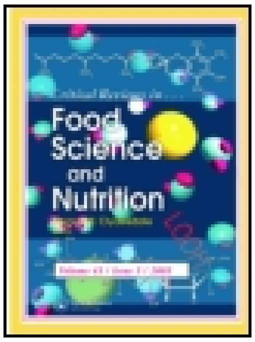

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Functional foods modulating inflammation and metabolism in chronic diseases: a systematic review

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REVIEW

Functional foods modulating inflammation and metabolism in chronic diseases: a systematic review

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ABSTRACT

Chronic diseases are responsible for approximately 71% global deaths. These are characterized by chronic low-grade inflammation and metabolic alterations. “Functional foods” have been attributed with anti-inflammatory properties, demonstrated in cell lines and murine models; however, studies in humans are inconclusive. The purpose of this systematic review is to identify clinical trials that analyzed changes in inflammatory and metabolic mediators, in response to consumption of specific functional foods. A total of 3581 trials were screened and 88 were included for this review. Foods identified to regulate inflammation included cranberries, grapes, pomegranate, strawberries, wheat, whole grain products, low fat dairy products, yogurt, green tea, cardamom, turmeric, soy foods, almonds, chia seeds, flaxseed, pistachios, algae oil, flaxseed oil and grape seed oil. Clinical trials that focus on a dietary pattern rich in functional foods are necessary to explore if the additive effect of these foods lead to more clinically relevant outcomes.

KEYWORDS

Chronic disease; cytokines; functional foods; immune system; inflammation; nutrients

Introduction

Approximately 71% of deaths worldwide are attributed to chronic diseases, such as obesity, type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), chronic respiratory disease and cancer (WHO 2018). The common characteristic of these diseases is chronic low-grade inflammation that leads to metabolic alterations (Franceschi and Campisi 2014). Inflammation is a physiologic response to harm that protects the host from invading organisms and provides healing to reestablish homeostasis. As a result of tissue damage or the presence of foreign organisms, the innate and adaptive arms of the immune system are activated and several inflammatory mediators like chemokines, cytokines, vasoactive amines, eicosanoids, and products of proteolytic cascades are synthesized and secreted (Newton and Dixit 2012). In response to the first inflammatory signals, the innate immune cells produce Tumor Necrosis Factor (TNF)-α, Interleukin (IL)-6 and IL-1β, these induce the liver to produce acute phase proteins, including proteins from the complement system, C Reactive Protein (CRP) and fibrinogen. The adaptive arm of the immune system, upon activation, produce Interferon (IFN)-γ, IL-2, IL-8, IL-12, IL-17, among other cytokines, depending on the type of effector response (Franceschi and Campisi 2014). Adhesion molecules and chemokines are also expressed during inflammatory processes, examples are Intercellular Adhesion Molecule (ICAM)-1, Vascular Cell Adhesion Molecule (VCAM)-1, selectins, Regulated on Activation Normal T Cell Expressed and Secreted (RANTES), Matrix Metalloproteinase (MMP)-9, and Monocyte Chemoattractant Protein (MCP)-1. The inflammatory response, if unregulated, may lead to tissue damage and can eventually be harmful. Thus, the immune system has several regulatory mechanisms to stop and prevent harmful inflammation. Among these, cytokines associated with an anti-inflammatory response are IL-10 and Transforming Growth Factor (TGF)-β, produced by several types of cells, mainly regulatory T cells (Treg); also, adiponectin is an adipokine produced by the adipose tissue and has been associated with an anti-inflammatory response, insulin sensitivity and adipose tissue homeostasis (Masternak and Bartke 2012). The measurement of some of these molecules may reflect the presence of inflammation in clinical trials focused on chronic diseases. For example, serum samples from obese individuals with metabolic syndrome show decreased levels of anti-inflammatory mediators IL-10 and TGF-β, and increased levels of proinflammatory mediators CRP, TNF-α, IL-6, IL-1β, IL-8 and IL-33; most of these are also present in CVD, insulin resistance (IR) and cancer (Monteiro and Azevedo 2010; Coussens and Werb 2002).

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Numerous health benefits have been attributed to a group of foods named "functional foods." Among these benefits, their anti-inflammatory capacity may be the most important. According to The European Commission's Concerted Action on Functional Food Science in Europe (FuFoSE), "a food product can only be considered functional if together with the basic nutritional impact it has beneficial effects on one or more functions of the human organism thus either improving the general and physical conditions and/or decreasing the risk of the evolution of diseases. The amount of intake and form of the functional food should be as it is normally expected for dietary purposes. Therefore, it could not be in the form of pill or capsule just as normal food form" (Diplock et al. 1999). Specific nutrients have been identified to regulate inflammatory pathways, thereby conferring them anti-inflammatory properties; well studied examples are omega-3 fatty acids (Calder 2003; Harbige 2003), polyphenols (Gorzynik-Debicka et al. 2018; Alarcon De La Lastra and Villegas 2005), and fiber (Ma et al. 2006; King, Egan, and Geesey 2003). These nutrients have different molecular mechanisms by which they can regulate the immune response toward a more anti-inflammatory profile; some of these mechanisms include blocking signals, downregulation of pro-inflammatory mediators, or activation of anti-inflammatory pathways (Wu et al. 2018). Fiber may regulate inflammation indirectly through the metabolites derived from its fermentation by the intestinal microbiota, in particular short chain fatty acids, which have been shown to exert potent anti-inflammatory results (Vinolo et al. 2011).

Although clinical investigations have studied the effect of specific nutrients on chronic diseases, most of them recommend pharmaceutical supplements at high doses (instead of using their natural source in foods); the results are focused on clinical, anthropometric or metabolic outcomes, not on the measurement of inflammatory mediators; moreover, the studies that report their anti-inflammatory effect are still inconclusive (Mocellin et al. 2016; Lin et al. 2016; Gioxari et al. 2018; Lopez-Huertas 2012; Rangel-Huerta et al. 2012; Sahebkar et al. 2015; Amiot, Riva, and Vinet 2016; Fernandes et al. 2017; Fedorak and Madsen 2004; Wedlake et al. 2014; Khor et al. 2018).

The main purpose of this systematic review is to identify clinical trials that evaluate the impact of the consumption of functional foods on the regulation of pro- and anti-inflammatory mediators in individuals with chronic inflammatory diseases, compared with a control group. We also noted, where available, the effect of the food on metabolic parameters. A secondary outcome reported in this study is the recommended daily intake of these foods and information concerning the length of intervention time before an anti-inflammatory effect was observed.

Methods

A critical and systematic review of relevant and original studies on human populations was performed, using a specific set of mesh terms, in the PUBMED database (only English language). For the web search all possible combinations with the following words were used:

Patients: chronic disease, obesity, metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, osteoarthritis, arthritis, and cancer.

Intervention: functional food and food.

Outcome: inflammation, interleukins, and cytokines.

After the web search was performed, a new search was made using specific foods (using the same search pattern) to identify all relevant studies. The quality of the trials was evaluated according to the GRADE system to decide which articles would be included in this systematic review (Kavanagh 2009). Trial studies were eligible if they included adult patients with any chronic disease, if the intervention was consumption of a particular food with a regular specified frequency, if it was compared to an appropriate control group (without intervention, using a placebo or any other food not known to possess immune-modulating properties), and if the outcome reported included any molecular marker of inflammation. In case any important data was missing, an e-mail was sent to the corresponding author requesting the information; the author had two months to reply or that article was omitted from this review. Neither length of patient follow-up nor year of publication were considered exclusion criteria. All articles identified as duplicates or trials that used nutritional supplements instead of foods as intervention were omitted from this review.

The summary measures were disease, quantity of functional food indicated, time of patient follow up and levels of inflammatory parameters. Additionally, where available, we included levels of metabolic indicators.

Results and discussion

A total of 3581 articles were identified between May and September of 2019 in the MESH search. From these, 3388 were excluded because they did not report the main outcome of this review. Five articles were identified through other sources. As a result, 198 clinical trials were thoroughly screened for eligibility and 73 were excluded because they did not comply with eligibility criteria or were duplicated (Figure 1). A total of 30 articles were excluded because their interventions consisted on the use of an active compound or a supplement, 14 included healthy population, 11 had a wide risk of bias for their analysis or methodology, 9 did not report inflammatory parameters, 7 did not have a control group or it was inadequate for our objective, authors from 3 articles did not reply when we requested additional information and were therefore excluded. Finally, 88 articles were included in this review. The articles were published between the years 1981 and 2018.

The main chronic diseases reported were overweight/obesity, T2DM, metabolic syndrome (MetS), renal disease (RD), and CVD. The results were organized according to food groups. Supplementary Table 1 contains a summary of the articles, including author, year of publication, study type, the details of the interventions and inflammatory and metabolic parameters measured.

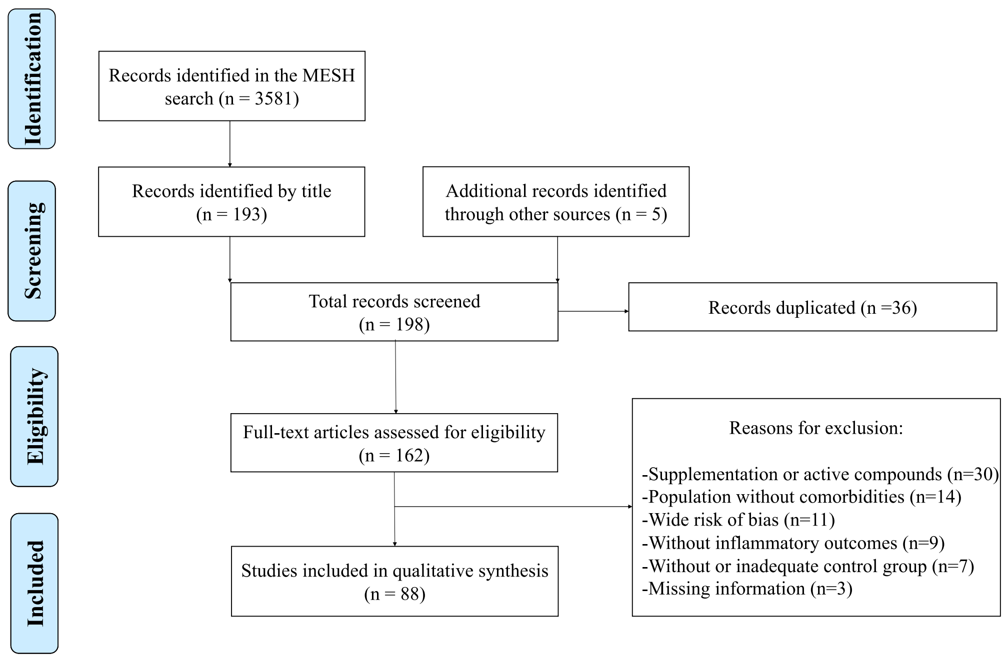

Figure 1. Flowchart of selection and inclusion of clinical trials. For the literature search we used a specific set of mesh terms in the PUBMED data base. A total of 3581 trials were screened and after selection, 88 were included in this review.

Fruits and vegetables

It has been commonly known that a high consumption of fruits and vegetables protect against chronic diseases because of their nutrients and bioactive components (vitamins, minerals, fiber, and phytochemicals), these components could also be involved in the modulation of inflammation (Prasad, Sung, and Aggarwal 2012).

Cranberries

Cranberry is a fruit characterized for its high content of antioxidants, vitamin C, citric, quinic and malic acids, and other phytochemicals. Some benefits have been attributed to cranberries mainly in the urinary tract and cardiovascular system (Cunningham et al. 2004). Polyphenolics and A-type proanthocyanidins are some of the phytochemicals associated with the reduction of urinary tract infections (RR = 0.74, 95% CI: 0.55–0.98), probably because of their interference with the adhesion of bacteria to epithelial cells (Fu et al. 2017). Additionally, the presence of cranberries-derived metabolites correlated with endothelial vasodilation, therefore they could exert a positive effect in cardiovascular function (Rodriguez-Mateos et al. 2016).

In MetS, the consumption of cranberry juice had no effect in inflammatory or metabolic parameters compared to placebo (Simão et al. 2013). However, in the cranberry group, lipid peroxidation markers malondialdehyde and 4-hydroxynonenal (MDA & HNE) were lower at the end of the interventions compared with the placebo group (1.7 ± 0.7 vs 3.2 ± 0.8 μM, $p < 0.05$) (Basu, Betts et al. 2011). Schell et al. randomized 25 adults with T2DM and visceral adiposity to consume a breakfast high in fats and dried cranberries or breakfast high in fats and ripe banana (Schell, Betts et al. 2017). Inflammatory and metabolic postprandial parameters were measured. After 2 h glucose decreased in the cranberry group compared to control group (161 ± 8.7 vs 191 ± 7.7 mg/dl, $p < 0.05$). After 4 h, IL-18 (308.2 ± 11.2 vs 341.7 ± 12.7 mg/dl, $p < 0.05$) and glucose (152 ± 8.5 vs 176 ± 5.9 mg/dl, $p < 0.05$) decreased compared to control. Furthermore, the cranberry group had lower levels of MDA & HNE after 4 h compared to the placebo group (1.6 ± 0.8 vs 3.3 ± 1.1 μM, $p < 0.05$).

In summary, dried cranberries and not cranberry juice were shown to reduce IL-18 in patients with T2DM. A positive effect in glucose metabolism was observed in patients with MetS. Importantly, reduction of lipid perdoxidation was demonstrated in both, T2DM and MetS patients.

Grapes

Grape is a phenol-rich fruit that contains resveratrol. This potent antioxidant component is in the skin and seeds of red, purple and black grapes, and it has been associated with several health benefits attributed to the Mediterranean diet (Xia et al. 2010).

Bardagjy, et al. analyzed the effect of the consumption of freeze-dried whole grape powder in 20 obese adults and found a significant increase in sVCAM-1 (Bardagjy et al. 2018). In a similar intervention in individuals with MetS without dyslipidemia, the freeze-dried whole grape powder increased levels of IL-10 and adiponectin (Barona et al. 2012). When analyzing individuals with MetS and dyslipidemia no benefits were observed. In similar studies, no effect was reported with the consumption of grape products on inflammatory or metabolic parameters, in patients with chronic kidney disease (CKD) on hemodialysis, and in obese individuals (Janiques et al. 2014; Zunino et al. 2014). A grape extract containing resveratrol (GECR) was compared

Table 1. Summary of the inflammation modulating effect of foods in chronic diseases.

Food Group	Food	Overweight/obesity	T2DM	MetS	GID	KD	OA	Cancer	CVD	NAFLD	References
Fruits and vegetables	Carrot	😐									161
	Cranberry		🙂	😐😐							13, 129, 136
	Grape	☹😐	😐	🙂		😐					9, 11, 60, 145, 170
	Grapefruit	😐									29
	Pomegranate		🙂🙂	😐		🙂			😐😐		6, 97, 120, 133, 138, 139
	Strawberry	😐😐😐	😐	☹			🙂🙂				12, 15, 16, 32, 96, 130, 169
Whole grain products	Wheat								🙂		158
	Whole grain products	🙂🙂🙂😐😐		😐							18, 76, 80, 123, 150, 152
	Sorghum	😐									141
Animal source food	Low-fat dairy products			🙂							31
	Yogurt	🙂😐	🙂🙂								59, 105, 149, 166
	Sardines		😐								8
Tea and spices	Black tea								😐		160
	Green tea	😐	😐	😐					🙂		14, 17, 43, 110
	Cardamom	🙂									66
	Nigella Sativa				😐						108
	Red pepper	😐									107
	Turmeric	😐			🙂	🙂😐					67, 74, 107, 127
Legumes	Soy foods			🙂🙂		🙂😐😐😐			☹	🙂	1, 7, 35, 63, 95, 101, 135, 144
	Spanish beans	😐									54
	Yellow pea	😐									81
Nuts and seeds	Almonds		🙂🙂😐						😐		25, 48, 62, 86
	Chia seeds	😐	🙂						😐		106, 146, 153
	Flaxseed	😐	😐			🙂					57, 68, 121
	Hazelnut	😐									142
	Nut Mixes			🙂😐							21, 82
	Pistachios		😐😐	🙂							49, 116, 128

Oils						
Algae	🙂					103
Canola	😐					10
Fish	😐😐	😐	😐		🙂😐😐	26, 44, 99, 117, 133, 135, 147
Flaxseed		🙂🙂		🙂		53, 83, 115
Grape seed	🙂					58
Nigella sativa	☹					90
Rapeseed	🙂					79

T2DM: Type 2 Diabetes Mellitus; **MetS:** Metabolic Syndrome; **GID:** Gastrointestinal Disease; **KD:** Kidney Disease; **OA:** Osteoarthristis; **NAFLD:** Nonalcoholic Fatty Liver Disease. The number of emoji faces represent the number of articles that provided the evidence of the effect: 🙂 Anti-inflammatory effect; 😐 no demonstrated effect; ☹ proinflammatory effect.

with a grape extract lacking resveratrol (GELR) and placebo in individuals with T2DM, hypertension (HT) and coronary artery disease (CAD) (Tomé-Carneiro et al. 2013). Although at the end of interventions no differences were observed in inflammatory parameters, before starting treatment the GECR group had the highest levels of IL-6, which were significantly reduced overtime.

In summary, grape consumption seems to increase the anti-inflammatory mediators IL-10 and adiponectin in MetS, this could promote tolerogenic mechanisms.

Pomegranate

Pomegranate contains several antioxidants, phenolic compounds (flavonoids, anthocyanins, ellagitannins, flavones, flavonol-3-ols, anthocyanidins, anthocyanins), hydroxycinnamic acids, hydroxybenzoic acids, conjugated and non-conjugated fatty acids, phytosterols, vitamins and minerals, all of which could be involved in the modulation of inflammation (Akhtar, Ismail, and Layla 2019). Their mechanism has been associated with cyclooxygenase-2 (COX-2) inhibition and the consequent reduction in inducible Nitric Oxide (iNO), prostaglandin E-2 (PGE-2), inflammatory cytokines, and reactive oxygen species (ROS) (Akhtar, Ismail, and Layla 2019).

The effect of pomegranate was investigated in HT volunteers randomized to drink pomegranate juice or water (Asgary et al. 2014). Two weeks after intervention, volunteers that consumed pomegranate juice presented a significant reduction in high sensitivity C Reactive Protein (hs-CRP), ICAM-1 and VCAM-1. When compared to placebo, the pomegranate juice group had higher levels of E-Selectin and lower levels of ICAM. Additionally, a decrease was observed in systolic and diastolic blood pressure. In MetS, the consumption of pomegranate juice had no effect on hs-CRP, but surprisingly, higher levels of very low density lipoprotein cholesterol (VLDL-C) and triglycerides (TG) were observed (Moazzen and Alizadeh 2017). Sohrab, et al. analyzed the effect of drinking pomegranate juice for 12 weeks in subjects with T2DM (Sohrab et al. 2014). After the intervention, hs-CRP and IL-6 were lower in the intervention group compared to the control group. A subsequent analysis reported that those who drank pomegranate juice had lower levels of soluble E-selectin (sE-selectin) (Sohrab et al. 2018). In a study by Razani et al., hospitalized patients with ischemic heart disease (IHD) were randomized to drink pomegranate juice or water for 5 days (Razani, Dastani, and Kazerani 2017). No differences were found in inflammatory or metabolic parameters, but a positive effect was observed in levels of MDA and troponin in patients that consumed pomegranate juice compared to control, these results suggest less damage to the heart. In another clinical trial, patients with chronic hemodialysis were randomized to drink pomegranate juice or placebo for 1 year (Shema-Didi et al. 2012). At the end of the intervention, TNF-α and IL-6 were lower in the intervention compared to the control group. Moreover, lower levels of oxidative stress indicators, fewer hospitalizations due to infections, and fewer cases of worsening carotid artery thickness were observed in the intervention group compared to control; however, after three months of discontinuation, the benefits were lost.

Overall, consumption of pomegranate juice seems to reduce inflammation in individuals with T2DM and RD; moreover, some benefits in metabolic and clinical outcomes were observed in HT and IHD. However, adverse metabolic results were reported in individuals with MetS, possibly caused by the sugar and fructose content in juice.

Strawberry

Strawberry is a fruit rich in flavonoids (anthocyanins and catechins), flavonols (quercetin and kaempferol), phenolic and ellagic acids, glutathione, and ascorbic acid. Due to its high content of antioxidants, it could regulate inflammation in chronic diseases (Hannum 2004).

In a study that included 27 subjects with MetS, individuals were randomized to consume a strawberry beverage and water or just water (Basu et al. 2010). After 8 weeks of intervention, there was a reduction of VCAM-1, total cholesterol (TC) and LDL cholesterol (LDL-C) in the intervention compared with control group. In a subsequent study (Basu et al. 2014), 60 volunteers with abdominal adiposity and elevated serum lipids were randomly assigned to drink a low dose freeze-dried strawberry beverage (equivalent to 250 g/day of fresh strawberries), high dose freeze-dried strawberry beverage (equivalent to 500 g/day of fresh strawberries), placebo low dose beverage or placebo high dose beverage. After 12 weeks, inflammatory parameters were not affected with either intervention, but a benefit was described in the reduction of TC, LDL-C and MDA levels in the group that consumed the high dose strawberry beverage compared to the other groups. The same freeze-dried strawberry beverage (equivalent to 500 g/day of fresh strawberries), or placebo, was randomly indicated to 17 obese adults with knee osteoarthritis for 12 weeks (Basu et al. 2018). Authors reported that high sensitivity TNF-α (hsTNF-α) and soluble TNF-Receptor2 (sTNF-R2) decreased in the strawberry group compared to control group. The effect of strawberry beverages were also studied in overweight/obese adults (Ellis et al. 2011) and women with T2DM (Moazen et al. 2013). After 6 weeks, no significant differences were found in inflammatory and metabolic parameters between groups, in either study. Another study randomized 17 obese adults with knee osteoarthritis to drink a strawberry beverage or placebo (Schell, Scofield et al. 2017). After 12 weeks of intervention, a significant reduction of IL-6, IL-1β and MMP-3 was observed in individuals that consumed the strawberry beverage compared with control. Interestingly, in the intervention group, a reduction of constant pain, intermittent pain and total pain was described, measured by the intermittent and constant osteoarthritis pain questionnaire (ICOAP). A different study included 20 obese adults randomized to consume a frozen strawberry powder spread over several foods and drinks or placebo (Zunino et al. 2012). Diet was individualized and controlled for all participants. Even so, after 3 weeks of intervention, no differences were observed in inflammatory parameters, but TC was lower in the group that consumed strawberry powder compared with placebo.

In summary, a positive benefit in reducing inflammation was observed with the consumption of strawberry beverages specifically in MetS and obese adults with osteoarthritis. Additionally, strawberries contributed to reduction of TC, LDL-C and displayed antioxidant effects in overweight/obese individuals. Clinically, consumption of strawberries helped reduce pain in patients with osteoarthritis.

Other fruits and vegetables

Several plant foods have been found to contain high amounts of diverse antioxidant compounds, vitamins and minerals (Prasad, Sung, and Aggarwal 2012); however, few have been investigated for their possible anti-inflammatory effects on humans. The effects of purple carrot and grapefruit are described.

A study included 16 overweight/obese men, randomized to consume dried purple carrot or dried orange carrot (Wright, Netzel, and Sakzewski 2013). It is important to note that purple carrots have 4.6 times more phenolic compounds and 2 times more α-carotene than orange carrots (Alasalvar et al. 2001); even so, no differences were observed in CRP or metabolic parameters.

Another study analyzed overweight/obese adults that consumed fresh Rio red grapefruit compared to control (Dow et al. 2013). Both groups were advised to consume a standard diet restricted in vegetables and fruits with high content of polyphenols and carotenoids. Inflammatory parameters were not affected by the intake of grapefruit. However, it is important to note that 10 individuals that had baseline hs-CRP $\geq$3.0 mg/L showed decreased levels of this molecule after intervention (4.1 ± 0.7 to 3.3 ± 1.2 mg/L, $p = 0.08$). This suggests that individuals with high baseline levels of hs-CRP could benefit from regular grapefruit consumption.

More high-quality studies are necessary to evaluate the effects of fruits and vegetables on inflammation and metabolism.

Whole grain products

In comparison with fruits and vegetables, whole grains have more insoluble fiber, bound phenolic compounds, vitamin E, and phytosterols (Neacsu et al. 2013; Zhang and Hamaker 2010; Fardet 2010). Fiber from whole grain products has been attributed with multiple health benefits, including better digestion and establishment of a well-balanced microbiota that promotes a healthy gut barrier, prevents establishment of pathogens and provides immune-modulating nutrients (Zeng, Lazarova, and Bordonaro 2014).

Most of the trials analyzed the effect of the consumption of whole wheat products, compared to refined wheat products as a control, on serum cytokines and some metabolic parameters, on overweight and obese adults (Brownlee et al. 2010; Kopf et al. 2018; Lambert-Porcheron et al. 2017; Roager et al. 2019; Vitaglione et al. 2015). Even though, no differences were observed in inflammatory or metabolic parameters between groups, some studies reported lower levels of lipopolysaccharide binding protein (LBP) (Kopf et al. 2018) and TNF-α (Vitaglione et al. 2015) in the groups that consumed whole wheat products. The consumption of a biscuit high in slowly digestible starch, compared to a rusk biscuit low in slowly digestible starch, resulted in lower fasting blood glucose (FBG) levels (Lambert-Porcheron et al. 2017). Interestingly, when whole grain products were consumed *ad libitum*, compared to refined products consumed *ad libitum*, levels of CRP, IL-6 and IL-1β were reduced (Roager et al. 2019); additionally, a positive outcome was observed in reduced body weight and sagittal abdominal diameter, and increased fat free-mass in the group that consumed whole grains *ad libitum*. Another study compared a group that consumed sorghum products with a group that consumed wheat products; both groups followed a hypocaloric diet (Stefoska-Needham et al. 2017). At the end of the interventions no differences were observed.

Whittaker et al. included 22 adults with acute coronary syndrome (ACS) to consume organic khorasan wheat products or organic semi whole wheat products as a control group for 8 weeks (Whittaker et al. 2015). A washout period of 8 weeks was implemented between interventions. Several differences were observed, levels of TNF-α, fasting blood glucose (FBG), total cholesterol (TC), LDL-C and insulin decreased in the group consuming organic khorasan wheat products compared with control; additionally, oxidative markers (L-derived ROS, M-derived ROS, L-lipoperox and M-lipoperox) were also reduced significantly in the intervention group. In overweight/obese individuals with MetS, a diet based on whole grain cereal products did not result in differences in inflammatory or metabolic parameters, when compared to a diet based on refined cereal products (Vetrani et al. 2016). On the other hand, an increase in serum propionate production was observed in the individuals that consumed the whole grain diet, which probably resulted from fiber fermentation by the microbiota in the colon. The increase in propionate could lead to a reduction in postprandial insulin concentrations.

In summary, the consumption of whole grains can regulate inflammation and some metabolic parameters in overweight/obesity and ACS; moreover, it promotes propionate production, particularly when whole grain products are consumed *ad libitum*, as part of a whole grain rich diet.

Animal source food

Yogurt

Yogurt is a fermented dairy product that constitutes a natural source of probiotics that can survive their passage through the stomach and intestine. Yogurt is also an adequate source of protein and calcium, among other nutrients. Jaffari et al. evaluated the effect of low fat yogurt enriched with vitamin D versus low fat yogurt, in postmenopausal women with T2DM (Jafari et al. 2016). After 12 weeks of intervention, hs-CRP, FBG, insulin and HOMA-IR (homeostatic model assessment of insulin resistance) were reduced in the individuals that consumed vitamin D enriched yogurt, whereas omentin levels were increased. The increase in omentin has an important clinical significance because it is an anti-inflammatory adipokine associated with insulin sensitivity, glucose metabolism and cardiovascular protection (Watanabe et al. 2011). There were other important differences like lower BMI, waist circumference and percentage of fat mass in women that consumed vitamin D enriched yogurt.

Meijil et al. randomized 35 overweight and obese adults to consume low-fat dairy products or fruit-derived products rich in carbohydrates during 8 weeks (van Meijl and Mensink 2010). At the end of the interventions, sTNFR-2 was higher in the group that consumed low-fat dairy products compared with the group that consumed fruit-derived products. One of the biological mechanisms that can restrict the potentially harmful effects of TNF-α is the inducible proteolytic cleavage of cell surface TNF receptors. This results in the downregulation of the membrane receptors and the formation of soluble forms of the receptor which, by competing for TNF, can block its function (Sedger and McDermott 2014). Studies have indicated that cleavage of the TNF receptors occurs constantly and is enhanced in inflammatory conditions. Thus, production of TNF in chronic diseases is therefore likely to result in increased serum concentrations of sTNFR that have an antagonist function. It has been correlated with BMI ($r = 0.50$), fat-free mass ($r = 0.61$), and waist-to-hip ratio ($r = 0.39$) (Fernández-Real et al. 1998).

In another clinical trial conducted by Neyestani, et al., 90 adults with T2DM were randomized to drink a Persian yogurt drink fortified with different concentrations of calcium and vitamin D (CDD: 500 mg calcium and 1000 IU vitamin D3; DD: 300 mg calcium and 1000 IU vitamin D3; PD: 300 mg calcium and no detectable vitamin D3) (Neyestani et al. 2012). This study reported that 73.3% of patients had vitamin D deficiency at baseline, so it is not unexpected that supplementation with vitamin D resulted in lower fibrinogen levels compared with the group that did not receive vitamin D. In epidemiological studies vitamin D deficiency has been associated with elevated levels of fibrinogen (Mellenthin et al. 2014) and cardiovascular complications (Kannel et al. 1987), since fibrinogen is an important component of the main mechanisms of cardiovascular disease (inflammation, thrombogenesis and atherogenesis) (Libby 2006). Moreover, in the last years, vitamin D supplementation has been associated with increased insulin sensitivity, mostly in individuals with vitamin D deficiency, but results are still controversial (Krul-Poel et al. 2017). In this study, HOMA-IR was lower in the groups that consumed vitamin D fortified yogurt than in those without vitamin D. It is important to mention that even though patients were consuming the yogurt fortified with vitamin D, they did not reach normal serum concentrations (Neyestani et al. 2012).

A study by Zarrati, et al. included 75 overweight/obese adults. Participants were randomized to drink a yogurt supplemented with probiotics in addition to a low calorie diet (PLCD), a yogurt supplemented with probiotics without a low calorie diet (PWLCD) or a standard yogurt and low calorie diet (SLCD) (Zarrati et al. 2014). The probiotic yogurt was prepared with the starter cultures *Streptococcus thermophilus* and *Lactobacillus bulgaricus,* and was enriched with probiotic cultures based on lactobacilli and bifidobacteria (*Lactobacillus acidophilus* LA5, *Lactobacillus casei* DN001, *Bifidobacterium lactis* BB12). The concentration of each probiotic strain was 1×10^7 colony-forming units/mL. Standard yogurt was prepared with the same starter cultures *S. thermophilus* and *L. bulgaricus*. According to basal and final measurements, the three groups showed significant reductions in hs-CRP, IL-17 and TNF-α. Comparison between groups showed changes in these molecules were different; however, the addition of a low-calorie diet to the probiotic yogurt seems to enhance the benefits. The importance of probiotics in chronic inflammatory conditions is related to the establishment of a healthy gut microbiota, which contributes to the integrity of the intestinal mucosal barrier function. Gut microbiota also favors the production of metabolites, such as short chain fatty acids, through prebiotic fermentation. These metabolites possess epigenetic mediated metabolic- and immune-modulating mechanisms. For example, probiotics have been shown to restore and prevent relapse in inflammatory bowel disease (Derwa et al. 2017; Kim, Keogh, and Clifton 2018).

Overall, the most evident benefits for the regulation of inflammatory parameters in overweight, obesity and T2DM, were demonstrated in yogurt fortified with vitamin D and yogurt enriched with diverse strains of probiotics. In individuals with overweight and obesity the consumption of yogurt in addition to a low-calorie diet is effective in modulating inflammation.

Other animal source food

Sardines are affordable fish rich in omega-3 fatty acids, eicosapentaenoic, docosahexaenoic and alpha-linolenic acids (EPA, DHA and ALA). These provide a beneficial effect preventing heart diseases by lowering lipoprotein levels, they are also associated with other positive health outcomes related to their anti-inflammatory properties. Moreover, fish is an excellent source of protein and contains no carbohydrates, these characteristics contribute to glucose control in patients with T2DM (Evert et al. 2014).

In a pilot trial that included 35 adults with T2DM, patients were randomized to a standard diet enriched with sardines or a standard diet (Balfegó et al. 2016). No differences were found among groups; however, after 6 months of intervention, the sardine group had a significant reduction in HOMA-IR and an increase in total adiponectin. These results suggest that frequent consumption of sardines may contribute to insulin sensitivity and, because of the increased levels of adiponectin, to reduced inflammation. The control group had a significant reduction of HOMA-IR that could be associated with the dietary intervention, but showed an increase in TNF-α, which suggests an exacerbation of inflammation.

In another study, 24 women with MetS were randomized to consume low-fat dairy products (milk, yogurt and cheese) or carbohydrate rich products (granola bars and juice) (Dugan et al. 2016). After 6 weeks of intervention, the dairy products group had lower levels of TNF-α and MCP-1 compared with control group.

To summarize, dairy products could help regulate inflammation in individuals with MetS. More studies are necessary to evaluate the effect of other animal source foods rich in omega-3 fatty acids, probiotics, or other anti-inflammatory components.

Tea and spices

Through history, cultures around the world have added spices and herbs to food preparations, not only to add flavor and color, but also for medicinal purposes (Low 2006). Some molecular components in tea and spices are antioxidants and have been identified to possess anti-inflammatory properties through different mechanisms (Howitz and Sinclair 2008). The following section describes teas, spices, and condiments studied for their anti-inflammatory properties.

Green tea

For years green tea has been consumed for its health benefits, which have been recently related to its antimicrobial and antioxidant properties. These benefits are linked to its high content of catechins, which include epicatechin, epicatechin-3-gallate, epigallocatechin, and, the most abundant, epigallocatechin-3-gallate (EGCG) (Nikoo, Regenstein, and Gavlighi 2018). EGCG is the most biologically active component of green tea, in animal models it has been shown to be effective in modulating multiple aspects of innate and adaptive immunity; particularly, the anti-inflammatory and T cell-suppressing effects of green tea appear to have a potential clinical application (Wu et al. 2018).

In a study by Basu, et al., 35 adults with MetS were randomized to consume, for 8 weeks, 4 cups of green tea, 2 capsules of green tea extract, or water (Basu, Du et al. 2011). No differences were found between groups. Nevertheless, groups that consumed green tea showed reduced levels of plasma serum amyloid alpha (SAA) compared with control. SAA is a group of proteins related to the acute phase response and functions as a cytokine-like protein, so it has become recognized in inflammatory pathways (Sack 2018). Because of its lipophilicity, SAA is related to lipid transport and metabolism, as well as atherosclerosis, and could be involved in reduced levels of adiponectin; moreover, it is correlated with BMI ($r = 0.8$) (Yang et al. 2006).

Bogdanski et al. randomized 56 obese adults with HT to consume green tea extract or placebo (Bogdanski et al. 2012). After 3 months of intervention, a higher reduction in CRP, TNF-α, TC, LDL-C, TG, HOMA-IR and insulin, and an increase in high density lipoprotein-cholesterol (HDL-C) were observed in the green tea group compared with the placebo group. Additionally, a positive change in systolic and diastolic blood pressure was observed in the green tea group compared to control. No differences were observed in hs-CRP or metabolic parameters, in adults with prediabetes or T2DM that consumed less than 1 bag of green tea a day for 2 months, compared to control (Fukino et al. 2005).

Obese women with pre-hypertension that consumed green tea extract showed no differences in inflammatory or metabolic parameters, but a positive change in systolic blood pressure was observed, when compared to control (Nogueira et al. 2017).

Overall, consumption of green tea for at least 3 months reduces inflammation and improves metabolism in obesity and HT. Additionally, it could help regulate blood pressure.

Turmeric

A spice commonly used in Indian cuisine is turmeric, which has been widely studied in the recent decade. Its active ingredient, curcumin, constitutes approximately 2–5% of turmeric powder (Chainani-Wu 2003). This compound regulates some pathways involved in the inflammatory response (AhR, IL-1β, PKD and COX), energy metabolism (mTOR), and cellular stress response (AKT) (Howitz and Sinclair 2008). Curcumin has been studied in multiple clinical trials, but few studies have used turmeric root. For this review, 16 articles were excluded because they used the active compound curcumin instead of turmeric.

The bactericidal effect of turmeric was analyzed in 36 adults infected with H. pylori, individuals were randomized to take turmeric tablets or drug treatment for 4 weeks (Koosirirat et al. 2010). A gastric biopsy was obtained from individuals and mRNA expression of *Il1b*, *Tnfa* and *Il18* was measured. No differences were found among groups. The percentage of individuals that cleared the infection was lower in the group that received turmeric than in the group that received drug treatment (5.9 vs 78.9, $p < 0.0001$).

Adults with diabetic nephropathy (DN) were randomized to consume turmeric or placebo for 2 months (Khajehdehi et al. 2011). At the end of intervention, the turmeric group had lower levels of urinary IL-8, serum TGF-β, and proteinuria, compared with the placebo group. The decrease in proteinuria is an important finding that may prove the clinical relevance of turmeric in patients that suffer from DN. In a similar study, 71 adults with chronic hemodialysis were randomized to take turmeric or placebo for 12 weeks (Samadian et al. 2017). Although no differences were observed between groups, the turmeric group had a significant reduction in IL-6. It is important to note that before the intervention, albumin levels were lower in the turmeric group and at the end of the intervention there were not differences between groups, so the recovery in albumin levels was statistically and clinically significant.

In summary, turmeric is a spice with multiple benefits and a powerful antioxidant, and should be recommended to reduce inflammation; importantly, in individuals with nephropathy or in hemodialysis, turmeric may help reduce proteinuria.

Other spices and condiments

Among other spices, cardamom is common in Indian and middle-eastern cuisine, it has been attributed with properties such as antioxidant, diuretic, anti-cancer and anti-inflammatory (Majdalawieh and Carr 2010; Gilani et al. 2008). In a clinical trial, 80 overweight/obese women with IR were randomized to take cardamom or placebo capsules (Kazemi et al. 2017). Hs-CRP decreased in the cardamom group after intervention, compared with control.

Red pepper is rich in vitamin C, vitamin E, carotenoids and, importantly, capsaicin (Palevitch and Craker 1996). Studies on capsaicin have shown positive effects decreasing TC and TG levels, it has anti-lithogenic properties, protects the integrity of red blood cells, and has antioxidant and anti-inflammatory effects (Srinivasan 2016). The effect of red pepper was compared with turmeric or placebo, added to food preparations, in women with overweight or obesity (Nieman et al. 2012). After 4 weeks of intervention, no differences were found in inflammation or metabolism.

Nigella sativa (also known as black seed) contains an array of nutrients, including unsaturated fatty acids, cardiac glycosides, saponins, flavonoids, vitamin C, calcium, iron and phosphorus (Kooti et al. 2016). In a clinical trial, 48 adults with mild or moderate ulcerative colitis (UC) were randomized to consume *Nigella sativa* powder or placebo for 6 weeks (Nikkhah-Bodaghi et al. 2019). Surprisingly, the individuals from the intervention group had increased levels of hs-CRP and TNF-α, compared with the placebo group. This report could suggest that *Nigella sativa* has immune stimulating and pro-inflammatory effects, which could be helpful as an adjuvant in the treatment of infectious diseases but should be indicated with caution.

Black tea is a staple and one of the most frequently consumed beverages worldwide; drinking tea has been considered a health promoting habit since ancient times. *Camellia sinensis*, from which tea is produced, is a plant rich in polyphenols, amino acids, volatile compounds, and alkaloids, that have been demonstrated in vitro to block signaling pathways that lead to the activation of transcription factors that promote the expression of pro-inflammatory genes. Theaflavins, which are the main polyphenolic compounds of black tea are responsible for most of the physiological effects of black tea in prevention of cardiovascular diseases, particularly atherosclerosis and coronary heart disease (Singh et al. 2017; Khan and Mukhtar 2013). A study included 66 adults with CAD, individuals were randomized to a group that consumed black tea or to a control group (Widlansky et al. 2005). After 4 weeks of intervention, no differences were found in CRP or metabolic markers between groups.

All in all, tea and multiple spices are commonly used as part of culinary traditions and for their medicinal properties; however, existing studies describing their impact on inflammation are controversial. More clinical trials, considering different doses or presentations of the wide variety of tea and spices, are necessary to provide scientific evidence of their anti-inflammatory effect. Nevertheless, their continued use as part of food preparation and tradition is recommended.

Legumes

Since ancient times, legumes have been the main source of protein in many cultures of the world and continue to be so mainly because of their accessibility. Its health benefits have been attributed to the high amounts of fiber and minerals they provide (Tharanathan and Mahadevamma 2003).

Soy

Soy is a legume that contains an important source of aminoacids and polyphenols (Friedman and Brandon 2001). The most abundant polyphenols in soy are isoflavones. These have been attributed benefits for women undergoing menopause and for cardiovascular system health (Han et al. 2002).

Acharjee, et al. analyzed the effect of the addition of half a cup of soy nuts to the standard diet of 11 postmenopausal women with MetS, and compared them with a control group that consumed a standard diet (Acharjee et al. 2015). After 8 weeks of intervention CRP, sICAM-1, and TG, decreased in the intervention group compared with control. Additionally, diastolic blood pressure decreased in women that consumed soy nuts. In the same study, a subanalysis indicated that in women without MetS, neither systolic and diastolic pressure, nor CRP decreased with the consumption of soy. In a crossover trial that included 42 postmenopausal women with MetS, participants were randomized to eat roasted soy nut (instead of red meat), soy nut protein (instead of red meat) or no soy nut (one serving of red meat/day), during 8 weeks (Azadbakht et al. 2007). The three groups were instructed to follow a diet based on the "Dietary Approaches to Stop Hypertension" (DASH) recommendations. After the interventions, differences among groups included CRP, TNF-α and E-selectin; the group that consumed roasted soy nut had the highest improvements in inflammatory parameters, which suggests an added benefit for consuming the whole food. Authors analyzed the patients' food diary and reported that the control group that consumed red meat also consumed more total fat and less polyunsaturated fatty acids and fiber.

No effect was observed in adults with end-stage renal disease (ESRD) on chronic hemodialysis that consumed soy products, compared to control (Fanti et al. 2006). Fortyfive adults with nonalcoholic fatty liver disease (NAFLD) were included in a study by Kani et al.; individuals were randomized to a low-calorie and low-carbohydrate diet containing soy, a low-calorie and low-carbohydrate diet, or a low-calorie diet (Kani et al. 2017). After 8 weeks, the first group had lower levels of hs-CRP than the other groups. Another study analyzed the effect of soymilk in 25 adults with DN (Miraghajani et al. 2012). Patients were randomized to drink 240 mL/day of soymilk or cow milk, but no differences were detected among groups. In a crossover trial, Nasca et al. evaluated the effect of soy consumption in 12 postmenopausal women with HT (Nasca, Zhou, and Welty 2008). Women were randomized to consume soybeans (replacing 25 g of non-soy protein) and were indicated to follow the "Therapeutic Lifestyle Change" recommendations (TLC), or to follow the TLC recommendations (control group). The soy group consumed more energy, less total fat and saturated fat compared with control. In a previous study in the same cohort of patients, no differences were found in physical activity (Welty et al. 2007). At the end of the interventions, sVCAM-1, LDL-C and Apo B decreased in the soy diet group compared with the control group. The effect of the consumption of kinako (soy product) was evaluated in 30 women with MetS, but no differences were observed when compared with the control group (Simão et al. 2012). In a clinical trial with 38 adults in hemodialysis, individuals were randomized to consume whey soy protein, soy protein, or placebo (Tomayko et al. 2015). After 6 months of intervention, IL-6 was lower in both soy groups, compared with placebo group.

In summary, postmenopausal women with MetS and subjects with NAFLD may benefit from soy consumption to regulate some inflammatory parameters. Moreover, soy consumption could help reduce TC and TG levels, and may be beneficial in HT control.

Other legumes

A randomized controlled trial included 30 overweight/obese adults (Hermsdorff et al. 2011). The intervention group consumed a diet based on legumes (lentils, chickpeas, peas, or beans, but no soybean legumes), and the control group consumed a diet restricted in legumes. Both groups had a 30% restriction of total energy requirement and the interventions lasted 8 weeks. At the end of interventions, no differences were observed between groups.

Lambert et al. included 44 overweight or obese adults and randomized them to consume yellow pea fiber distributed in three biscuits or placebo (three biscuits without yellow pea fiber) for 12 weeks (Lambert et al. 2017). To avoid gastrointestinal symptoms, fiber was gradually increased, 5 g at a time. Leptin was lower in the pea fiber group after intervention. Additionally, FBG, insulin, gastric inhibitory peptide, glucagon-like peptide 1, ghrelin, amylin and peptide YY, were measured during the oral glucose tolerance test and, compared with placebo, the results suggest that intake of yellow pea fiber could regulate postprandial glucose metabolism.

Overall, the beneficial effects demonstrated from the consumption of legumes could be explained by their high fiber content and the fact that, in these clinical trials, animal protein was replaced by legume protein. Saturated fatty acid consumption was consequently reduced in the diet of the participants. Also, fiber contributed to better glucose metabolism and may have aided in better digestion. Soy consumption could regulate inflammation in postmenopausal women with MetS, HT, in individuals with NAFLD and in maintenance hemodialysis.

Nuts and seeds

Several epidemiological studies have focused on nuts and seeds because of their association with prevention of CVD and T2DM. Their protective effect is related to their content of unsaturated fatty acids, fiber, and antioxidants such as vitamin E, all of which have anti-inflammatory properties. They are also a good source of protein (Jiang et al. 2006).

Almonds

Almonds are a type of nut rich in fatty acids (35 to 67 g/100 g of almonds), protein (14 to 61 g/100 g of almonds) and fiber (2.5 to 14 g/100 g of almonds); its nutrient content depends on the region it was cultivated. It is important to note that the fatty acids contained in almonds are mainly mono and polyunsaturated; moreover, almonds are rich in vitamins E, biotin, folate, niacin, pantothenic acid, pyridoxin, riboflavin and thiamin (Yada, Lapsley, and Huang 2011).

In a randomized crossover trial, 45 adults with CAD were studied (Chen et al. 2015). The intervention consisted in consuming almonds and following the National Cholesterol Education Program (NCEP) Step I recommendations, for 22 weeks; the control group followed the NCEP Step I recommendations. No differences were found among groups.

In another clinical trial, 20 adults with T2DM were randomized to consume 20% of total energy intake from almonds, or to a control group (Gulati, Misra, and Pandey 2017). After 24 weeks of intervention, the reduction in hs-CRP was higher in intervention than in control group. Also, FBG, TC and LDL-C were significantly reduced in the group that consumed almonds compared with control. Importantly, levels of adiponectin increased in the intervention group. In a similar article, 20 adults with T2DM were randomized to consume 20% of total energy intake from almonds and follow the NCEP Step II recommendations, or to follow the NCEP Step II recommendations (Liu et al. 2013). Both interventions lasted 4 weeks. After the intervention, the almond group showed a decrease in CRP and IL-6, compared with control. In a study that included 84 adults with T2DM, individuals were randomized to consume almonds or isocaloric cookies (Jung et al. 2018). After 4 weeks, no differences were found in inflammatory parameters among groups. Differences between groups were observed in TC and LDL-C.

To summarize, almonds can help lower inflammation as was demonstrated by the reduction in CRP and IL-6 in individuals with T2DM. Moreover, consumption of almonds mainly produces a metabolic effect, lowering levels of glucose, TC, and LDL-C, while increasing levels of the anti-inflammatory adipokine, adiponectin.

Chia

Chia is a seed originated in South America which has been used for its medicinal properties since the 16th century. It is high in fat (21.5 to 32.72 g/100 g of chia), protein (18.5-22.3 g/100 g of chia), and fiber (20 to 40 g/100 g of chia). Furthermore, it has a high content of antioxidant phenolic compounds (8.19 g/100 g of chia) (Cahill 2003). Chia seeds have been attributed several health-promoting and anti-inflammatory properties, mainly because of its high content of omega-3 fatty acid ALA (75% of its weight) (Valdivia-López and Tecante 2015).

To prove its effect in chronic low-grade inflammation, Nieman et al. randomized 76 obese adults to consume chia seeds or placebo during 12 weeks (Nieman et al. 2009). No differences between groups were observed, except for ALA levels, which dramatically increased in the group that consumed chia compared with placebo (24.4% *vs* −2.8%, $p = 0.012$). Another study reported no differences in CRP or metabolic parameters, in 26 adults with HT randomized to consume chia flour or placebo, after 12 weeks of intervention (Toscano et al. 2014).

Vuksan et al. randomized 77 adults with T2DM and a BMI between 25 and 40 kg/m^2 to consume chia or bran and oats as placebo (Vuksan et al. 2017). After 6 weeks of intervention, the chia group had lower levels of CRP and higher levels of adiponectin, compared to the placebo group. Additionally, total body weight and waist circumference were reduced significantly in the intervention group compared with placebo.

Overall, chia consumption by overweight and obese individuals with T2DM, for more than 6 weeks, may regulate inflammation, improve metabolism and reduce body weight.

Flaxseed

Flaxseed is also rich in ALA (approximately 52% of total fatty acids), protein, fiber, and vitamin E. Several benefits have been attributed to this seed, such as cancer prevention, serum lipid regulation, anti-inflammatory and antioxidant (Oomah 2001).

In a randomized crossover trial, Hutchins et al. included 25 pre-diabetic adults (Hutchins et al. 2013). They were supplemented with 26 g/day of flaxseed, 13 g/day of flaxseed or not supplemented (control), for 12 weeks. No significant differences were found in inflammatory parameters post-intervention; however, FBG was significantly reduced in the group that consumed 13 g of flaxseed compared with control. Insulin was significantly lower in the group that consumed 13 g compared to both, the group that consumed 26 g (mean change -2 ± 4.7 *vs* 1 ± 4.3, $p = 0.021$) and the control group (mean change -2 ± 4.7 *vs* 2 ± 6.8, $p = 0.013$). Similarly, the HOMA-IR was significantly lower in the group that consumed 13 g compared to both, the group that received 26 g (mean change -2 ± 4.7 *vs* 4 ± 1.2, $p = 0.012$) and the control group (mean change -2 ± 4.7 *vs* 0.7 ± 1.8, $p = 0.08$). Authors analyzed the nutrient composition from the participants' diet and reported that the consumption of vitamin E and soluble fiber was higher in the group that consumed 26 g of flaxseed, which is explained by the higher consumption of flaxseed. The reduction observed in insulin resistance could be related to the high fiber content of flaxseed. It is well known that a high amount of fiber in the intestine may delay nutrient absorption, promote production of short chain fatty acids and bring balance to the microbiota (Weickert and Pfeiffer 2008).

In a study that included 30 patients in hemodialysis with lipid abnormalities, individuals were randomized to consume 40 g a day of flaxseed or to a control group (Khalatbari Soltani et al. 2013). After 8 weeks of intervention, the group that consumed flaxseed had reduced levels of CRP, TC, LDL-C and TG, and increased levels of HDL-C, compared with control group. In a randomized crossover trial, 9 obese insulin resistant adults were advised to consume flaxseed or wheat bran for 12 weeks (Rhee and Brunt 2011). No differences in inflammatory parameters were found among flaxseed and wheat bran groups; however, a significant reduction in FBG was observed in the flaxseed group compared with the wheat bran group.

Flaxseed was proven to have a positive effect reducing CRP in adults in hemodialysis with lipid abnormalities. Moreover, the metabolic benefits of flaxseed were consistent in the regulation of insulin resistance and dyslipidemia.

Pistachios

Pistachios have been part of the eastern diet since ancient times. They are attributed with several cardiovascular and metabolic benefits due to their high content of polyunsaturated fatty acids (approximately 30% of total fat), and their high content of fiber, antioxidants, potassium, magnesium, and vitamins K and E (Dreher 2012).

Gulati et al. included 60 adults with MetS, individuals were randomized to consume 20% of total energy from pistachios for 24 weeks, or to a control group (Gulati et al. 2014). The group that consumed pistachios had reduced levels of hs-CRP, TNF-α, FBG, TC and LDL-C, and increased levels of adiponectin, compared with control. In a very similar study, 30 patients with T2DM were randomized to consume 20% of their total energy from pistachios or to a control group (Sauder et al. 2015). After 4 weeks of intervention, no differences were observed between groups in inflammatory parameters, but the pistachios group had lower TC and TG than the control group.

Another study by Parham et al. randomized 48 adults with T2DM to consume 50 g of pistachios or placebo for 12 weeks (Parham et al. 2014). No differences were observed in CRP, but lower levels of FBG and glycated hemoglobin (HbA1c) were reported in the intervention group, compared with placebo.

In summary, the high content of fat, fiber, antioxidants, vitamins, and minerals in pistachios may contribute to the modulation of inflammation and lipid metabolism in individuals with MetS and T2DM.

Nut mixes and other nuts

Casas-Agustench et al. analyzed the effect of consuming a mixture of nuts (walnuts, almonds and hazelnuts) and standard dietary recommendations for 12 weeks, compared with standard dietary recommendations (control group) (Casas-Agustench et al. 2011). The study included 50 adults with MetS. At the end of the intervention, differences among groups were observed in lower levels of IL-6, insulin and HOMA-IR, in the intervention group. A similar study analyzed the effect of consumption of mixed nuts (walnuts, peanuts, and pine nuts), compared to a control group, in 60 adults with MetS (Lee et al. 2014). However, after 6 weeks, no differences were observed.

Another study included 107 overweight/obese adults, randomly assigned to consume 60 g/day of hazelnuts, 30 g/day of hazelnuts or no hazelnuts (control) for 12 weeks (Tey et al. 2013). At the end of intervention, no differences were observed in either inflammatory or metabolic parameters among groups.

These studies show that nut mixes could be effective in reducing IL-6 and modulating insulin metabolism, preferably those that include walnuts, almonds and hazelnuts.

Oils

Oils contain saturated, monounsaturated, and polyunsaturated fatty acids, each in different proportions. Some examples of vegetable oils containing less amounts of saturated fatty acids are rapeseed, flaxseed, safflower, sunflower, almond, peanut and grape oils (Orsavova et al. 2015; Khattab and Zeitoun 2013). Other oils with higher proportions of mono and polyunsaturated fatty acids are those obtained from cold-water fish and algae (Kris-Etherton, Grieger, and Etherton 2009).

Fish oil

Even though several vegetable oils contain high quantities of polyunsaturated fatty acids, omega-3 fatty acids, EPA and DHA, are more abundant in cold-water fish oil because fish feed on algae rich in DHA and EPA (Kris-Etherton, Grieger, and Etherton 2009). Both fatty acids have been demonstrated to have positive effects on cardiovascular health, such as reduction of TG and increase of HDL-C (Eslick et al. 2009).

In a clinical trial that randomized 37 women with breast cancer to consume fish oil or placebo for 30 days no differences were observed in hs-CRP, lymphocyte populations or metabolic parameters (da Silva Paixão et al. 2017).

In a study that included 50 overweight/obese adults, individuals were randomized to consume fish oil or placebo for 6 weeks (Gammelmark et al. 2012). By the end of intervention, no differences were observed in inflammatory parameters. However, higher levels of adiponectin and FBG were observed in the fish oil group compared with placebo. It is important to note that baseline levels of FBG were significantly higher in the fish oil group than the placebo group. No differences were observed in another study that included 11 obese men, randomly assigned to consume fish oil or placebo for 6 weeks (Plat et al. 2007).

Two similar studies investigated the effect of fish oil on inflammatory cytokines in colorectal cancer patients (Mocellin et al. 2013; Silva et al. 2012). Both studies randomized patients to consume 2 g of fish oil or placebo, for 9 weeks. Mocellin et al. included 11 patients undergoing chemotherapy treatment and found that the fish oil group had significantly lower CRP levels compared with placebo. Silva et al. included 18 patients receiving chemotherapy election treatment, and by the end of intervention found no differences among groups.

In a study that included 34 women with MetS, patients were randomized to consume fish oil or to a control group (Simão et al. 2012). After 90 days of intervention, no differences were observed between groups. The study by Toupchian et al. found no differences in *Tnfa* and *Il6* gene expression in peripheral blood mononuclear cells (PBMCs) from adults with T2DM that consumed fish oil, compared to control, after 8 weeks of intervention (Toupchian et al. 2018).

Overall, according to the clinical studies analyzed in this review, fish oil consumption has little or no effect regulating systemic inflammation. Still, tissue specific inflammation may be impacted with fish oil supplementation. Also, the increase in adiponectin levels could benefit overweight/obese individuals consuming fish oil.

Flaxseed oil

While fish oil is the main source of DHA and EPA, flaxseed oil is one of the main sources of the fatty acid ALA. Although the human organism is not very efficient converting ALA into DHA and EPA, the total content of polyunsaturated fatty acids (about 52%) in flaxseed oil seems to show promise in reducing inflammation (Riediger et al. 2008).

In a clinical trial by Hashemzadeh et al., 60 adults with T2DM and coronary heart disease (CHD) were randomized to consume flaxseed oil or placebo for 12 weeks (Hashemzadeh et al. 2017). A reduced gene expression of *Tnfa* and *Il1* was observed in the group supplemented with flaxseed oil compared to placebo. Furthermore, up-regulation of *Pparg* and down-regulation of lipoprotein (a) gene expression were reported in the flaxseed oil group, compared with the placebo group. In a different study, a reduction of CRP levels was demonstrated in adults in chronic hemodialysis that consumed flaxseed oil for 120 days, compared with placebo (Lemos et al. 2012).

Pan et al. included 68 participants with T2DM. They were randomized to consume 360 mg/day of flaxseed oil or placebo (rice flour devoid of soluble fiber) (Pan et al. 2007). After 12 weeks of intervention, hs-CRP and HbA1c levels were lower in intervention group than in placebo. Results on hs-CRP and IL-6 were obtained from a subsequent publication (Pan et al. 2008).

In summary, flaxseed oil proved to be efficient in lowering inflammation in individuals with T2DM and in individuals undergoing chronic hemodialysis. Also, patients with T2DM could benefit from the consumption of this oil to reduce HbA1c levels.

Other oils

In a trial by Baril-Gravel et al., 45 adults with abdominal obesity were randomized to one of five groups: canola oil enriched with oleic acid and DHA, canola oil enriched with oleic acid, canola oil, mix of flax and safflower oils or mix of corn and safflower oils (Baril-Gravel et al. 2015). After 4 weeks of intervention, when comparing all groups, individuals in the canola oil group had a reduction in hs-CRP. The highest increase of hs-CRP, in addition to a reduction in adiponectin, was observed in individuals that consumed the mix of flax and safflower oils; the group that consumed canola oil enriched with oleic acid and DHA had the highest increase in adiponectin. Irandoost et al. compared grape seed oil with sunflower seed oil in a study that included 39 overweight/obese women with IR (Irandoost, Ebrahimi-Mameghani, and Pirouzpanah 2013). In both interventions, the oil provided 15% of total energy intake; also, participants consumed a calorie restricted diet (500 kcal subtracted from total energy requirement). After 8 weeks, hs-CRP was significantly lower in the grape seed oil group compared with the sunflower oil group.

A study included 18 obese men randomized to consume rapeseed oil or olive oil for 4 weeks (Kruse et al. 2015). Authors chose rapeseed oil because it contains the same amount of monounsaturated fatty acids than olive oil but contains more polyunsaturated fatty acids. However, to assign the observed effects exclusively to the fatty acid contents in the oils, nutrient depleted cold-pressed extra virgin olive oil and nutrient depleted refined rapeseed oil were used. When comparing both groups, no differences were found in serum CRP and IL-6. Furthermore, *Il1b* and *Il6* mRNA were measured from a periumbilical adipose tissue biopsy, taken 4 hours after an overnight fasting and again after breakfast. *Il6* mRNA was lower in the rapeseed oil group in the fasted state and increased 4 h after the test meal. These transcriptional changes may suggest an inflammatory response in adipose tissue after feeding. This is consistent with other studies that demonstrate that during the fasting state metabolic changes occur that cause a switch toward oxidative phosphorylation, and this switch activates anti-inflammatory pathways (Mattson 2008). This adaptation process is part of the protection mechanisms activated in response to stress. Moreover, this process is reversed upon feeding, where the cells' metabolism switches back to glycolysis and may activate inflammatory pathways, demonstrated in this study by the increased expression of *Il6* mRNA. Even so, these changes were not reflected in the cytokine proteins measured in peripheral blood.

In a study that included 84 obese women, participants were randomized to consume Nigella sativa oil capsules or sunflower oil capsules as placebo (Mahdavi et al. 2016). For all participants, a calorie restricted diet was indicated (500 kcal subtracted from total energy requirement). After 8 weeks of intervention, the Nigella sativa oil group had lower levels of TNF-α and hs-CRP, compared with the placebo group. Neff, et al. included 36 overweight/obese adults, volunteers were randomized to consume algal DHA oil or a mixture of corn and soybean oils as placebo (Neff et al. 2011). After 4 months of intervention, the group that consumed algal oil had lower levels of TNF-α and higher levels of TC, compared with the placebo group. The cytokine results were provided by the authors.

The oils that were investigated in this review had positive results regulating inflammatory responses in individuals with obesity, T2DM, and colorectal cancer.

Summary of evidence

Table 1 gives an overview of all the foods analyzed. Foods able to modify inflammatory molecules in chronic diseases are indicated, these include cranberries, grape, pomegranate, strawberry, wheat, whole grain products, dairy products,

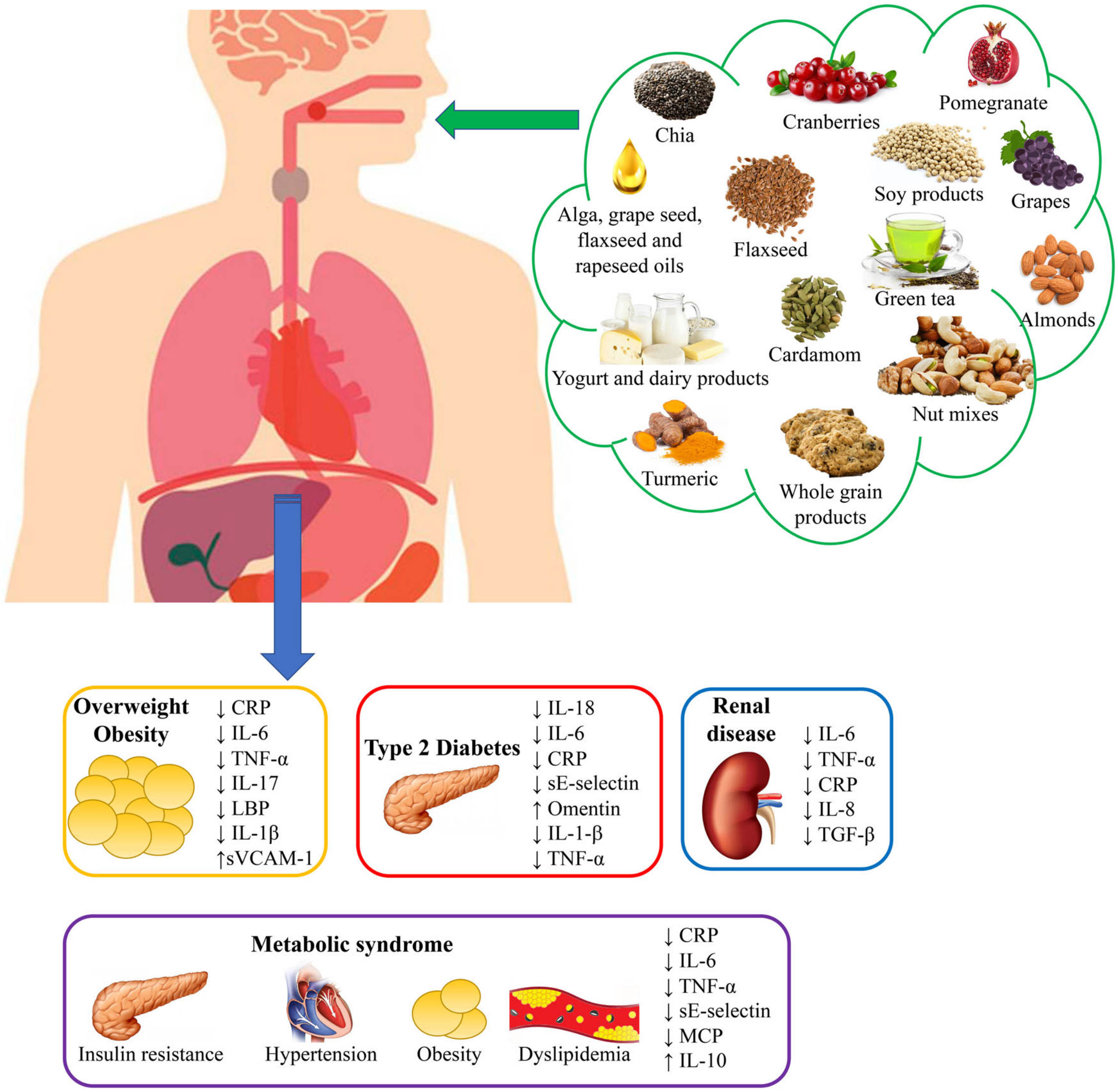

Figure 2. Graphical abstract of functional foods that modulate inflammation in chronic diseases. In this review several foods were described for their ability to modulate cytokines and other inflammation-related molecules in individuals with overweight/obesity, type 2 diabetes, renal disease and metabolic syndrome.

yogurt, green tea, cardamom, turmeric, soy foods, almonds, chia seeds, flaxseed, pistachios, algae oil, flaxseed oil and grapeseed oil. Chronic diseases that have been thoroughly studied and demonstrated to be more sensitive to food-mediated immune modulation are overweight/obesity, T2DM, MetS, and RD. Figure 2 illustrates foods demonstrated to have a positive effect downregulating inflammation for each disease. Only the conditions with more available information were included. It is important to note that for the purpose of this review authors identified foods with anti-inflammatory effects that were studied in clinical trials, however, other foods available may also have immune modulating properties.

Discussion

The importance of an adequate diet to maintain good health and homeostasis has been universally acknowledged. The Western dietary pattern—characterized by foods high in saturated fatty acids, hydrogenated oils, red meat and sodium, very low in high fiber foods like fruits, vegetables and whole grains, and low in fish and legumes— is associated with the development of low-grade inflammation, metabolic disturbances, dysbiosis in the gut microbiota and leaky gut, which sustains a proinflammatory vicious cycle (Franceschi and Campisi 2014; Monteiro and Azevedo 2010; Prasad, Sung, and Aggarwal 2012). On the other hand, the Mediterranean dietary pattern—characterized by foods high in unsaturated fatty acids, high fiber foods including fruits, vegetables, legumes and whole grains, high in fish and omega-3 fatty acids, and low in foods rich in saturated fatty acids, hydrogenated oils and sodium—has been associated with anti-inflammation, metabolic homeostasis, eubiosis in the gut microbiota and a healthy intestinal barrier. These factors lead to overall health and homeostasis. Because the Mediterranean dietary pattern has been associated with these health benefits, evidence on the foods, from all food groups, that have been proven to possess anti-inflammatory properties in a clinical setting were analyzed in this systematic review.

We analyzed several fruits and vegetables, dried cranberries, grapes, pomegranate and strawberries had effects at reducing molecules associated with inflammation and metabolic alterations; even so, in some of the reports no effect was observed when compared to placebo. It is important to highlight the effect of grapes in increasing levels of IL-10 and adiponectin in individuals with metabolic syndrome. IL-10 is a potent anti-inflammatory cytokine, secreted by a number of immune cells, mainly regulatory T lymphocytes, its effect in tissues, including the adipose tissue, is to regulate inflammation and promote repair mechanisms. Adiponectin is an adipokine mainly secreted in the adipose tissue by adipocytes and other cell populations, it has an anti-inflammatory and regulatory effect on immune cells, and it is strongly involved in adipose tissue homeostasis (Monteiro and Azevedo 2010; Coussens and Werb 2002). The increase of both of these molecules may confer health benefits to individuals with MetS; however, no effect was observed in obese individuals. Strawberries demonstrated to have an anti-inflammatory effect, not only observed in the reduction of inflammatory cytokines, but importantly the effect was clinically observed in the reduction of pain in patients with osteoarthritis. This finding may be applied in the treatment of this population, since the addition of strawberries to the diet of patients with osteoarthritis may help manage pain and this alone can make a difference in their quality of life.

Whole grain products had the most positive impact in reducing inflammation in overweight and obese individuals. This is probably related to the high fiber content in these foods. Fiber, both soluble and insoluble, has been demonstrated to modulate the gut microbiota, this in turn shapes the immune response, both locally and systemically, toward a tolerogenic anti-inflammatory environment (Neacsu et al. 2013; Zeng, Lazarova, and Bordonaro 2014; Zhang and Hamaker 2010; Fardet 2010). Yogurt also had demonstrated anti-inflammatory effects in the same population and in T2DM, the effect was enhanced in yogurt fortified with vitamin D and enriched with probiotics. These may be responsible for the observed effects that, like fiber, may modulate the gut microbiota (Derwa et al. 2017; Kim, Keogh, and Clifton 2018). By reducing inflammation through the consumption of whole grain foods and yogurt in individuals with overweight and obesity, the development of associated diseases may be prevented. We stress the importance of recommending the addition of these foods to patients in the clinic.

It was surprising to discover that black and green tea had little effect in inflammation. Tea has constantly been associated with antioxidant and anti-inflammatory properties (Singh et al. 2017; Khan and Mukhtar 2013), and only one study demonstrated an anti-inflammatory effect in patients with CVD. Several factors may have influenced the results, including the type of dietary pattern the subjects consumed and the exposure to oxidizing agents, such as pollutants, which may have neutralized the antioxidant compounds in green tea. This is an important concern in the clinical trials analyzed, few controlled the diet of the study participants and this is an important confounding variable that should be controlled to have a more reliable observation of the specific effect of the food analyzed, although we understand the challenge of controlling the diet of the study population. On the other hand, turmeric had a positive effect in reducing inflammation in gastrointestinal disease. Few spices had a demonstrated effect on inflammation in clinical trials, probably because spices are usually added in small amounts to food preparations, we think that a sensible recommendation is to use a great variety of spices in small amounts to promote an added effect, as we have discussed, but also to protect the tissues from possible adverse effects that may be observed with higher doses (Low 2006; Chainani-Wu 2003).

In the Legumes group, only soy foods were anti-inflammatory in individuals with MetS, KD and NAFLD; importantly, soy proved effective at reducing blood cholesterol and triglyceride levels. Other legumes did not have a significant effect in inflammation but did show other health benefits in glucose and lipid metabolism. These effects may be related not only to their bioactive components and fiber, but also to the increase of plant-based protein to the expense of animal protein, some authors have associated this exchange to a lower risk of developing chronic diseases (Tharanathan and Mahadevamma 2003). Most of the Nuts and seeds group had an anti-inflammatory effect, these included almonds, chia seeds, flaxseed, nut mixes and pistachios in T2DM, MetS and KD. As in the case of legumes, these nuts and seeds had an important metabolic effect. Almonds also showed an increase in adiponectin, which, as mentioned above, is essential for adipose tissue homeostasis. An important finding is that chia seeds helped reduce body weight and waist circumference in overweight and obese individuals. This may also be related to the effect soluble fiber in chia may have in the modulation of the gut microbiota, an important player in the development of obesity, and the intestinal barrier, which also plays a key role in endotoxemia and systemic inflammation (Valdivia-López and Tecante 2015). Among the Oils group, flaxseed oil had the most consistent effect in T2DM and KD, probably because of its high content of ALA fatty acids. Surprisingly, in spite of its high content of omega-3 fatty acids, fish oil had little effect in reducing inflammatory molecules; however, fish oil, like sardines increased levels of adiponectin, so even if inflammatory cytokines were not reduced, the increase in adiponectin suggests that these may regulate the immune response and, as in other foods analyzed, promote adipose tissue healing. The immune-modulating mechanisms of these foods were more thoroughly discussed in the previous section.

It is interesting that no one food had a dramatic effect in reducing inflammation. But this is to be expected because foods have small amounts of bioactive compounds, not to be compared to pharmacological products. Still, it is amazing to observe that one food may have a detectable effect. If all of these foods were consumed together as a dietary pattern, we would expect to see the sum of the individual foods' effects and lead to results that may be tangible not only at the molecular level but measured also in clinical parameters. Of course, this must be demonstrated in a clinical trial where a dietary pattern is administered to a human population and compared with a control group.

Conclusion

There is a tendency toward a beneficial effect by consuming the foods analyzed in this review, even though some of the studies show no statistically significant differences in inflammatory and metabolic parameters. It is important to emphasize that the diet of an individual—the total amount of food consumed in a day— has an integral effect in the health of each subject. Therefore, it is biologically challenging to demonstrate the effect of any given food or nutrient without controlling the rest of the subject's diet and other habits that may interfere with the results, such as physical activity, stress levels and smoking, among others. These factors could explain many of the confusing or contradictory results observed in clinical trials. Overall, we conclude that consumption of the foods reviewed here will help modulate inflammation and metabolism of individuals with chronic inflammatory diseases. We recommend the consumption of these food groups—fruits and vegetables, fish, yogurt, whole grain products, spices, tea, nuts and seeds, omega-3 rich and polyunsaturated oils—together and frequently as part of the habitual diet, for individuals with overweight/obesity, type 2 diabetes, hypertension, cancer and other chronic diseases.

One limitation of this research is that the inflammatory response could vary among the different conditions, so an anti-inflammatory food portion for a given condition could be insufficient for a different one. Moreover, the individual characteristics of each patient should be considered, as well as the individuals' access to food, before recommending a functional food. For example, consumption of nuts and seeds have been associated with higher incomes, so in some regions these may not be affordable (Jiang et al. 2006).

More clinical trials are necessary to confirm that these functional foods, given together as a dietary pattern, have immune regulatory properties. Low doses of nutrients and substances contained in functional foods are beneficial for health; however, higher doses could be harmful. For this reason, supplements should be recommended with caution.

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Supplemental added to complete or make up a deficiency More (Definitions, Synonyms, Translation)