RCT, but four articles analyzed in the present review are non-randomized clinical and received 'unclear risk of bias' in questions related exclusively to RCT.

Results

Trial selection

We identified a total of 1,815 articles. After review of title and abstract, we excluded 1,783 articles, which 1,765 reports were deemed irrelevant and 18 reports were duplicates. The remaining 32 articles were reviewed in full, and 16 reports

Table 2. Main characteristics of studies included in the systematic review.

Author/Year/Country	Sample characteristics (M/W)	Type of nuts	Dose of nuts	Study design (Follow-up time)	Control group	Intervention group	Results	Supports the effect of nuts
Randomized Clinical Trials								
Jenkins et al. 2002 Canada	n = 27 (15/12) People with hyperlipidemia BMI = 25.5 ± 4 kg/m^2 Age = 64 ± 9 y	Almond	37–73.6 g/d	RCT, Crossover (4-wk intervention and 2 wk washout)	G0: Low-saturated fat (<5% energy) whole-wheat muffin	G1: Almonds (73.6 ± 3 g/d) G2: Almonds (37 ± 2 g/d) + whole-wheat muffin	G1 and G2 x G0: ↓ Ox-LDL	Yes
Jenkins et al. 2008 Canada	n = 27 (15/12) People with hyperlipidemia BMI = 25.5 ± 4 kg/m^2 Age = 64 ± 9 y	Almond	37–73.6 g/d	RCT, Crossover (4-wk intervention and 2 wk washout)	G0: Low-saturated fat (<5% energy) whole-wheat muffin	G1: Almonds (73.6 ± 3 g/d) G2: Almonds (37 ± 2 g/d) + whole-wheat muffin	G1 x G0: ↓ serum MDA G1 and G2 x G0:↓ urinary isoprostanes	Yes
Liu et al. 2013 China	n = 21 (9/12) People with DM2 and hyperlipidemia BMI 26 ± 0.7 kg/m^2 Age 58 ± 2 y	Almonds	20% of daily calorie intake (∼56 g/d)	RCT, Crossover (4-wk intervention and 2 wk washout)	Isocaloric diet without nuts	Isocaloric diet with almonds	↔plasma MDA ↔ plasma TAC ↑ Lag time of LDL oxidation ↓ Ox-LDL ↓ plasma protein carbonyls	Yes
Jung et al. 2018 Korea	n = 84 (11/73) Overweight or obese people BMI 25.4 ± 0.22 kg/m^2 Age 52.4 ± 0.6 y	Almonds	56 g/d	RCT, Crossover (4-wk intervention and 2 wk washout)	Isocaloric cookies	Almonds	↔ plasma MDA ↔ Ox-LDL ↔ plasma protein carbonyls	No
Darvish Damavandi et al. 2019 Iran	n = 43 (9/34) People with DM2 BMI (controls) 28.6 ± 3.1 kg/m^2 BMI (intervention) 28.7 ± 5.8 kg/m^2 Age 30 − 75 y	Cashews	10% of daily calorie intake	RCT (8-wk intervention)	Normal dietary pattern	10% of daily calorie intake from cashews	↔ plasma TAC ↔PON-1	No
Lopez-Uriarte et al. 2010 Spain	n = 50 (28/22) People with MetS BMI < 35 kg/m^2 Age ± 51.8 y (range 26–63)	Mixed raw nuts with skin (15 g/d of walnuts, 7.5 g/d of almonds and 7.5 g/d of hazelnuts	30 g/d	RCT (12-wk intervention)	Healthy diet (AHA guideline)	Healthy diet supplemented with mixed nuts	↔Ox-LDL ↔Lag phase of conjugated diene formation ↔Vmax ↔Cmax ↔Urine 8-isoprostanes (ng/mmol creatinine) ↓Urine 8-oxo-dG (nmol/mmol creatinine)	Yes
McKay et al. 2018 United States of America	n = 26 (21/5) Overweight or obese people BMI: M = 29.4 (0.7) / W = 28.4 (0.9) kg/m^2 Age ≥ 45 y	Pecan	∼ 42.5 g/2000 kcal	RCT, Crossover (4-wk intervention and 2-wk washout)	Typical American diet	15% of daily calorie intake All meals provided	↔ in lag time Ox-LDL and total phenolics	No
Kay et al. 2010 United States of America	n = 28 (10/18) People with hyperlipidemia BMI 26.8 ± 0.7 kg/m^2 Age 35-61 y	Pistachio	10 or 20% of daily calorie intake (32-126 g/d)	RCT, Crossover (4-wk intervention and 2-wk washout)	G0: Lower-fat control diet without pistachios	G1: 10% of daily calorie intake (32-63 g/d); 30% total fat G2: 20% of daily calorie intake (63-126 g/d); 34% of total fat	G1 and G2 vs G0: ↓ Ox-LDL ↔ GSH	Yes
Hernández-Alonso et al. 2014 Spain	n = 54 (29/25) Prediabetic subjects BMI 28.9 (28.2, 29.6) kg/m^2 Age 55 (53.4, 56.8) y	Pistachio	57 g/d	RCT, Crossover (4-mo intervention and 2-wk washout)	Control diet adjusted in lipids (mainly olive oil)	Pistachio supplementation	↔ Ox-LDL	No
Damasceno et al. 2011 Spain	n = 18 (9/9) People with hypercholesterolemia BMI 25.7 ± 2.3 kg/m^2 Age 55 y (53.4, 56.8)	Walnut (W) and almond (A)	22% of daily calorie intake W = 40-54g A = 50-75g	RCT, Crossover (4-wk intervention)	G0: Supplemental virgin olive oil	G1: Supplemental walnuts G2: Supplemental almonds	↔ plasma MDA ↔ Ox-LDL	No

(*continued*)

Table 2. Continued.

Author/Year/Country	Sample characteristics (M/W)	Type of nuts	Dose of nuts	Study design (Follow-up time)	Control group	Intervention group	Results	Supports the effect of nuts
Davis et al. 2007 South Africa	n = 64 (29/35) People with MetS BMI not informed Age 45 ± 10 y	Walnut and Cashew nut	20% of daily calorie intake	RCT (8-wk intervention)	G0: Prudent diet without nuts	G1: Prudent diet + Walnuts G2: Prudent diet + Cashew	↔ serum ORAC ↔GSH ↔GSSG ↔diacron reactive metabolites	No
Caldas et al. 2020	n = 64 men Overweight people BMI 29.76 ± 0.3 kg/m^2 Age 27 ± 0.9 y	Peanuts	56g of high-oleic or conventional peanuts	RCT (4-wk intervention)	G0: Hypocaloric diet (- 250 kcal)	G1: Hypocaloric diet + 56g/d conventional peanut G2: Hypocaloric diet plus 56g/d high-oleic peanut	G0: ↓ MDA G0, G1 and G2: ↔ GST ↔ SOD ↔ NO	No
One arm								
Jalali-Khanabadi, Mozaffari-Khosravi, and Parsaeyan 2010 Iran	n = 30 Men with hyperlipidemia BMI 24.29 ± 2.15 kg/m^2 Age 45.57 ± 7.14 y	Almonds	60 g/d	One arm (4-wk intervention)	-	Normal diet + Supplementation of almonds	↔Lag time of conjugated diene formation ↔OD-max ↔V-max ↔T-max	No
Cominetti et al. 2011 Brazil	n = 37 Morbidly obese women BMI (controls) 44.5 ± 3.9 kg/m^2 BMI (intervention) 45.3 ± 4.2 kg/m^2 Age > 18 y	Brazil nut	1 unit (~ 5g)	One arm (8-wk intervention)	–	Supplementation of one Brazil nut/d	↑ plasma and erythrocyte Se ↑ erythrocyte GPx	Yes
Stockler-Pinto et al. 2014 Brazil	n = 40 Hemodialysis patients BMI not informed Age 53.3 ± 16.1 y	Brazil nut	1 unit (~ 5g/d)	One arm (3-mo intervention)	–	Supplementation of one Brazil nut/d (321.8 ± 15.1 μg of Se/d)	↑ plasma and erythrocyte Se ↑ erythrocyte GSH-Px ↓ 8-OHdG ↓ plasma 8-isoprostane	Yes
Cardozo, Stockler-Pinto, and Mafra 2016 Brazil	n = 25 (9/16) Hemodialysis patients BMI 24.4 ± 3.2 kg/m^2 Age 57.1 ± 12.0 y	Brazil nut	1 unit (~ 5g) offering 290.5 μg of Se	Two-arm (3-mo)	Standard care without supplementation	Supplementation of 1 Brazil nut/d	↑ Nrf2 and NQO1 ↓ serum MDA	Yes

Legend: M, men, **W,** women, **BMI,** body mass index, **G0,** control group, **G1,** intervention group 1, **G2,** intervention group 2, **LDL,** low density lipoproteins, **Ox-LDL,** oxidized LDL, **TAC,** total antioxidant capacity, **MDA,** malondialdehyde, **SOD,** superoxide dismutase, **8-oxo-dG,** 8-oxo- 7,8-dihydro-20-deoxyguanosine, **8-OHdG,** 8-hydroxy-2-deoxyguanosine, **GPx,** glutathione peroxidase, **DNA,** deoxyribonucleic acid, **MetS,** metabolic syndrome, **GSH,** reduced glutathione, **GSSG**, oxidized glutathione, **GST** glutathione S transferase, **NO** nitric oxide, **ORAC**, oxygen radical absorbance capacity, **GSH-PX**, reduced glutathione peroxidase, **AHA,** American Heart Association, **OD-max,** maximal amount of lipids peroxide products accumulation in mmol/L of conjugated dienes per mmol of low-density lipoprotein cholesterol during the lipid oxidation course, **V-max,** maximal rate of oxidation in mmol/L of conjugated dienes production per mmol of LDL per minute in during the lipid oxidation course, **T-max**, time needed (in minutes) to gained the maximal rate of lipid peroxide products accumulation during the lipid oxidation course, **DM2,** type 2 diabetes mellitus, **Se,** selenium, **PON-1,** paraoxonase-1.

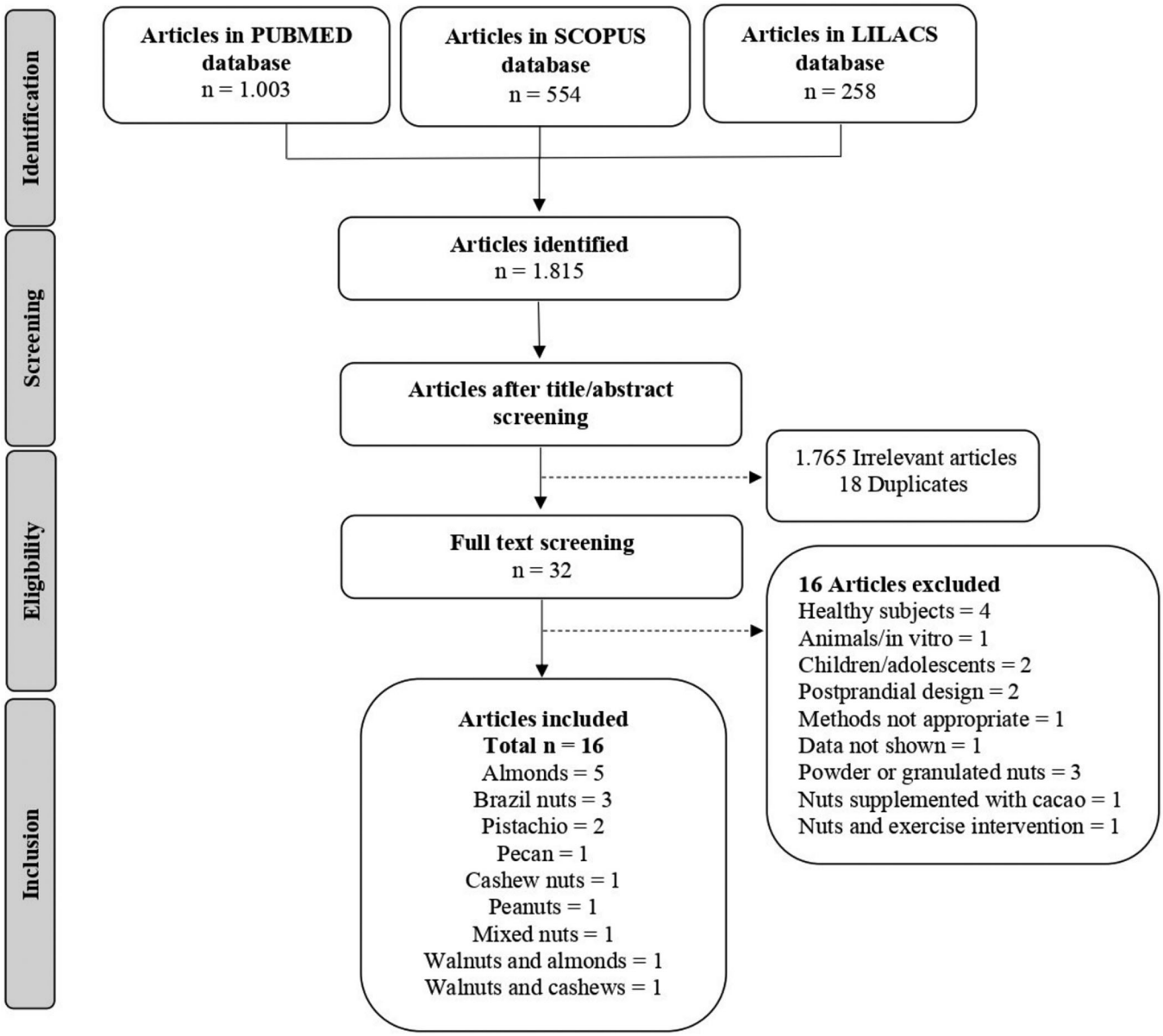

Figure 1. Flowchart of search strategy and articles included.

were excluded for not meeting inclusion criteria. The most common reasons for study exclusion were healthy samples, animal or in vitro studies, age of participants (children or adolescents), postprandial design, inappropriate methodology, values not informed (data not shown), interventions with granulated or powder nuts, concomitant supplementation of nuts and cacao, interventions with nuts and exercise (Figure 1).

Study characteristics

Design and subjects

From 16 studies included, 12 were RCT (Jenkins et al. 2002; Davis et al. 2007; Jenkins et al. 2008; Kay et al. 2010; López-Uriarte et al. 2010; Damasceno et al. 2011; Liu et al. 2013; Hernández-Alonso et al. 2014; Jung et al. 2018; McKay et al. 2018; Damavandi et al. 2019) and 4 were clinical trials with one or two arm comparing baseline and post-intervention values of oxidative stress biomarkers (Jalali-Khanabadi, Mozaffari-Khosravi, and Parsaeyan 2010; Cominetti et al. 2011; Stockler-Pinto et al. 2014; Cardozo, Stockler-Pinto, and Mafra 2016). From the RCT, 8 were crossover (Jenkins et al. 2002; Jenkins et al. 2008; Kay et al. 2010; Damasceno et al. 2011; Liu et al. 2013; Hernández-Alonso et al. 2014; Jung et al. 2018; McKay et al. 2018).

These trials were conducted in subjects of both sexes, age $\geq$ 18 years and at least one cardiometabolic risk factor including overweight or obesity, dyslipidemia, hypertension, metabolic syndrome (MetS), prediabetes or type 2 diabetes mellitus (DM2) (Table 2).

Intervention characteristics

Almonds were the nut type most frequent in interventions ($n = 5$) followed by Brazil nuts ($n = 3$), pistachio ($n = 2$), pecan ($n = 1$), cashew nuts ($n = 1$), peanuts ($n = 1$), mixed nuts (walnuts, almonds and hazelnuts) ($n = 1$), walnuts and

Table 3. Nuts composition (in a 30 g serving).

	Calories (kcal)	Total Fat (g)	SFA (g)	MUFA (g)	PUFA (g)	Protein (g)	Fiber (g)	Se (μg)	Total Polyphenol (mg) *
Brazil nuts	198	20.2	4.9	7.2	7.4	4.3	2.3	575.1	73.2
Cashew nuts	166	13.2	2.3	7.1	2.3	5.5	1.0	5.9	69.8
Almonds	174	15.0	1.1	9.5	3.7	6.4	3.8	1.2	86.1
Pecan	208	21.7	1.8	12.3	6.5	2.8	2.9	1.1	385.2
Pistachio	168	13.7	1.8	7.1	4.3	6.1	3.2	2.1	69.8
Walnuts	197	19.6	1.8	2.7	14.2	4.6	2.0	1.3	472.4
Peanuts	170	14.7	1.8	7.3	4.6	7.7	2.5	2.1	121.8

Composition of whole raw nuts based on USDA database (USDA Food Data Central, 2019) and Phenol-Explorer database (Phenol Explorer database 3.6 on polyphenol content in foods).
SFA: Saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; Se: selenium.

almonds in independent groups ($n = 1$), walnuts and cashew nuts also in independent groups ($n = 1$) (Table 2).

The intervention period ranges between four weeks and six months, but four ($n = 9$) and eight weeks ($n = 3$) were more common. The lowest dose was 30 g/d, and the higher dose was 73.6 g/d, excepted for Brazil nuts (5 g/d), which presented the lowest dose. The lower dose of Brazil nuts is justified by the high selenium (Se) and saturated fatty acids (SFA) content in these nuts whose Upper Tolerable Intake (UL) could be reached with few units of this nut (Table 3). Three studies adopted the percentage of daily calorie intake (10–22%) to establish a nut dose. Nuts were supplemented in the habitual diet context or were analyzed with healthy diet orientations to an isocaloric diet. In five included studies, oxidative stress was a secondary outcome (Table 2).

Oxidative stress biomarkers

We included a total of 16 articles that addressed at least one biomarker of oxidative stress: oxidized Low-Density Lipoprotein (ox-LDL) (8 trials), plasma malondialdehyde (MDA) (3 trials), erythrocyte glutathione peroxidase (GPx) (3 trials), plasma protein carbonyls (2 trials), lag-time of conjugated diene formation (2 trial), plasma total antioxidant capacity (TAC) (2 trials), plasma and erythrocyte Se (2 trials), plasma GPx (1 trial), serum MDA (2 trial), urinary isoprostanes (1 trial), plasma isoprostanes (1 trial), paraoxonase-1 (PON-1) (1 trial), lag time of LDL oxidation (1 trial), serum Oxygen radical absorbance capacity (ORAC) (1 trial), reduced glutathione (GSH) (1 trial), oxidized glutathione (GSSG) (1 trial), glutathione S transferase (GST) (1 trial), diacron reactive metabolits (1 trial), conjugated dienes and lipid peroxide products (OD-max, V-max, T-max) (1 trial), urinary 8-oxo-7,8-dihydro-20-deoxyguanosine (8-oxo-dG) (1 trial), plasma 8-hydroxy-2-deoxyguanosine (8-OHdG) (1 trial), nitric oxide (NO) (1 trial). Half of the included studies ($n = 8$) reported a beneficial effect of nut consumption on at least one oxidative stress biomarker analyzed (Table 2).

Outcomes by nut types

Almonds. Subjects with hyperlipidemia received full-dose almonds (73.6 g/d) or half-dose almonds (37 g/day) in a crossover intervention (four weeks intervention, two weeks washout). Compared to the control group (low-saturated fat (<5% energy) whole-wheat muffin), both doses of almonds reduced ox-LDL and urinary isoprostanes, but only full-dose almond was able to reduce serum MDA (Jenkins et al. 2002; Jenkins et al. 2008). Another crossover intervention (four weeks intervention, two weeks washout) with subjects with hyperlipidemia and DM2 reported a reduction in ox-LDL, plasma protein carbonyls while increase lag time of LDL oxidation after almonds consumption (56 g/d) compared to the control group (isocaloric diet). However, no changes in MDA and TAC were achieved (Liu et al. 2013). Jung et al. (2018) also do not observe any changes in plasma MDA, ox-LDL, or plasma protein carbonyls after four weeks of 56 g/d almonds supplementation in overweight or obese subjects, compared with the control group (isocaloric cookies) (Jung et al. 2018). Even with a high dose of almonds (60 g/day), hyperlipidemic men do not change the lag time of conjugated diene formation, OD-max, V-max, and T-max after four weeks intervention (Jalali-Khanabadi, Mozaffari-Khosravi, and Parsaeyan 2010).

Brazil nuts. Two interventions supplemented only one Brazil nut/day, and both of them report improvement on analyzed biomarkers. Morbidly obese women presented higher values of plasma and erythrocyte Se as well as erythrocyte GPx after eight weeks of intervention (Cominetti et al. 2011). Hemodialysis patients had the same results after three months, and also reduced 8-OHdG and plasma 8-isoprostanes (Stockler-Pinto et al. 2014). Another study with hemodialysis patients observed an increase on nuclear factor-E2-related factor 2 (Nrf2) and NAD(P)H dehydrogenase [quinone] (NQO1), and a reduction in serum MDA after three months intervention with one Brazil nut/day (Cardozo, Stockler-Pinto, and Mafra 2016).

Cashew nuts. People with DM2 received 10% of daily calorie intake from cashew nuts for eight weeks. At the end of the intervention, no changes in plasma TAC and PON-1 were achieved compared to the control group (typical dietary pattern) (Damavandi et al. 2019)

Pecan. The lag time to ox-LDL in overweight and obese subjects does not suffer any change after four weeks of pecan supplementation (± 42.5 g/2000 kcal) in a crossover intervention compared to control group (typical American diet) (McKay et al. 2018).

Pistachio. In a crossover intervention (4 weeks), subjects with hypercholesterolemia received 10% or 20% of daily calorie intake from pistachios (32–63 g/d or 63–126 g/d, respectively). Compared to the control (lower-fat diet free of

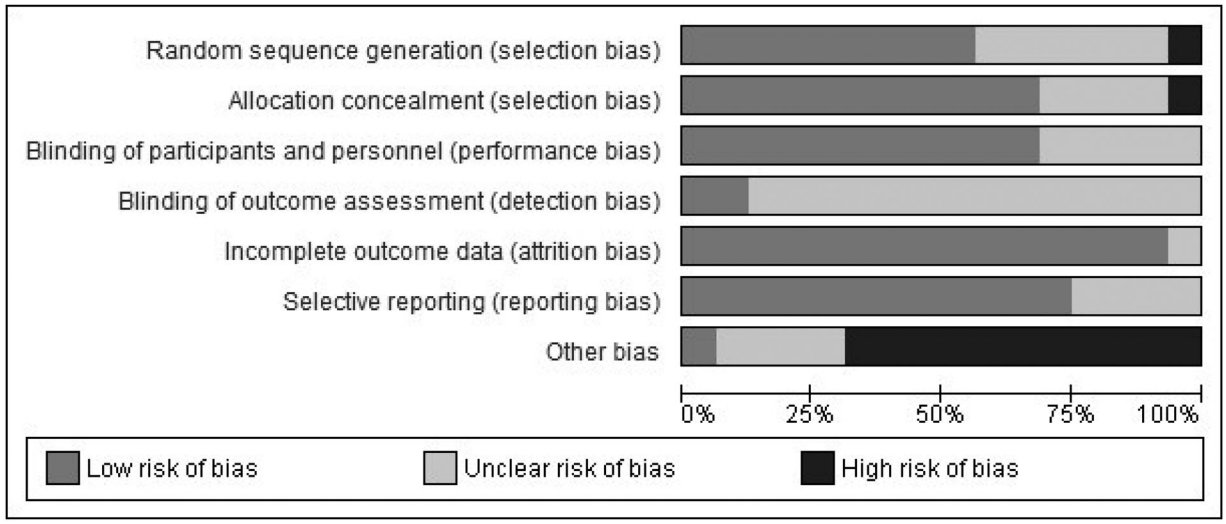

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

nuts), there was a reduction in ox-LDL, without changes in GSH (Kay et al. 2010). With a lower dose of pistachios (57 g/d), people in prediabetes condition do not change ox-LDL levels after four months supplementation compared to the control group (diet adjust in lipids, mainly olive oil) (Hernández-Alonso et al. 2014).

Peanuts. Overweight men (the most were healthy) were instructed to follow a hypocaloric diet (−250 kcal). They were divided into three groups: control (diet free of nuts), conventional peanuts (56 g/d), or high-oleic peanuts (56 g/d) for four weeks. At the end of the intervention, nitric oxide, GST, and SOD activity remained unchanged (Caldas et al. 2020).

Mixed nuts. Subjects with metabolic syndrome (MetS) were supplemented with 30 g of mixed nuts (15 g/d of walnuts, 7.5 g/d of almonds, and 7.5 g/d of hazelnuts) for 12 weeks. At the end of the intervention, only urine 8-oxo-dG reduced, and the other biomarkers remained unchanged (ox-LDL, the lag phase of conjugated diene formation, V-max, C-max, Urine 8-isoprostanes) (López-Uriarte et al. 2010). In another study, participants with Mets were separated into two groups: one received walnuts (20% of daily calorie intake), and the other received cashews (20% of daily calorie intake). After eight weeks, no changes were measured in reduced glutathione (GSH), oxidized glutathione (GSSG), oxygen radical absorbance capacity (ORAC), and diacron reactive metabolites (Davis et al. 2007). In another study, the supplementation of almonds (50–70 g/d) or walnuts (40–54 g/d) during four weeks, do not change plasma MDA and ox-LDL levels in people with hypercholesterolemia (Damasceno et al. 2011).

Risk of bias

The summary of the review authors' judgments about each risk of bias item for each included study is presented in supplemental Figure 1. Three studies were one or two-arm clinical trials being classified as 'Unclear risk of bias' for random sequence generation, allocation concealment and blinding of participants since these questions are specific to RCT (Jalali-Khanabadi, Mozaffari-Khosravi, and Parsaeyan 2010; Cominetti et al. 2011; Stockler-Pinto et al. 2014; Cardozo, Stockler-Pinto, and Mafra 2016). One clinical trial was considered as 'high risk' for the same questions since there was a control group not randomly assigned (Cardozo, Stockler-Pinto, and Mafra 2016). Two other trials were classified as 'Unclear' because they do not report in detail the randomization method (López-Uriarte et al. 2010; Damavandi et al. 2019). Only two studies declared the blinding of outcome assessment and were considered 'Low risk of bias' (Jenkins et al. 2008; McKay et al. 2018); the others were considered 'Unclear'. We do not detect any incomplete outcome data. Four articles do not report the Clinical Trial number, so they were classified as 'Unclear' to selective reporting (Jalali-Khanabadi, Mozaffari-Khosravi, and Parsaeyan 2010; Cominetti et al. 2011; Stockler-Pinto et al. 2014; McKay et al. 2018). Most of the studies were classified at 'High risk for other bias' because they do not report diet composition or nuts composition in detail, which can be a confounder factor. Figure 2 shows the percentages of each risk of bias, according to the review authors.

Discussion

To the best of our knowledge, this is the first study that systematically reviewed the effect of nuts on oxidative stress biomarkers in humans. Half of the studies ($n = 8$) included in this review reported at least one benefit in oxidative stress biomarker after nuts consumption (Jenkins et al. 2002; Jenkins et al. 2008; Kay et al. 2010; López-Uriarte et al. 2010; Cominetti et al. 2011; Liu et al. 2013; Stockler-Pinto et al. 2014; Cardozo, Stockler-Pinto, and Mafra 2016). Nuts are nutrient-dense foods, which means the richest source of monounsaturated fatty acids (MUFA), vitamins, minerals, phytosterols compounds, protein, and fiber (De Souza et al. 2017). In the Mediterranean diet context, the benefit of nuts consumption is well established (Mattioli et al. 2017), but the independent nuts effect is controversial. In this sense,

we discussed the included studies according to nuts effects against oxidative stress and related-antioxidant proprieties of nuts, study limitations, and perspectives.

Nuts against oxidative stress

Regarding nuts consumption against oxidative stress, ox-LDL was the biomarker most adopted to evaluate this relationship. Reactive oxygen species (ROS) are increased in pro-oxidant state and are chemically able to modify LDL to ox-LDL, which plays a role in atherosclerosis triggering, in a synergic way with immune cells (Kattoor, Kanuri, and Mehta 2019). Inflammatory signaling pathways are activated by these oxidized lipids and leads to cellular dysfunction and atherosclerotic plaques development (Qin et al. 2017).

The consumption of antioxidant food sources can prevent the pro-oxidant state and excessive LDL oxidation. There is also evidence that MUFA-rich diet reduces the susceptibility of LDL to oxidation; however, little is known about the mechanism underlying this effect (Lapointe, Couillard, and Lemieux 2006). Besides MUFA, nuts have a high content of bioactive compounds, which difficult to isolate the protective effect of MUFA on oxidative stress. The bioactive compounds category includes the polyphenols whose effect and mechanisms are better known.

Diet provides about 1 g/day of polyphenols, which means that they are the most abundant dietary antioxidants (Pérez-Jiménez et al. 2010). The flavonoids, i.e., quercetin, catechins, and anthocyanins, correspond for around 60% of all polyphenols identified (Törrönen 2011). They protect human the body against oxidative stress damage (1) breaking the lipid peroxidation chain reaction by radical species scavenging, (2) preventing free radical formation by pro-oxidant metal chelation, (3) suppressing lipid peroxidation by antioxidants recycling, (4) and preserving the HDL-associated paraoxonase activity (Lapointe, Couillard, and Lemieux 2006).

Nuts are one of the principal food sources of MUFA and polyphenols. Pecan and almonds are richest in MUFA content compared to Brazil nuts, cashews, pistachio, and walnuts, while walnuts and pecan have the highest polyphenol content (Table 3). In the present review, eight articles measured changes in ox-LDL after nuts consumption, five reported reductions, and three do not report any significant changes in this biomarker. Jenkins et al. demonstrated that almonds supplementation reduced ox-LDL in subjects with dyslipidemia after supplementation of a full-dose (73 ± 3 g/d, 22% of energy) or half dose of almonds during four weeks (Jenkins et al. 2002). Liu et al. reported similar results after four weeks of almonds supplementation (∼ 56 g/d) in people with dyslipidemia and DM2 (Liu et al. 2013). Pistachio supplementation also was effective in ox-LDL reduction after four weeks of intervention (10 or 20% of daily calorie intake) in subjects with hyperlipidemia (Kay et al. 2010).

Interventions with Brazil nuts commonly are conducted with 1 unit/day or less than 20 g/d supplementation. This is justified by the high Se content and high bioavailability in Brazil nuts. While the other nuts have less than 7 µg of Se in a 30 g portion size, Brazil nuts have about 575.1 µg in the same dose (**Table 3**). In Brazil nuts trials, enzymes related to Se metabolism and antioxidant defense are generally well described. Selenium is an essential micronutrient and component of several selenoproteins that regulate antioxidant state, thyroid hormone metabolism, and immune function (Cominetti et al. 2011). Selenium deficiency can lead to decreased glutathione peroxidase (GSH-Px or GPx), an important enzyme that protects membrane lipids and other intra or extracellular components from oxidative damage (Stockler-Pinto et al. 2014).

Brazil nuts supplementation also reduces isoprostanes derived from arachidonic acid peroxidation (Jenkins et al. 2008; Stockler-Pinto et al. 2014) probably due to better GPx activity. Further lipids peroxidation, reduced GPx activity also can increase DNA damage (Stockler-Pinto et al. 2014). Lower GPx activity leads to over ROS production, and more hydroxyl radicals (HO·) become available to react with guanine in C8 position, forming deoxyguanosine (8-OHdG) (López-Uriarte et al. 2010; Stockler-Pinto et al. 2014). For this reason, 8-OHdG is one of the most abundant oxidative products of DNA and results in genomic instability and oxidative stress disorders (López-Uriarte et al. 2010; Stockler-Pinto et al. 2014).

When Se and GPx levels are adequate, the ROS production and DNA damage reduce. Two articles support that Brazil nut supplementation increase plasma Se, and erythrocyte GPx activity (Cominetti et al. 2011; Stockler-Pinto et al. 2014). The supplementation of only one Brazil nut/day seemed to be effective in restore GPx levels and reduce DNA damage in subjects with Se deficiency (López-Uriarte et al. 2010; Stockler-Pinto et al. 2014). However, when Se intake is adequate, the GPx activity seems to reaches a plateau. Adults with Se deficiency were supplemented with 37 µg/day of selenomethionine, which was sufficient to reach the maximum enzyme activity (Xia et al. 2005). A cohort study demonstrated that people with daily intake of 109.1 ± 43.6 µg/day on baseline did not increase GPx-3 activity after selenomethionine supplementation, even when consuming 200 µg/day (Combs et al. 2012). Generally, studies with Brazil nuts report approximately 200 µg in only one unit of Brazil nut. For this reason, low doses of Brazil nut usually are sufficient to reach the maximum GPx activity.

Antioxidant compounds and nutrients present in nuts as polyphenols, phytosterols, and selenium can activate the Nrf2 pathway. Nrf2 stimulates the transcription of antioxidant response element (ARE) genes, and the encode of detoxifying enzymes and antioxidant enzymes, including GPx (Stockler-Pinto et al. 2014). Nfr2 pathway also activates NQO1 that stabilizes proteins protecting them against oxidative degradation (Ross and Siegel 2017) while the reduction in MDA reduces the peroxidation of lipids (Cardozo, Stockler-Pinto, and Mafra 2016). Only one study evaluated the effect of Brazil nut on Nrf2 and reported that the three months supplementation (one unit/day) increased the Nrf2 and NQO1 while reduced MDA (Cardozo, Stockler-Pinto, and Mafra 2016).

In the face of evidence, we propose that Se, MUFA, and bioactive compounds (polyphenols, phytosterols) are the

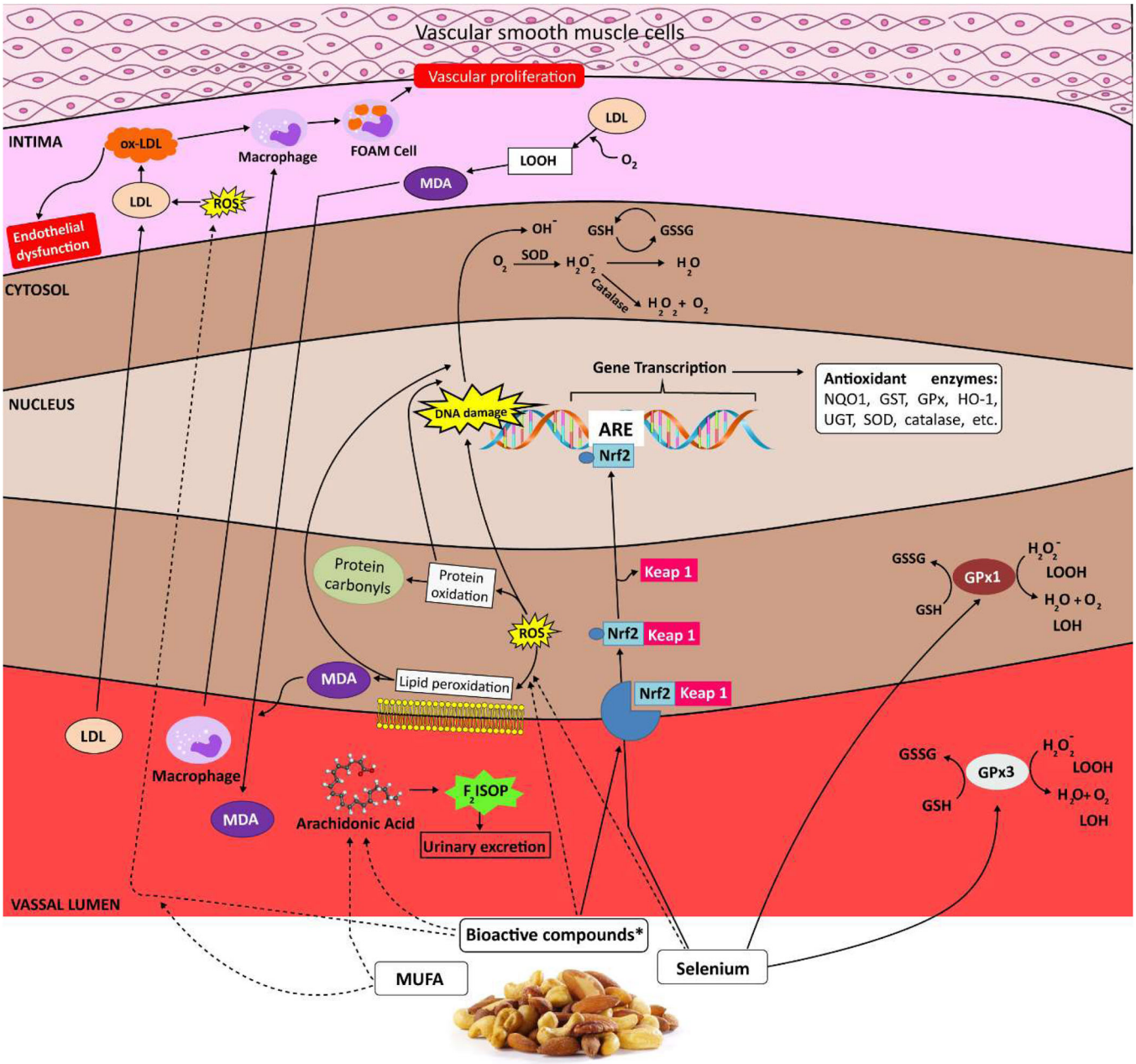

Figure 3. Schematic presentation of the main pathways modulated by nuts to oxidative stress control. This model proposes that selenium, MUFA, and *bioactive compounds (polyphenols, phytosterols) are the main responsible for nuts benefits on oxidative stress modulation, by which **Selenium** (1) upregulate GPx3 activity in plasma and GPx1 in the cytosol, (2) upregulate the Nrf2 pathway, (3) inhibits lipid and proteins peroxidation. **Bioactive compounds** (1) upregulate Nrf2 pathway, (2) inhibits lipid and proteins peroxidation, (3) inhibits LDL oxidation, (4) and arachidonic acid peroxidation. **MUFA** (1) inhibits arachidonic acid peroxidation, and (2) LDL oxidation. LDL: Low Density Lipoproteins, ox-LDL: oxidized low density lipoprotein, ROS: reactive oxygen species, MDA: malondialdehyde, LOOH: lipid peroxid, LOH: lipid alcohol, H2O2: hydrogen peroxid, DNA: deoxyribonucleic acid, ARE: antioxidant response element, Nrf2: nuclear factor erythroid 2-related factor 2, GPx: glutathione peroxidase, F2-ISOP: F2-isoprostanes, GSH: reduced glutathione, GSSG: oxidised glutathione, NQO1: NAD(P)H dehydrogenase [quinone], GST: Glutathione S-transferases, HO-1: heme oxygenase-1, UGTs: UDP-glucuronosyltransferase, SOD: superoxide dismutase.

main responsible for nuts benefits on oxidative stress modulation (Figure 3). Selenium improves GPx activity by the following steps. In the cytosol, the O2·— is a superoxide radical neutralized to H_2O_2 in a first phase and water and molecular oxygen in a second phase, by antioxidant enzymes (SOD, catalase, glutathione peroxidase, glutathione reductase). Reduced glutathione (GSH) is a substrate converted to the oxidized form (GSSG) in the process. After, GSH is regenerated by glutathione reductase with subsequent oxidation of NADPH. GPx1 acts in the cytosol, while GPx3 is located on vassal lumen and several human tissues.

Selenium also upregulates the Nrf2 pathway, which improves the expression of antioxidant response element (ARE) genes. Protein kinases are activated and react with the protein Keap-1, culminating in Keap-1/Nrf2 dissociation. Then, Nrf2 migrates to the nucleus where binds to ARE genes, triggering the transcription of antioxidant enzymes. In other mechanisms, Se inhibited membrane lipids and proteins peroxidation. Reactive oxygen species can oxidate lipids and proteins and lead to protein carbonylation and malondialdehyde (MDA). MDA is a final product of lipid peroxidation frequently measured as thiobarbituric acid reactive substances (TBARS).

Similar to Se, bioactive compounds (e.g. polyphenols, phytosterols) upregulate the Nrf2 pathway, inhibited membrane lipids and proteins peroxidation, but also prevent LDL and arachidonic acid peroxidation. This process occurs by inhibiting the reaction between ROS and LDL in the subendothelial space. This reaction culminates in ox-LDL formation and macrophages chemoattract. The macrophages engulf ox-LDL which result in foam cells formation. Foam cells and vascular smooth muscle cells (VSMC) proliferation start atherogenesis and amplify ROS production. Consequently, products of lipid peroxidation as lipid hydroperoxide (LOOH), MDA, and F2-Isoprostane (F2-ISOP) also increase. Probably MUFA is involved in other mechanisms, but inhibition of arachidonic acid and LDL peroxidation are better described.

Despite the evidence about the preventive role of nuts consumption on reduction of oxidative stress biomarkers, some studies failed to demonstrate improvement in oxidative stress biomarkers after some weeks of intervention. Aspects related to study design, follow-up duration, the dose of nuts, type of nuts, region of nuts growth, and control group contribute to controversy results in literature research. Four weeks follow-up interventions may have limited power to detect a chronic effect in oxidative stress after nuts supplementation, especially in samples with endocrine and metabolic disorders like obesity, dyslipidemia, DM2, MetS, hypertension, and kidney disease. Different results can be partly explained by diversity in nut composition, especially in the type of fat content. While MUFA can reduce oxidation, PUFA can have a pro-oxidant effect because it is the main substrate for LDL oxidation (López-Uriarte et al. 2010). Almonds, pistachio, pecan, and peanuts are richer in MUFA, but walnuts are especially high in PUFA (14.2 g/30g) and probably exert a minor effect in oxidative stress prevention (**Table 3**).

Besides, the high content of PUFAS in some nuts could be counteracted by the polyphenols and vitamin activity (López-Uriarte et al. 2010). At present, little is known about the bioavailability of polyphenols (usually is low). The metabolization of these bioactive compounds is too fast, and they are distributed for human tissues to act in synergic antioxidant defense pathways that can difficult the identification in plasma or serum (McKay et al. 2018) (López-Uriarte et al. 2010). In this regard, the food matrix of nut and interaction with human body pathways needs to be further investigated and we recommend assessing more than a single oxidative stress biomarker in future clinical trials.

Compared to other nuts, Brazil nut has the highest SFA content (4.9 g/30g). However, only 5 g/d of Brazil nuts is offered in most studies. This quantity is sufficient to increase Se intake without significant increase in SFA intake. For this reason, SFA from Brazil nuts are not related to pro-oxidant effect. Studies have demonstrated benefic effects of Brazil nuts that are mainly attributed to its high Se content (Cominetti et al. 2011; Stockler-Pinto et al. 2014). In summary, nuts supplementation seemed to be effective in ox-LDL reduction. The nutrients and bioactive compounds content in nuts, especially selenium, phytosterols, polyphenols, and MUFA can be related to the antioxidant pathways. However, the mechanisms need to be further investigated and confirmed. On the other hand, Brazil nuts antioxidant effect is better established as regards selenium content and up-regulation of GPx activity and NRF2 pathway. Also, Brazil nut could be easier to recommend in guidelines and dietary counseling because a lower dose is necessary to achieve an antioxidant effect.

Limitations

From the sixteen studies included in this systematic review, five assessed oxidative stress biomarkers or antioxidant defenses as a secondary outcome (Jenkins et al. 2002; Cominetti et al. 2011; Damasceno et al. 2011; Jung et al. 2018; McKay et al. 2018). Moreover, the majority of studies evaluate two or less oxidative stress biomarkers, which means that negative results may be insufficient to conclude that nuts did not affect oxidative stress. We hypothesized that some biomarkers, i.e. ox-LDL and GPx, can be more responsible to nuts supplementations, but the extent of reduced oxidative stress may be limited. Considering that plasma and serum measurements of oxidative stress biomarkers are difficult because of the highly reactive nature of these molecules, the assessment of more than one biomarker is necessary (Stephens, Khanolkar, and Bain 2009). Reductions in oxidative stress biomarkers only are possible if their values are over the normal range in the baseline. Since there are no cutoffs to oxidative stress biomarkers, we cannot confirm if the subjects included in the interventions were in the oxidative state in baseline and could benefit from nuts consumption.

Micronutrients content in nuts may change a little depending on the region in which they were grown (Yada, Huang, and Lapsley 2013), but great variability can occur in Se content of Brazil nuts (100-1000 mg/g^{-1} dry weight) (Cardoso et al. 2017), so different compositions in nuts may have contributed to divergent results between the clinical trials. Despite this, only three studies determined the chemical composition of nuts administered in the intervention (Cominetti et al. 2011; Damasceno et al. 2011; Jung et al. 2018). Besides that, different nut types naturally differ in nutrients content, which difficult comparisons between trials with different types of nut. Finally, we could not perform a meta-analysis due to the different units of measurement reported for ox-LDL (the most common biomarker).

Future perspectives

Further investigations should determine the chemical composition of nuts used in each intervention, whereas nutrients content depends on the growing soil (Yada, Huang, and Lapsley 2013; Cardoso et al. 2017). Also, the diet composition of each group should be presented in the papers. In addition, the evaluation of the nuts effect on oxidative stress must use multiple biomarkers because several pathways are involved in antioxidant defenses. In this sense, biomolecular

research can be a useful tool to confirm the pathways modulated by nuts and their compounds.

In healthy subjects, nuts exert a preventive effect against oxidative stress which difficult significative changes in oxidative stress biomarkers in healthy samples. For this reason, cardiometabolic risk samples are more recommended to investigate how nuts are able to modulate oxidative stress. Finally, more studies are necessary to investigate if the high PUFA content in walnuts can contribute to increase oxidative status.

Conclusion

Whilst there were several studies where one or more biomarkers changed it was not consistent, so the chronic consumption of nuts for oxidative stress control remains controversial. Almonds are the nut type more studied with promising effects, while walnuts seems to be less effective because of higher PUFA content that would contribute to LDL oxidation. The Brazil nut effect is clearer due to high selenium content; micronutrient able to modulate GPx activity and gene expression related to Nrf2. Lower dose (5 g/d) of Brazil nuts is sufficient to beneficial effect, while the other nuts need a higher dose (>40 g/d). In addition, MUFA, and bioactive compounds (e.g. polyphenols, and phytosterols) also are responsible for nuts benefits on oxidative stress modulation, however, more studies are needed to confirm and comprehend the mechanisms described.

Disclosure statement

The authors have no conflict of interest to declare.

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