



# The Role of Nutrition on Meta-inflammation: Insights and Potential Targets in Communicable and Chronic Disease Management

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## Abstract

**Purpose of Review** Chronic low-grade inflammation may contribute to the onset and progression of communicable and chronic diseases. This review examined the effects and eventual mediation roles of different nutritional factors on inflammation.

**Recent Findings** Potential nutritional compounds influencing inflammation processes include macro and micronutrients, bioactive molecules (polyphenols), specific food components, and culinary ingredients as well as standardized dietary patterns, eating habits, and chrononutrition features. Therefore, research in this field is still required, taking into account critical aspects of heterogeneity including type of population, minimum and maximum intakes and adverse effects, cooking methods, physiopathological status, and times of intervention. Moreover, the integrative analysis of traditional variables (age, sex, metabolic profile, clinical history, body phenotype, habitual dietary intake, physical activity levels, and lifestyle) together with individualized issues (genetic background, epigenetic signatures, microbiota composition, gene expression profiles, and metabolomic fingerprints) may contribute to the knowledge and prescription of more personalized treatments aimed to improving the precision medical management of inflammation as well as the design of anti-inflammatory diets in chronic and communicable diseases.

**Keywords** Inflammation · Disease · Nutrition · Anti-inflammatory diets · Bioactive compounds · Personalized nutrition

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## Introduction

Inflammation is a pivotal component of innate immunity in response to endogenous and exogenous harmful stimuli (i.e., toxic chemicals, environmental agents, trauma, and pathogens/viral infection), which is physiologically challenged as a defense mechanism for injury removal and wound healing processes [1].

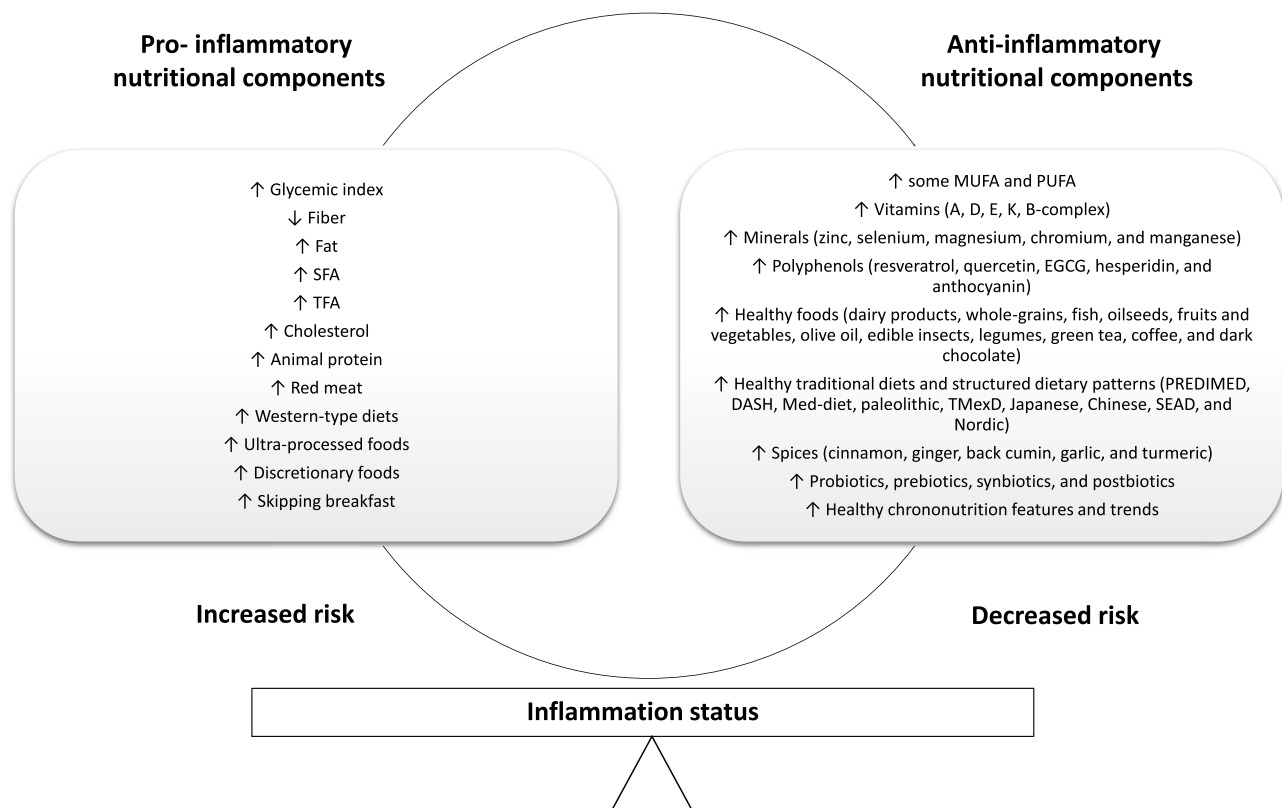
Based on timing and pathological features, inflammation can be acute and chronic [2]. Acute inflammation is usually of short duration (minutes to days) consisting of the migration of lymphocytes/neutrophils and macrophages to the inflammatory site, which stimulate the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin 6 (IL-6), and high motility group box-1 (HMGB-1) as well as cell aggregation and enzyme breakdown [3]. Moreover, the activation of NOD-like receptors (NLRs) such as NLRP3, NLRP1, and NLRC4 results in the recruitment of a highly regulated protein complex (known as inflammasome), whose activation initiates downstream inflammatory cytokine production,

mainly interleukin 1 beta (IL-1 $\beta$ ) and interleukin 18 (IL-18) in response to cellular stress [4]. Other intermediaries encompass chemokines, lipid mediators, acute-phase proteins such as C-reactive protein (CRP), transcriptional factors including the nuclear factor kappa B (NF- $\kappa$ B), and major immune cell types [5].

However, uncontrolled acute inflammation may become a permanent condition leading to expanded tissue damage, hemodynamic changes, and organ failure [6]. In fact, chronic inflammation has been linked to the development of non-communicable diseases such as obesity and associated comorbidities [7]. In this regard, obesity leads to abnormal fat accumulation in adipocytes, immune cell infiltration, and pro-inflammatory milieu that disrupt the insulin signaling cascade inducing insulin resistance [8]. Besides, inflammation and oxidative stress interactions are critical to understand the pathophysiology of obesity, involving impairments of endoplasmic reticulum functions, hypoxia in the adipose tissue, mitochondrial alterations, and reactive oxygen species overproduction [9]. Furthermore, gut microbiota seems to be implicated in the development of obesity-related low-grade inflammation involving lipopolysaccharides translocation and toll-like

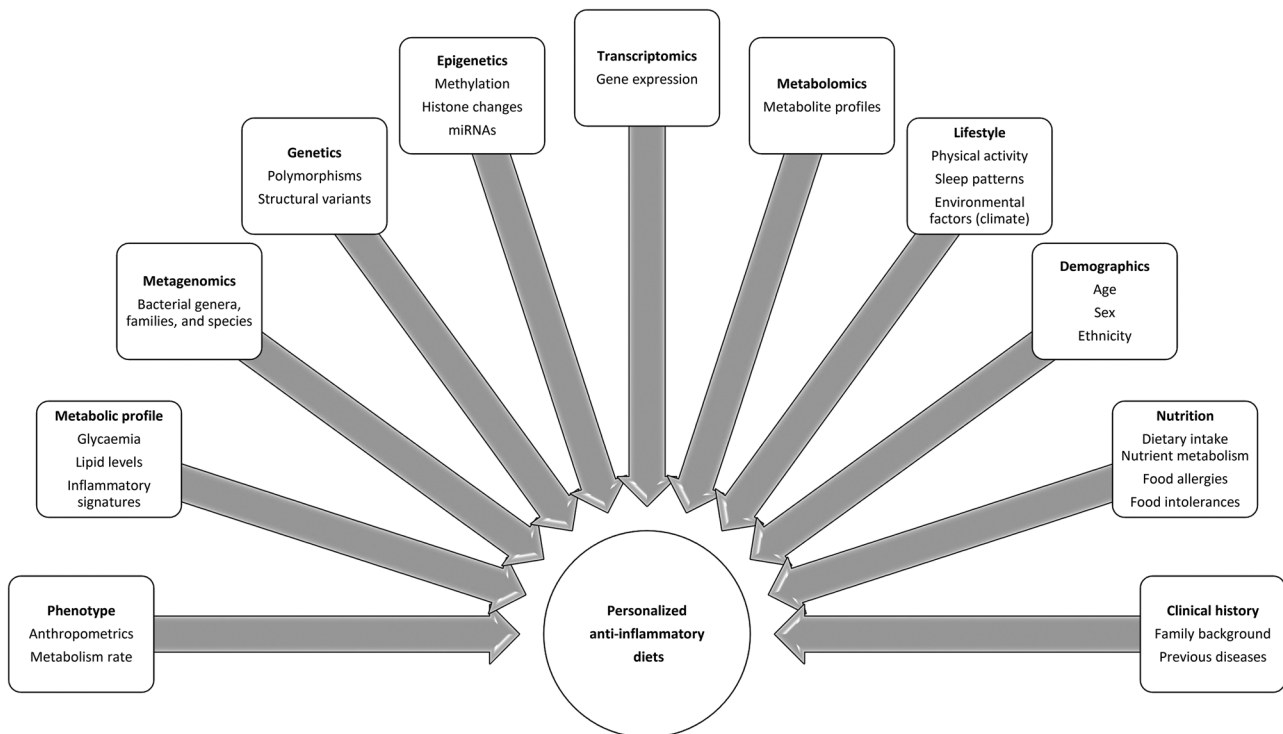
receptor 4 (TLR-4) binding, which trigger a state of blood endotoxemia [10]. The resulting unresolved immune activation not only affects local tissues, but also systemic physiology that is termed meta-inflammation [11].

Therefore, it is relevant to identify the triggers that activate pro-inflammatory cascades in order to identify potential targets as well as implement precision intervention strategies for health care [12]. In this context, cumulative population-based evidence supports the role of nutrition on inflammatory pathways [13]. In this critical review, the effects and eventual mediation of different nutritional factors on inflammation are discussed, including specific nutrients (types of carbohydrates, protein sources, structural fatty acids, micronutrients, and trace elements) and bioactive compounds (polyphenols); staple-characterized dietary patterns (i.e., Western, Mediterranean, and Nordic diets); therapeutic diets (i.e., DASH approach); common culinary ingredients (species and herbs); and chrononutrition features (Fig. 1). Moreover, the potential of prescribing personalized anti-inflammatory diets based on social, phenotypical, clinical, genetic/epigenetic, and metabolic/metabolomic characteristics with a precision medicine scope is postulated (Fig. 2).



**Fig. 1** Nutritional factors associated with inflammatory outcomes in humans. DASH, Dietary Approaches to Stop Hypertension; EGCG, epigallocatechin-3-gallate; Med-diet, Mediterranean diet; MUFA, monounsaturated fatty acids; PREDIMED, Prevención con Dieta

Mediterránea; PUFA, polyunsaturated fatty acids; SEAD, Southern European Atlantic Diet; SFA, saturated fatty acids; TFA, trans fatty acids; TMexD, traditional Mexican diet



**Fig. 2** Precision information for the prescription of personalized anti-inflammatory nutritional strategies

## The Role of Nutrition on Inflammation

### Macronutrients

#### Total Carbohydrates

Dietary carbohydrates exert differential effects on health depending on quantity and quality features [14]. Interestingly, a low-carbohydrate diet (20% of total energy) significantly improved the subclinical inflammatory state (lower serum levels of IL-1Ra and IL-6) in diabetic patients [15]. Notably, the adherence to a low-carbohydrate diet (35% of total energy) reduced the levels of inflammatory markers in women with obesity [16]. Also, it was found an overall favorable effect of a low-carbohydrate diet ( $\leq 30$  g/day) on inflammation in subjects with severe obesity [17]. Additionally, a very low carbohydrate diet (12% of total energy) resulted in relevant reductions in inflammation compared to a low-fat diet (24% of total energy), as reported elsewhere [18].

#### Glycemic Index

The glycemic index (GI) has been devised to physiologically assess the carbohydrate quality from different foods based on effects on postprandial plasma glucose

concentrations [19]. Interestingly, a high-GI diet (based on cooked vermicelli pasta,  $GI = 35$ ) significantly increased the activation rates of NF- $\kappa$ B in mononuclear cells in lean healthy subjects [20]. Indeed, the negative metabolic and inflammatory responses induced by a high-GI diet ( $GI > 70$ ) were counteracted by a low-GI diet ( $GI < 55$ ) in diabetic patients [21]. Furthermore, findings from the DIOGenes trial revealed that low-GI carbohydrates (15 points of difference regarding high-GI carbohydrates) may reduce low-grade inflammation in subjects with overweight or obesity following a weight maintenance diet after weight loss [22].

#### Fiber

Dietary fiber may provide health benefits involving some immunological mechanisms [23]. Accordingly, fiber intake equal or more than 15 g/1000 kcal has been associated with decreased blood CRP levels in diabetic patients [24]. Accordingly, a randomized intervention trial demonstrated that fiber intake (30 g/day) from a diet naturally rich in fiber or from a supplement can substantially reduce the circulating levels of CRP in lean normotensive participants [25]. Moreover, significant inverse linear associations were detected between dietary fiber intake (mean

16.8 g/day) and CRP serum concentrations in middle age adults [26].

### Total Fat

Dietary fat elicit a number of essential functions in the organism; however, excessive fat consumption may lead to obesity and related low-grade inflammatory processes [27]. Indeed, clinical evidence indicates that high-fat diets (i.e., nearly 75% of total energy) cause overproduction of circulating free fatty acids and systemic inflammation [28]. Consistently, a low-fat diet (25% of energy needs) was associated with lower plasma IL-6 levels in diabetic patients [29].

### Saturated Fatty Acids

There is increasing evidence concerning the fact that dietary saturated fatty acids (SFAs) act as an important link between obesity and inflammation [30]. Interestingly, subjects consuming more than 10% energy as saturated dietary fat had increased serum levels of CRP compared to subjects having a normal saturated fat intake (<7% of caloric intake) in young Asian Indians [31]. Likewise, ingestion of SFA (100 mL of dairy cream with 70% saturated fat content) resulted in lipid-induced increases in plasma CRP in women independently of obesity status [32].

### Monounsaturated Fatty Acids

Monounsaturated fatty acids (MUFAs) are assumed as a healthy type of fat, being the oleic acid (OA) the most commonly consumed MUFA in daily nutrition [33]. In this context, a cross-sectional epidemiologic study in Japanese population reported a significant inverse relationship between the intake of OA (mean 6.94% of total energy) and serum CRP concentrations [34]. Further controlled trials with different doses of MUFA for the treatment of inflammatory features are warranted.

### Polyunsaturated Fatty Acids

In the last years, a plethora of evidence has supported the beneficial effects of polyunsaturated fatty acids (PUFAs) in the prevention of cardiovascular and other chronic diseases with an inflammatory basis [35]. In this context, the intakes of the n-3 PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were inversely associated with plasma levels of soluble TNF receptors 1 and 2 in healthy individuals [36]. Moreover, total dietary n-3 PUFAs inversely correlated with blood levels of CRP and IL-6 in women [37].

Additionally, some clinical trials have evaluated the effects of prescribing diets high in PUFA or through PUFA

supplementation on inflammatory outcomes. For instance, fish oil supplementation (38.2 g/day EPA + DHA during 90 days) lowered the blood levels of pro-inflammatory markers in hypertensive patients [38]. Similarly, healthy young adults receiving n-3 PUFA (2.5 g/day, 2085 mg EPA and 348 mg DHA) for 12 weeks underwent a 14% decrease in serum IL-6 levels [39]. Likewise, low (1.25 g/day) or high (2.5 g/day) doses of n-3 PUFA supplementation for 4 months reduced inflammation responses (specifically serum IL-6 and TNF- $\alpha$  concentrations) in overweight adults [40].

### Trans Fatty Acids

*Trans* fatty acids (TFAs) are mainly industrially formed by the hydrogenation of vegetable oils or from ruminant-derived foods including dairy products and meats [41]. TFA intake has been positively associated with plasma biomarkers of inflammation (including CRP, VCAM-1, E-selectin) in women [42]. In this same population, the consumption of TFA was positively associated with the plasma levels of soluble TNF receptors 1 and 2, mainly in women with higher body mass index [43]. Furthermore, serum CRP concentrations were elevated after TFA consumption (8% of total fat) in men [44].

### Dietary Cholesterol

Excessive cholesterol may have deleterious effects on health including some processes affecting inflammation status [45]. For example, highest quartile of serum CRP concentrations (5.9 mg/L) was associated with higher intake of dietary cholesterol (189 mg/day) among Iranian adults [46]. Likewise, in a large representative Middle East population, positive correlations between dietary cholesterol and plasma CRP levels were found [47].

### Protein Quantity and Quality

Both the quantity and quality of dietary protein are main determinants of nutritional values and body/endocrine homeostasis [48]. Among participants of the Framingham Heart Study Offspring cohort, dietary protein intake (particularly from plant sources) was inversely associated with serum markers of inflammation such as IL-6 and CRP [49]. Moreover, consuming high (30% of total energy) or low (10% of total energy) protein diets resulted in reduced blood CRP concentrations in morbidly obese individuals [50].

Regarding protein sources, diets characterized by higher intakes of animal protein (high levels of fatty and processed meats) were positively associated with certain blood pro-inflammatory markers such as CRP, IL-6, TNF- $\alpha$ , IL-8, serum amyloid A, and glycoprotein acetylation [51].

Furthermore, findings from the RESMENA dietary study (30% energy from protein) revealed positive associations between animal and meat protein intakes and inflammation, whereas vegetable- or fish-derived proteins had no significant influence on inflammatory status [52].

## Micronutrients

### Vitamins

Longitudinal and observational studies have shown some associations between dietary vitamin intakes and inflammatory features. For instance, consumption of vitamins C and E or carotene were inversely associated with the probability of having serum CRP concentrations > 3 mg/L in American adults [53]. In the cross-sectional KORA study, dose–response analyses revealed that participants, who regularly ingested more than 78 mg vitamin E/day, had 22% lower serum CRP levels than subjects who were not exposed to any extra vitamin E sources [54].

In addition, the intakes of dietary supplements containing vitamin E and C as well as B-complex vitamins (B1, B2, B3, B5, B6, B9, and B12) were associated with lower blood CRP levels in women [55]. Moreover, subjects in the upper tertile of changes in dietary vitamin K<sub>1</sub> (phyloquinone) intake (after 1-year of follow-up) showed a greater reduction in IL-6 and TNF- $\alpha$  plasma concentrations than those in the lowest tertile group [56]. Also, dietary B5 vitamin intake was inversely related to serum CRP concentrations in healthy Korean adults [57]. Furthermore, participants who consumed > 310 mg/day of dietary choline (commonly grouped within the B-complex vitamins) had lower blood concentrations of CRP, IL-6, and TNF- $\alpha$  in healthy adults [58]. Findings of clinical trials exploring the impact of vitamins on inflammation status are systematically summarized (Table 1). Some studies have found relevant benefits on lowering inflammation after vitamin supplementation.

### Minerals and Trace Elements

Minerals and trace elements are essential for structural, immunological, and metabolic functions in the human organism [93]. In this regard, high magnesium consumption was related to lower plasma concentrations of potential markers of systemic inflammation (CRP, sTNF-R2, and IL-6) in postmenopausal women [94]. Similarly, magnesium intake from dietary sources was found to be inversely correlated with plasma IL-6 in women from the Nurses' Health Study cohort [95]. Likewise, a nested case–control study reported an opposite association concerning dietary manganese and circulating levels of serum pro-inflammatory cytokines in postmenopausal women [96]. Also, changes in

lymphocyte proliferation and *IL-2R* expression have been reported to be early markers of mild zinc dietary deficiency in healthy men [97]. In addition, dietary copper intake has been directly associated with blood CRP concentrations in adults [98]. In turn, iron deficit may be exacerbated by the effects of obesity-related inflammation on gut iron absorption [99]. Furthermore, main outcomes regarding the anti-inflammatory effects of supplementation with certain minerals on humans are shown (Table 2).

## Bioactive Compounds

### Polyphenols

Polyphenols are a large family of bioactive molecules widely occurring in plant-based foods, with potent antioxidant and anti-inflammatory properties [136]. In this context, it was reported that total flavonoid intake was inversely associated with serum CRP concentration in American adults [137]. Also, inverse relationships between flavanone consumption and blood IL-6 concentrations were reported in a multiethnic cohort [138]. Likewise, higher isoflavone intake (highest quartile = 1.61–78.8 mg/day) was related to lower plasma CRP in healthy premenopausal women [139]. Besides, lower serum levels of IL-8 were found among women showing high intakes of flavones, flavanones, and total flavonoids (highest quintiles = 264 ng/L, 273 ng/L, and 276 ng/L, respectively) [140]. Moreover, elevated total flavonoids intake and tea consumption inversely correlated with CRP levels in Taiwanese [141]. Of note, a number of randomized clinical trials have tested the anti-inflammatory potential of several polyphenols, whose results are summarized (Table 3).

### Specific Foods

#### Red Meat

Concerning implications on inflammation, greater total (median 54 g/day), unprocessed (median 47 g/day), and processed red meat intakes (median 4 g/day) have been associated with unfavorable plasma concentrations of inflammatory biomarkers (including CRP and ferritin) in women [168]. Within the Multiethnic Cohort Study, red and processed meat consumption positively correlated with serum CRP levels [169]. Likewise, the consumption of processed meat was associated with increased levels of serum CRP (difference of 38% for each 50 g/day higher intake) in British adults [170]. In adjusted models, red meat consumption was significantly associated with blood CRP in a large American sample [171].

**Table 1** Clinical trials analyzing the anti-inflammatory effects of certain vitamins and bioactive compounds

Vitamin	Study design	Dose/duration	Population	Main finding	Reference
A (retinyl palmitate)	RCT	10 000 IU/week or placebo until 6 weeks postpartum	Pregnant and lactating women: Experimental group ( <i>n</i> = 48) Placebo group ( <i>n</i> = 50)	↑ IFN- $\gamma$ :IL10 ratio	[59]
A (retinyl palmitate)	RCT	25,000 IU/day or placebo for 6 months	Patients with multiple sclerosis: Experimental group ( <i>n</i> = 18) Placebo group ( <i>n</i> = 17)	NS effects on IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$ , IL-2, IL-6, IL-17, IL-10, IL-13, IL-4, and TGF- $\beta$	[60]
A (retinyl palmitate)	RCT	25,000 IU/day or placebo for 6 months	Patients with multiple sclerosis Experimental group ( <i>n</i> = 18) Placebo group ( <i>n</i> = 17)	↑ Plasma CRP	[61]
B1	RCT	3 capsules $\times$ 100 mg/day) or placebo for 6 weeks	Hyperglycemic subjects Experimental group ( <i>n</i> = 12) Placebo group ( <i>n</i> = 12)	NS effects on blood CRP	[62]
B2	CIS	100 mg/day for 3 weeks	Crohn's disease patients with low ( <i>n</i> = 40) or high ( <i>n</i> = 30) fecal calprotectin (FC) levels	↓ Plasma IL-2 in low FC ↓ Plasma CRP in high FC	[63]
C	RCT	500 mg twice a day or free of supplements (control) for 8 weeks	Adults with obesity and/or hypertension Experimental group ( <i>n</i> = 31) Control group ( <i>n</i> = 33)	↓ Serum CRP and IL-6	[64]
C	RCT	250 mg three times per week or free of supplements (control) for 2 months	Chronic hemodialysis patients Experimental group ( <i>n</i> = 19) Control group ( <i>n</i> = 14)	NS effects on blood CRP	[65]
C	RCT	200 mg/day for 3 months and no treatment in the next 3 months (group 1) No treatment in the first 3 months and 200 mg/day for the next 3 months (group 2)	Hemodialysis patients Group 1 ( <i>n</i> = 48) Group 2 ( <i>n</i> = 52)	↓ Plasma CRP after supplementation, but returned to basal state after supplementation was withdrawn	[66]
C	RCT	1000 mg/day or placebo for 2 months	Healthy nonsmokers subjects Experimental group ( <i>n</i> = 128) Placebo group ( <i>n</i> = 138)	↓ Blood CRP among individuals with CRP > or = 1.0 mg/L	[67]
C	RCT	12 g/50 mL (intravenous) every 12 h or placebo for 7 days	Critical patients with COVID-19 Experimental group ( <i>n</i> = 27) Placebo group ( <i>n</i> = 29)	↓ Serum IL-6	[68]
Choline	RCT	~400 mg choline/day from eggs or supplement sources for 4 weeks	Subjects with metabolic syndrome ( <i>n</i> = 23)	↓ Serum IL-6 with both sources of choline ↓ Blood CRP only with eggs ↓ Blood CRP and ESR	[69]
D	RCT	300,000 IU or placebo for 90 days	Patients with ulcerative colitis Experimental group ( <i>n</i> = 46) Placebo group ( <i>n</i> = 40)		[70]
D	RCT	100,000 IU bolus followed by 4000 IU daily or matching placebo for 16 weeks	Adults with overweight or obesity Experimental group ( <i>n</i> = 28) Placebo group ( <i>n</i> = 26)	NS effects on serum levels of CRP, TNF, MCP-1, IFN- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL-10, IL-12, IL-18, IL-23, IL-33 NS effects on NF $\kappa$ B activity in PBMCs	[71]

Table 1 (continued)

Vitamin	Study design	Dose/duration	Population	Main finding	Reference
D	RCT	2000 IU/day plus low-calorie diet or placebo plus low-calorie diet for 8 weeks	Adults with overweight or obesity Experimental group ( <i>n</i> = 30) Placebo group ( <i>n</i> = 29)	↓ Plasma CRP and sICAM-1	[72]
D	RCT	50,000 IU/day plus low-calorie diet or placebo plus low-calorie diet for 12 weeks	Adults with obesity Experimental group ( <i>n</i> = 22) Placebo group ( <i>n</i> = 22)	↓ Serum IL-1 $\beta$ and TLR-4	[73]
D	RCT	7000 IU/day or placebo for 26 weeks	Adults with obesity Experimental group ( <i>n</i> = 26) Placebo group ( <i>n</i> = 26)	NS effects on blood CRP, IL-6, MCP-1, PAI-1, MMP-9, adiponectin, and leptin	[74]
D3	RCT	1000 IU/day (group 1); 2000 IU/day (group 2); or 4000 IU/day (group 3); or placebo for 3 months	African Americans Group 1 ( <i>n</i> = 67) Group 2 ( <i>n</i> = 76) Group 3 ( <i>n</i> = 78) Placebo ( <i>n</i> = 71)	NS effects on blood CRP, IL-6, IL-10, and sTNF-R2	[75]
D3	RCT	200,000 IU/day or placebo for 4 weeks	Women with overweight or obesity Experimental group ( <i>n</i> = 14) Placebo group ( <i>n</i> = 15)	↑ Plasma CRP and MDA	[76]
D3	RCT	200,000 IU/day or placebo for 4 weeks	Elderly women with vitamin D insufficiency Experimental group ( <i>n</i> = 20) Placebo group ( <i>n</i> = 20)	↓ Plasma CRP and AGP-A NS effects on blood MDA	[77]
D3	RCT	750 $\mu$ g/day (group 1); 1500 $\mu$ g/day (group 2); or placebo for 12 months	Older adults Group 1 ( <i>n</i> = 215) Group 2 ( <i>n</i> = 215) Placebo ( <i>n</i> = 214)	NS effects on blood CRP, IL-10, leptin, and adiponectin ↑ IL-6 in group 2 vs. placebo	[78]
E	RCT	1200 IU/day or placebo for 12 weeks	Patients with diabetic nephropathy Experimental group ( <i>n</i> = 30) Placebo group ( <i>n</i> = 30)	↓ Plasma TNF- $\alpha$ , MDA, MMP-2, MMP-9, and AGEs	[79]
E	RCT	600 IU/day or placebo for 10 weeks	Hemodialysis patients Experimental group ( <i>n</i> = 25) Placebo group ( <i>n</i> = 24)	↓ ICAM-1 and VCAM-1 NS effects on serum CRP and IL-6	[80]
Folic acid	RCT	5 mg/day or placebo for 4 weeks	Healthy cigarette smokers Experimental group ( <i>n</i> = 12) Placebo group ( <i>n</i> = 12)	↓ Plasma homocysteine, fibrinogen, and WCC	[81]
Folic acid	RCT	2.5 mg/day or placebo for 3 months	Healthy overweight volunteers Experimental group ( <i>n</i> = 30) Placebo group ( <i>n</i> = 30)	↓ Serum homocysteine, IL-8, MCP-1, and CRP	[82]
Folic acid	RCT	0.8 mg/day for 1 year or placebo	Men and postmenopausal women with homocysteine concentrations of 1.8 mg/L or higher Experimental group ( <i>n</i> = 264) Placebo group ( <i>n</i> = 266)	↓ Serum homocysteine NS effects on plasma CRP and sICAM-1	[83]

Table 1 (continued)

Vitamin	Study design	Dose/duration	Population	Main finding	Reference
Folic acid	RCT	1.25 mg/day or free of supplement (control) for 6 months	Patients with Alzheimer's disease Experimental group ( $n = 61$ ) Control group ( $n = 60$ )	↓ TNF $\alpha$ protein and mRNA levels	[84]
Folic acid	RCT	400 $\mu$ g/day or free of supplement (control) for 12 months	Patients with mild cognitive impairment Experimental group ( $n = 84$ ) Control group ( $n = 84$ )	↓ Blood homocysteine, IL-6 and TNF- $\alpha$	[85]
Folic acid plus vitamin B12	RCT	Folic acid 1.2 mg/day plus vitamin B12 50 $\mu$ g/day or placebo for 6 months	Patients with Alzheimer's disease Experimental group ( $n = 60$ ) Placebo group ( $n = 60$ )	↓ Serum homocysteine and TNF- $\alpha$	[86]
Folic acid plus vitamin B12	RCT	400 $\mu$ g/day folic acid (group 1); 25 $\mu$ g/day vitamin B12 (group 2); 400 $\mu$ g/day folic acid plus 25 $\mu$ g vitamin B12 (group 3); or free of supplement (control) for 6 months	Participants with mild cognitive impairment Group 1 ( $n = 60$ ) Group 2 ( $n = 60$ ) Group 3 ( $n = 60$ ) Control ( $n = 60$ )	↓ Blood homocysteine, IL-6, TNF- $\alpha$ , and MCP-1 (group 3 vs. control)	[87]
Folic acid plus vitamin B12	RCT	Folic acid (400 $\mu$ g/day) plus vitamin B12 (500 $\mu$ g/day) or placebo for 2 years	Elderly subjects with hyperhomocysteinemia Experimental group ( $n = 271$ ) Placebo group ( $n = 251$ )	NS effects on plasma CRP, ICAM-1, VCAM-1, VEGF, and SAA	[88]
Folic acid plus vitamin B12 plus vitamin B6	RCT	Daily folic acid (2.5 mg), vitamin B6 (50 mg), vitamin B12 (1 mg), or matching placebo for 7.3 years	Women at increased risk of CVD Experimental group ( $n = 150$ ) Placebo group ( $n = 150$ )	↓ Serum homocysteine NS effects on blood CRP, IL-6, fibrinogen, and ICAM-1	[89]
Folic acid plus vitamin B12 plus vitamin B6	RCT	Group 1: folic acid (0.8 mg/day)/vitamin B12 (0.4 mg/day)/vitamin B6 (40 mg/day); group 2: folic acid (0.8 mg/day)/vitamin B12 (0.4 mg/day); group 3: vitamin B6 (40 mg/day); or placebo for 6 months	Patients with suspected coronary artery disease Group 1 ( $n = 22$ ) Group 2 ( $n = 23$ ) Group 3 ( $n = 21$ ) Placebo ( $n = 24$ )	↓ Serum homocysteine (groups 1 and 2) NS effects on blood CRP, IL-6, neopterin, and sCD40L	[90]
K <sub>1</sub> (phylloquinone)	RCT	10 mg/day or placebo for 8 weeks	Patients with definitive rheumatoid arthritis Experimental group ( $n = 29$ ) Placebo group ( $n = 29$ )	NS effects on plasma IL-6	[91]
K <sub>1</sub> (phylloquinone)	RCT	500 $\mu$ g/day or placebo during two periods of 6 weeks of duration	Postmenopausal women ( $n = 31$ )	NS effects on blood IL-6, CRP, sICAM-1, sVCAM-1	[92]

RCT randomized controlled trial, CIS clinical intervention study, NS no significant, FC fecal calprotectin, IU international units, MDA malondialdehyde, NF- $\kappa$ B transcription nuclear factor kappa B, CRP C-reactive protein, IL-6 interleukin 6, TNF- $\alpha$  tumor necrosis factor alpha, IL-8 interleukin 8, IL-4 interleukin 4, IL-10 interleukin 10, IL-2 interleukin 2, IL-1 $\beta$  interleukin-1 $\beta$ , TLR-4 toll-like receptor 4, sTNF-R2 serum soluble tumor necrosis factor receptor 2, IFN- $\gamma$  interferon gamma, IL-17 interleukin 17, IL-18 interleukin 18, IL-13 interleukin 13, IL-23 interleukin 23, IL-33 interleukin 33, TGF- $\beta$  transforming growth factor  $\beta$ , ESR erythrocyte sedimentation rate, TNF tumor necrosis factor, MCP-1 monocyte chemoattractant protein-1, IFN- $\alpha$  interferon alpha, PBMCs peripheral blood mononuclear cells, ICAM-1 intercellular adhesion molecule-1, sICAM-1 soluble intercellular adhesion molecule-1, VCAM-1 vascular cell adhesion molecule 1, sVCAM-1 soluble vascular cell adhesion molecule 1, PAI-1 plasminogen activator inhibitor-1, MMP-2 matrix metalloproteinase-2, MMP-9 matrix metalloproteinase-9, AGP-A alpha 1-acid glycoprotein, AGEs advanced glycation endproducts, WCC white cell count, SAA serum amyloid A, VEGF vascular endothelial growth factor, sCD40L soluble CD40 ligand



**Table 2** Clinical trials analyzing the anti-inflammatory effects of certain minerals

Mineral	Study design	Dose/duration	Population	Main finding	Reference
Chromium	RCT	200 µg/day or placebo for 8 weeks	Patients with PCOS Experimental group (n = 30) Placebo group (n = 30)	↓ Plasma CRP and MDA	[100]
Chromium	RCT	200 µg/day or placebo for 8 weeks	20 patients with PCOS who were candidate for in vitro fertilization Experimental group (n = 20) Placebo group (n = 20)	↓ Blood CRP ↓ Gene expression of <i>IL-1</i> in PBMCs NS effects on gene expression of <i>IL-8</i> , <i>TNF-α</i> , <i>TGF-β</i> , and <i>VEGF</i> of in PBMCs	[101]
Chromium	RCT	400 µg/day or placebo for 3 months	Patients with NAFLD Experimental group (n = 23) Placebo group (n = 23)	↓ Serum TNF-α, CRP, and IL-6, and fetuin-A NS effects on blood IL-17	[102]
Chromium	RCT	400 µg/day (chromium picolinate); 400 µg/day (chromium dinicocysteinate); or placebo for 3 months	Patients with T2DM Chromium picolinate (n = 12) Chromium dinicocysteinate (n = 18) Placebo (n = 13)	↓ Plasma TNF-α (chromium dinicocysteinate vs. placebo)	[103]
Chromium	RCT	1000 µg/day or placebo for 16 weeks	Patients with metabolic syndrome Experimental group (n = 33) Placebo group (n = 30)	NS effects on blood CRP	[104]
Chromium	RCT	400 µg/day (chromium picolinate); 400 µg/day (chromium dinicocysteinate); or placebo for 3 months	Patients with T2DM Chromium picolinate (n = 25) Chromium dinicocysteinate (n = 24) Placebo (n = 25)	↓ Serum TNF-α (chromium dinicocysteinate vs. baseline)	[105]
Chromium + magnesium + zinc	RCT	300 mg/day magnesium plus 600 µg/day chromium plus 36 mg/day zinc or placebo for 24 weeks	Adults with metabolic syndrome Experimental group (n = 16) Placebo group (n = 16)	↓ Plasma CRP	[106]
Copper	RCT	2 mg/day or placebo for 8 weeks	Adults with moderately high cholesterol Experimental group (n = 35) Placebo group (n = 35)	NS effects on serum CRP and homocysteine	[107]
Iron	RCT	50 g/day meat; 20 g/day of fortified rice cereal (1.10 mg of iron); or 20 g/day of local rice cereal (0.04 mg of iron) for 1 year	6-month-old infants Meat group (n = 137) Fortified cereal group (n = 140) Local cereal group (n = 133)	↑ Plasma CRP and AGP-A	[108]
Iron	RCT	50 mg for 4 day/week or identical placebo for 38 weeks	Children with iron deficiency Experimental group (n = 22) Placebo group (n = 27)	NS effects on gut inflammation (measured by fecal calprotectin concentration)	[109]
Iron	RCT	6 mg/kg/day iron plus placebo; or 6 mg/kg/day plus 18 mg/day vitamin E for 8 weeks	Iron-deficient infants and toddlers Iron plus placebo (n = 22) Iron plus vitamin E (n = 14)	NS effects on gut inflammation (measured by fecal calprotectin concentration) and blood levels of TNF-α and IL-4	[110]
Magnesium	RCT	500 mg/day or placebo for 4 weeks	Healthy overweight volunteers Experimental group (n = 7) Placebo group (n = 7)	NS effects on plasma CRP, IL-6, and TNF-α, sICAM-1, sVCAM-1, and E-selectin	[111]
Magnesium	RCT	250 mg/day or placebo for 8 weeks	Middle-aged overweight women Experimental group (n = 35) Placebo group (n = 34)	↓ Gene expression of <i>CLU</i> , <i>C/QTNF9</i> , and <i>PPBP</i> NS effects on serum CRP, IL-6, and fibrinogen	[112]
Magnesium	RCT	320 mg/day or placebo for 7 weeks	Adults with poor sleep quality Experimental group (n = 46) Placebo group (n = 49)	↓ Blood CRP in participants with baseline values > 3.0 mg/L	[113]

Table 2 (continued)

Mineral	Study design	Dose/duration	Population	Main finding	Reference
Magnesium	RCT	300 mg/day or placebo for 6 months	COPD patients Experimental group ( <i>n</i> = 25) Placebo group ( <i>n</i> = 24)	↓ Plasma CRP NS effects on serum TNF- $\alpha$	[114]
Magnesium	RCT	30 ml of MgCl <sub>2</sub> 5% solution (equivalent to 382 mg of magnesium) per day or placebo for 3 months	Subjects with prediabetes and hypomagnesemia Experimental group ( <i>n</i> = 13) Placebo group ( <i>n</i> = 13)	NS effects on CRP, IL-6, TNF- $\alpha$ , and IL-10 levels	[115]
Magnesium	RCT	30 mL of MgCl <sub>2</sub> 5% solution (equivalent to 382 mg of magnesium) per day or placebo for 3 months	Subjects with new diagnosis of prediabetes and hypomagnesemia Experimental group ( <i>n</i> = 29) Placebo group ( <i>n</i> = 28)	↓ Blood CRP	[116]
Magnesium and zinc	RCT	250 mg of magnesium oxide plus 220 mg of zinc sulfate or placebo twice a day for 12 weeks	Subjects with PCOS Experimental group ( <i>n</i> = 30) Placebo group ( <i>n</i> = 30)	↓ Plasma CRP and protein carbonyl ↓ Gene expression of <i>IL-1</i> and <i>TNF-<math>\alpha</math></i>	[117]
Na and K	RCT	Supplemental Na (3.0 g/day); supplemental K (2.8 g/day) or placebo for 4 weeks	Pre-hypertensive patients ( <i>n</i> = 36)	↓ Blood IL-8 (K supplementation)	[118]
Selenium	RCT	200 $\mu$ g/day or placebo for 12 weeks	Patients with diabetic nephropathy Experimental group ( <i>n</i> = 30) Placebo group ( <i>n</i> = 30)	NS effects on plasma CRP, TGF- $\beta$ , AGEs, protein carbonyl, and MDA	[119]
Selenium	RCT	200 $\mu$ g/day or placebo for 12 weeks	Patients with CHF Experimental group ( <i>n</i> = 26) Placebo group ( <i>n</i> = 27)	NS effects on serum CRP	[120]
Selenium	RCT	200 $\mu$ g/day or placebo for 12 weeks	Hemodialysis patients Experimental group ( <i>n</i> = 40) Placebo group ( <i>n</i> = 40)	↓ Blood MDA and IL-6 NS effects on homocysteine, ferritin, and transferrin	[121]
Selenium	RCT	200 $\mu$ g/day or placebo for 6 weeks	Pregnant women with GDM Experimental group ( <i>n</i> = 35) Placebo group ( <i>n</i> = 35)	↓ Blood CRP and MDA	[122]
Selenium	RCT	200 $\mu$ g/day or placebo for 8 weeks	Women with PCOS Experimental group ( <i>n</i> = 32) Placebo group ( <i>n</i> = 32)	↓ Serum CRP and MDA	[123]
Selenium	RCT	200 $\mu$ g/day or placebo for 4 weeks	17 patients undergoing CABG surgery Experimental group ( <i>n</i> = 17) Placebo group ( <i>n</i> = 16)	↓ Plasma CRP and MDA	[124]
Selenium	RCT	200 $\mu$ g/day or placebo for 8 weeks	Patients with T2DM and CHD Experimental group ( <i>n</i> = 30) Placebo group ( <i>n</i> = 30)	↓ Blood CRP	[125]
Selenium	RCT	200 $\mu$ g or placebo twice daily for 14 days	Patients undergoing HSCT Experimental group ( <i>n</i> = 37) Placebo group ( <i>n</i> = 37)	NS effects on serum TNF- $\alpha$ , IL-1, and IL-6	[126]
Zinc	RCT	30 mg/day or placebo for 12 weeks	Women with premenstrual syndrome Experimental group ( <i>n</i> = 30) Placebo group ( <i>n</i> = 30)	NS effects on serum CRP	[127]

Table 2 (continued)

Mineral	Study design	Dose/duration	Population	Main finding	Reference
Zinc	RCT	45 mg/day or placebo for 6 months	Healthy elderly subjects Experimental group (n = 20) Placebo group (n = 20)	↓ Blood CRP, IL-6, MCP-1, VCAM-1, MDA, and secretory phospholipase A2 ↓ TNF-α, IL-1β, VCAM-1, and NF-κB activity in THP-1 cells and human aortic endothelial cells ↑ Anti-inflammatory proteins A20 and PPAR-α in THP-1 cells and human aortic endothelial cells NS effects on plasma CRP	[128]
Zinc	RCT	15 mg/day or placebo for 12 weeks	Women with migraine Experimental group (n = 30) Placebo group (n = 30)		[129]
Zinc	RCT	25 mg/day or placebo for 3 months	18 adult SCD patients Experimental group (n = 18) Placebo group (n = 18)	↓ TNF-α and IL-1β mRNAs in MNCs ↓ NF-κB binding in MNCs ↑ IL-2 and IL-2Rα mRNA in phytohemagglutinin-p-stimulated MNCs	[130]
Zinc	RCT	25 mg/day or placebo for 12 weeks	Patients with major depression Experimental group (n = 20) Placebo group (n = 17)	NS effects on serum IL-6 and TNF-α	[131]
Zinc	RCT	30 mg/day or placebo for 8 weeks	Women with obesity Experimental group (n = 20) Placebo group (n = 20)	↓ Blood CRP and IL-6 NS effects on serum leptin and adiponectin levels	[132]
Zinc	RCT	30 mg/day or placebo for 15 weeks	Subjects with obesity Experimental group (n = 18) Placebo group (n = 22)	↓ Plasma CRP	[133]
Zinc	RCT	50 mg/day or placebo for 8 weeks	24 women with PCOS Experimental group (n = 24) Placebo group (n = 24)	NS effects on serum CRP	[134]
Zinc	RCT	20 mg/day or placebo for 8 weeks	Prepubescent children with metabolic syndrome Experimental group (n = 30) Placebo group (n = 30)	↓ Blood CRP	[135]

RCT randomized controlled trial, NS no significant, PCOS polycystic ovary syndrome, COPD chronic obstructive pulmonary disease, SCD sickle-cell disease, CHF congestive heart failure, GDM gestational diabetes mellitus, CABG coronary artery bypass grafting surgery, T2DM type 2 diabetes mellitus, CHD coronary heart disease, NAFLD non-alcoholic fatty liver disease, HSCt hematopoietic stem cell transplantation, CRP C-reactive protein, IL-6 interleukin 6, TNF-α tumor necrosis factor alpha, IL-8 interleukin 8, IL-10 interleukin 10, IL-1 interleukin 1, IL-1β interleukin-1β, IL-2 interleukin 2, IL-4 interleukin 4, MDA malondialdehyde, PBMCs peripheral blood mononuclear cells, TGF-β transforming growth factor beta, VEGF vascular endothelial growth factor, IL-17 interleukin 17, AGP-A alpha 1-acid glycoprotein, CIQTNF9 tumor necrosis factor related protein 9, PPBP pro-platelet basic protein, TGF-β transforming growth factor β, AGEs advanced glycation endproducts, MCP-1 monocyte chemoattractant protein-1, VCAM-1 vascular cell adhesion molecule 1, NF-κB transcription nuclear factor kappa B, PPAR-α peroxyl-proliferator-activated receptor-alpha, MNCs mononuclear cells

**Table 3** Clinical trials analyzing the anti-inflammatory effects of certain polyphenols

Polyphenol	Study design	Dose/duration	Population	Main finding	Reference
Anthocyanin	RCT	40 mg/day (group 1); 80 mg/day (group 2); 320 mg/day (group 3); or placebo for 12 weeks	Patients with dyslipidemia Group 1 ( <i>n</i> = 44) Group 2 ( <i>n</i> = 40) Group 3 ( <i>n</i> = 42) Placebo ( <i>n</i> = 43)	↓ Blood TNF- $\alpha$ and IL-6 (group 2 vs. baseline) ↓ Blood TNF- $\alpha$ and IL-6, and MDA (group 3 vs. groups 1 and 2)	[142]
Anthocyanin	OLCT	320 mg/day for 4 weeks	Patients with T2DM ( <i>n</i> = 12) Patients at risk of T2DM ( <i>n</i> = 14) Healthy individuals ( <i>n</i> = 14)	↓ Plasma TNF- $\alpha$ , IL-6, and IL-18 (patients with T2DM, pre vs. post intervention) NS effects on IL-1R $\alpha$ , leptin, IL-8, and CRP in any group (pre vs. post intervention)	[143]
Anthocyanin	RCT	20 mg/day (group 1); 40 mg/day (group 2); 80 mg/day (group 3); 160 mg/day (group 4); 320 mg/day (group 5); or placebo for 14 days	Healthy young adults Group 1 ( <i>n</i> = 20) Group 2 ( <i>n</i> = 19) Group 3 ( <i>n</i> = 19) Group 4 ( <i>n</i> = 19) Group 5 ( <i>n</i> = 19) Placebo ( <i>n</i> = 15)	↓ Blood IL-10 (group 4 and 5 vs. placebo) ↓ IL-6 (groups 2 and 5 vs. placebo) NS effects on TNF- $\alpha$ in any group	[144]
Anthocyanin	RCT	640 mg/day or placebo for 4 weeks	Pre-hypertensive men Experimental group ( <i>n</i> = 16) Placebo group ( <i>n</i> = 15)	NS effects on serum CRP, IL-6, TNF- $\alpha$ , IL-4, MCP-1, P-selectin, ICAM, VCAM, and CD40L	[145]
Anthocyanin	RCT	320 mg/day or placebo for 28 days	Sedentary subjects Experimental group ( <i>n</i> = 16) Placebo group ( <i>n</i> = 16)	NS effects on blood CRP	[146]
EGCG	RCT	2 tablets 300 mg/day or placebo for 2 months	Patients with T2DM Experimental group ( <i>n</i> = 25) Placebo group ( <i>n</i> = 25)	NS changes in serum IL-6	[147]
EGCG	RCT	300 mg/day or placebo for 12 weeks	Pre-menopausal women with obesity Experimental group ( <i>n</i> = 43) Placebo group ( <i>n</i> = 40)	NS effects on blood CRP	[148]
Hesperidin	RCT	500 mg or placebo twice daily for 12 weeks	Patients with metabolic syndrome Experimental group ( <i>n</i> = 25) Placebo group ( <i>n</i> = 24)	↓ Plasma TNF- $\alpha$	[149]
Hesperidin	RCT	600 mg/day or placebo for 4 weeks	Patients with myocardial infarction Experimental group ( <i>n</i> = 38) Placebo group ( <i>n</i> = 37)	NS effects on serum CRP, IL-6, and leptin	[150]
Hesperidin	RCT	500 mg/day or placebo for 6 weeks	Patients with T2DM Experimental group ( <i>n</i> = 32) Placebo group ( <i>n</i> = 32)	↓ Blood TNF- $\alpha$ , CRP, and IL-6	[151]
Hesperidin	RCT	30 g/day flaxseed plus lifestyle (group 1); 1 g/day hesperidin plus lifestyle (group 2); 30 g/day flaxseed plus 1 g/day hesperidin plus lifestyle (group 3); or lifestyle alone (control) for 12 weeks	Patients with NAFLD Group 1 ( <i>n</i> = 24) Group 2 ( <i>n</i> = 22) Group 3 ( <i>n</i> = 25) Control ( <i>n</i> = 21)	↓ NF- $\kappa$ B (groups 1 and 2 vs. control) ↓ Plasma CRP (groups 2 and 3 vs. control)	[152]

Table 3 (continued)

Polyphenol	Study design	Dose/duration	Population	Main finding	Reference
Hesperidin	RCT	1 g/day plus lifestyle or placebo (only lifestyle) for 12 weeks	Patients with NAFLD Experimental group ( <i>n</i> =25) Placebo group ( <i>n</i> =25)	↓ Serum TNF- $\alpha$ , CRP, and NF- $\kappa$ B	[153]
Quercetin	RCT	500 mg/day or placebo for 8 weeks	Post-myocardial infarction patients Experimental group ( <i>n</i> =44) Placebo group ( <i>n</i> =44)	NS changes in blood IL-6, CRP, and TNF- $\alpha$	[154]
Quercetin	RCT	500 mg/day of quercetin plus 250 mg/day vitamin C (group 1); 500 mg/day of quercetin alone (group 2); 250 mg/day of vitamin C alone (group 3); or placebo for 8 weeks	Subjects with systematic and regular exercise Group 1 ( <i>n</i> =15) Group 2 ( <i>n</i> =15) Group 3 ( <i>n</i> =15) Placebo ( <i>n</i> =15)	↓ Plasma IL-6 and F2-isoprostane (group 1 vs. placebo)	[155]
Quercetin	RCT	100 mg/day (-)-epicatechin (group 1); 160 mg/day quercetin-3-glucoside (group 2); or placebo for 4 weeks	Pre-hypertensive adults Group 1 ( <i>n</i> =37) Group 2 ( <i>n</i> =37) Placebo ( <i>n</i> =37)	↓ Serum IL-1 $\beta$ (group 2 vs. placebo)	[156]
Quercetin	RCT	500 mg/day or placebo for 8 weeks	Women with rheumatoid arthritis Experimental group ( <i>n</i> =25) Placebo group ( <i>n</i> =25)	↓ Blood TNF- $\alpha$	[157]
Quercetin	RCT	500 mg/day (group 1); 1000 mg/day (group 2); or placebo for 12 weeks	Women Group 1 ( <i>n</i> =38) Group 2 ( <i>n</i> =40) Placebo ( <i>n</i> =42)	NS effects on plasma IL-6, TNF- $\alpha$ , and blood leucocyte subsets (groups 1 and 2 vs. placebo)	[158]
Quercetin	RCT	50 mg/day (group 1); 100 mg/day (group 2); or 150 mg/day (group 3) for 2 weeks	Healthy volunteers Group 1 ( <i>n</i> =11) Group 2 ( <i>n</i> =12) Group 3 ( <i>n</i> =11)	NS effects on serum TNF- $\alpha$	[159]
Quercetin	RCT	500 mg/day or placebo for 8 weeks	Women with rheumatoid arthritis Experimental group ( <i>n</i> =20) Placebo group ( <i>n</i> =20)	NS effects on blood CRP, MDA, and ox-LDL	[160]
Quercetin	RCT	162 mg/day or placebo for 6 weeks	Overweight-to-obese subjects with pre-hypertension Experimental group ( <i>n</i> =68) Placebo group ( <i>n</i> =68)	NS effects on serum CRP and TNF- $\alpha$	[161]
Resveratrol	RCT	480 mg/day or placebo for 4 weeks	Patients with T2DM and chronic periodontitis Experimental group ( <i>n</i> =21) Placebo group ( <i>n</i> =22)	NS effects on blood IL-6 and TNF- $\alpha$	[162]
Resveratrol	RCT	500 mg/day or placebo for 12 weeks	Patients with NAFLD Experimental group ( <i>n</i> =25) Placebo group ( <i>n</i> =25)	↓ Plasma IL-6, CRP, cytokerin-18, and NF- $\kappa$ B	[163]
Resveratrol	RCT	500 mg/day or placebo for 6 weeks	Patients with ulcerative colitis Experimental group ( <i>n</i> =25) Placebo group ( <i>n</i> =25)	↓ Serum TNF- $\alpha$ , CRP, and NF- $\kappa$ B	[164]

Table 3 (continued)

Polyphenol	Study design	Dose/duration	Population	Main finding	Reference
Resveratrol	RCT	500 mg/day or placebo for 30 days	Adult smokers Experimental group (n=25) Placebo group (n=25)	↓ CRP	[165]
Resveratrol	RCT	800 mg/day or placebo for 8 weeks	Patients with T2DM Experimental group (n=25) Placebo group (n=20)	NS effects on blood TNF- $\alpha$ , IL-6, CRP, and IL-1 $\beta$ NS effects on expression of genes <i>NF-<math>\kappa</math>B</i> , <i>TLR2</i> , and <i>TLR4</i>	[166]
Resveratrol	RCT	500 mg/day or placebo for 4 weeks	CKD patients Experimental group (n=9) Placebo group (n=11)	NS changes in plasma TNF- $\alpha$ , CRP, IL-6, and NF- $\kappa$ B	[167]

RCT randomized controlled trial, *OLCT* open-label clinical trial, NS no significant, *CKD* chronic kidney disease, *NAFLD* non-alcoholic fatty liver disease, *T2DM* type 2 diabetes mellitus, *EGCG* epigallocatechin-3-gallate, *CRP* C-reactive protein, *IL-6* interleukin 6, *TNF- $\alpha$*  tumor necrosis factor alpha, *IL-4* interleukin 4, *IL-8* interleukin 8, *IL-18* interleukin 18, *IL-1 $\beta$*  interleukin-1 $\beta$ , *NF- $\kappa$ B* transcription nuclear factor kappa B, *IL-1R $\alpha$*  interleukin-1R alpha, *MCP-1* monocyte chemoattractant protein, *ICAM* intercellular adhesion molecule, *VCAM* vascular cell adhesion molecule, *CD40L* CD40 ligand, *MDA* malondialdehyde, *ox-LDL* oxidized low density lipoprotein, *TLR2* toll-like receptor 2, *TLR4* toll-like receptor 4

## Dairy Products

In a cross-sectional study in Brazilians, increased yogurt consumption (median 10 g/day) appeared to exert an anti-inflammatory effect, whereas cheese consumption (median 10.7 g/day) could have potentiated a pro-inflammatory status [172]. In normal-weight adolescents, total dairy product and milk intakes were inversely associated with the serum concentrations of IL-6 [173]. Also, findings from the ATTICA study showed lower blood levels of CRP, IL-6, and TNF- $\alpha$  among individuals weekly consuming between 11 and 14 servings of dairy products compared to those consuming fewer than 8 servings per week [174].

## Fish

Findings from the ATTICA study revealed independent associations between habitual fish consumption (> 300 g of fish per week) and lower inflammatory marker levels among healthy adults, including reduced CRP, IL-6, TNF- $\alpha$ , serum amyloid A, and white blood cell counts [175]. During a 6-year follow-up, fish consumption (about 100 g/week) decreased endothelial dysfunction and low-grade inflammation in healthy adults [176]. Furthermore, a high frequency of fish intake was associated with lower peripheral white blood cell counts (a marker of chronic inflammation) in an apparently healthy Japanese population [177]. In fact, the neutrophil/lymphocyte ratio (a marker of systemic inflammation) significantly decreased as the weekly frequency of fish intake (0 day, 1–2 days, 3–4 days, or 5–7 days) increased [178].

## Edible Insects

In recent years, edible insects are being recognized as high-value food products with anti-inflammatory and antioxidant properties [179]. For example, cricket consumption (25 g/day) was associated with reduced systemic inflammation via microbiota modulation in healthy adults [180]. However, more research in humans is required to confirm these findings in order to recommend the habitual consumption of edible insects as an anti-inflammatory therapy.

## Fruits and Vegetables

Inverse associations were found between the intakes of fruits and vegetables and serum CRP levels in Iranian females [181]. Besides, Chinese women consuming high amounts of cruciferous vegetables (highest quintile > 140.6 g/day)

showed decreased circulating levels of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 [182]. In a randomized crossover trial, the consumption of cruciferous vegetables (14 g/kg body weight) during 14 days consistently reduced circulating IL-6 in healthy young adults [183].

### Oilseeds and Extra Virgin Olive Oil

In the multi-ethnic study of atherosclerosis, frequent nut and seed consumption (especially five or more times/week) was associated with lower levels of inflammatory markers, including IL-6 and CRP [184]. Moreover, in two large cohorts of Americans, subjects with a nut intake of five or more times/week had significantly lower blood concentrations of CRP and IL-6 compared to individuals in the frequency categories of never or almost never [185]. Likewise, a systematic review and meta-analysis of randomized controlled trials revealed that intakes of flaxseed and associated nutritional derivatives systematically reduced circulating CRP levels in obese subjects [186]. Using the same approach, acute high-oleic peanut consumption systematically led to stronger moderation of postprandial TNF- $\alpha$  concentrations in overweight/obese men [187].

Additionally, it has been shown that the incorporation of almonds (56 g/day during 4 weeks) into a healthy diet could improve inflammation and oxidative stress in Chinese diabetic patients [188]. A randomized trial also found that the consumption of almonds (10–20% isoenergetic replacement of control diet with almonds for 4 weeks) lowered serum CRP levels in healthy adults [189]. Indeed, plasma levels of TNF- $\alpha$  and IL-6 decreased after almond feeding (56 g/day for 90 days) in adolescents and young adults [190].

Furthermore, it has been reported that a daily dose of 50 mL of extra virgin olive oil (EVOO), administered over two periods of 3 weeks, decreased the plasma levels of IL-6 and CRP in stable coronary heart disease patients [191]. Besides, EVOO (50 mL) exerted acute postprandial anti-inflammatory and antioxidant effects in normolipemic, healthy subjects [192].

### Cereals and Whole Grains

Interestingly, the intake of cereal fiber was inversely associated with lower blood levels of CRP and TNF-R2 in diabetic women [193]. Moreover, concomitant reductions in serum TNF- $\alpha$  and increased plasma IL-10 were found after the consumption of whole-grain wheat (70 g/day during 8 weeks) in subjects with overweight and obesity [194]. In addition, findings from the GRAANDIOOS study showed that whole-grain wheat consumption (98 g/day for 12 weeks) may promote liver and inflammatory resilience in subjects with overweight/obesity and mild hypercholesterolemia [195].

### Legumes

Soy food consumption has been inversely related to circulating levels of inflammatory markers such as IL-6, TNF $\alpha$ , and soluble TNF receptors 1 and 2 in middle-aged Chinese women [196]. Consistently, a 6-week nutritional trial with a legume-enriched diet (a total of 24 packs of 65 g were consumed during the all the intervention phase) significantly reduced CRP concentrations in diabetic patients compared with a habitual diet [197]. Moreover, a legume-based hypocaloric diet (160–235 g/day for 8 weeks) consistently reduced pro-inflammatory status and improved metabolic features in overweight/obese subjects [198].

### Green Tea and Coffee

In obese women, green tea extract (450 mg/day) supplementation during 8 weeks improved oxidative stress biomarkers and reduced IL-6 circulating levels [199]. Also, green tea consumption (379 mg/day) by 3 months reduced serum CRP and TNF- $\alpha$  concentration in obese, hypertensive patients [200]. Furthermore, high coffee consumption (8 cups/day) exerted beneficial effects on subclinical inflammation in habitual coffee drinkers [201]. Consistently, coffee consumption was inversely associated with markers of inflammation and endothelial dysfunction in healthy and diabetic women [202]. Among older non-Hispanic Whites, heavy coffee drinkers (equal or more than 2.5 cups/day) presented lower systemic inflammation [203]. On the other hand, analyses from the ATTICA study reported an increase on inflammation markers (including IL-6, TNF- $\alpha$ , and CRP) after moderate-to-high coffee consumption (> 200 mL coffee/d), emphasizing the importance of the dose in outcomes [204].

### Dark Chocolate

Available evidence suggests that regular consumption of dark may reduce inflammation, especially in consumers of up to 1 serving (20 g) of dark chocolate every 3 days [205]. In a randomized parallel clinical trial, diabetic patients, who received dark chocolate (30 g of 84% dark chocolate during 8 weeks) along with a healthy lifestyle, had lower levels of inflammatory markers (CRP, TNF- $\alpha$ , and IL-6) compared with those subjects who only followed general lifestyle guidelines [206]. Indeed, acute dark chocolate intake (50 g) elicited anti-inflammatory outcomes both by increasing IL-10 expression and by attenuating the intracellular pro-inflammatory stress response [207]. Moreover, healthy women presented lower blood levels of CRP after the ingestion of dark chocolate (100 g per day during one week), which was not detected in men [208].

## Spices and Culinary Ingredients

Over the past several decades, several investigations have ascertained the efficacious role of spices and herbs in preventing and combating various chronic diseases [209]. The diverse range of health properties of these culinary ingredients are attributed to bioactive constituents such as sulfur-containing molecules, tannins, alkaloids, and phenolic diterpenes, with potential anti-inflammatory properties [210]. Findings of clinical trials exploring the impact of spices on inflammation status are summarized (Table 4).

## Probiotics, Prebiotics, Synbiotics, and Postbiotics

Probiotics, prebiotics, and synbiotics are either beneficial microorganisms, substrates (polysaccharides and oligosaccharides), or combinations that eventually may also alleviate inflammatory symptoms [240]. In diabetic patients, probiotic and synbiotic supplementation is recommended to decrease inflammatory manifestations by consistently reducing the circulating levels of CRP and TNF- $\alpha$  [241]. Regarding bowel disease, it has been recently reported that the use of probiotics (based on *Lactobacillus* and *Bifidobacterium*) and synbiotics can promote anti-inflammatory reactions and balance the intestinal homeostasis [242].

In addition, the anti-inflammatory effects of short-chain fatty acids (nonviable bacterial products known as postbiotics) are mediated by inhibiting the NF- $\kappa$ B pathway, Treg cell differentiation, and pro-inflammatory cytokine blockade in gut epithelial cells [243]. For example, *Lactobacillus casei* DG and derived postbiotics suppressed IL-8, IL-1 $\alpha$ , IL-6, and TLR-4 expression levels in colonic mucosa from patients with irritable bowel syndrome [244].

## Dietary Patterns

### Traditional Healthy Diets

Overall, plant-based diets have shown to improve the obesity-related inflammation status [245]. Remarkably, the beneficial effect of the vegetarian diet on blood CRP and IL-6 levels was mediated by BMI in North Americans [246]. In addition, a systematic review and meta-analysis revealed that vegetarian-based dietary patterns also lowered immune biomarkers such as fibrinogen and total leukocyte concentrations [247].

A systematic review of observational and intervention trials revealed a beneficial influence of the Nordic diet (based on staple foods from Nordic countries) on low-grade inflammation amelioration [248]. Potential mechanisms include the downregulation of pro-inflammatory genes in individuals with features of the metabolic syndrome, particularly *TNFRSF1A* and *RELA* [249].

The Southern European Atlantic Diet (SEAD) is the traditional diet of Northern Portugal and Galicia, Spain, which is characterized by greater intakes of fish, milk, potatoes, fruit, vegetable and olive oil, and red wine [250]. Overall, SEAD adherence has been associated with reduced plasma concentrations of inflammatory markers (predominately CRP) and lowered cardio-metabolic risk [251].

Regarding Asian regions, a healthy Japanese dietary pattern (rich in mushrooms, seaweed, soyabean products and potatoes, vegetables, fish/shellfish, and fruits) seems to exert anti-inflammatory effects and improve mental health in local consumers [252]. Likewise, several herbs from traditional Chinese medicine have shown to suppress pro-inflammatory pathways and control inflammation-associated diseases [253].

Furthermore, the traditional Mexican diet (TMexD) has shown to reduce the risk of systemic inflammation and insulin resistance in women of Mexican descent [254]. Specific foods of the TMexD include maize, beans, chili, squash, tomato, nopal, and onion, which are high in fiber, vitamins, minerals, and capsaicinoids, with potential anti-inflammatory and antioxidant properties [255].

In a pooled cross-sectional study, a Paleolithic diet (based on the consumption of diversity of vegetables and fruits, lean meat, fish, nuts, and sources of calcium) was associated with lower levels of systemic inflammation and oxidative stress in humans [256].

Moreover, the consumption of the DASH eating pattern (characterized by high consumption of fruits and vegetables, low-fat dairy products, and complex carbohydrates) during 6 weeks reduced the circulating levels of CRP among adolescents with metabolic syndrome [257]. In female adults, the DASH diet was cross-sectionally associated with lower serum CRP levels, but not with IL-17A concentrations in Iranians [258]. Quantitative estimations revealed that the DASH diet reduced CRP by 13% after 4 weeks of follow-up [259].

Findings from the PREDIMED trial have shown the anti-inflammatory effect of the Med-diet (rich in vegetables and fruits, fiber, and vitamins C and E) since it down-regulates cellular and circulating inflammatory biomarkers involved in atherogenesis development [260]. In this cohort, the Med-Diet reduced the serum CRP and IL-6 levels as well as endothelial and monocyte adhesion molecules and pro-inflammatory chemokines [261]. Additionally, the Med-diet (including EVOO and vegetables) decreased the plasma concentrations of TNFR60 in patients at high cardiovascular risk after 1 year of follow-up [262]. In the long term (3 years), the PREDIMED trial confirmed the anti-inflammatory effect of the Med-diet by decreasing the levels of IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$  compared to a control low-fat diet [263].



**Table 4** Clinical trials analyzing the anti-inflammatory effects of certain spices and culinary ingredients

Spice/ingredient	Study design	Dose/duration	Population	Main finding	Reference
Black cumin ( <i>Nigella sativa</i> )	RCT	2 capsules/day (500 mg each) or placebo for 8 weeks	Patients with rheumatoid arthritis Experimental group ( $n=23$ ) Placebo group ( $n=16$ )	↑ Serum IL-10 ↓ MDA and nitric oxide NS effects on blood TNF- $\alpha$	[211]
Black cumin ( <i>Nigella sativa</i> )	RCT	1000 mg oil/day or placebo for 8 weeks	Patients with Behcet's disease Experimental group ( $n=47$ ) Placebo group ( $n=42$ )	NS effects on blood TNF- $\alpha$ , IL-10, CRP, and MDA	[212]
Black cumin ( <i>Nigella sativa</i> )	RCT	3 g/day plus a low-calorie diet or placebo plus low-calorie diet for 8 weeks	45 women with obesity Experimental group ( $n=45$ ) Placebo group ( $n=45$ )	↓ Blood CRP and TNF- $\alpha$ NS effects on serum IL-6	[213]
Cardamom	RCT	3 g day <sup>-1</sup> or identical placebo for 8 weeks	Pre-diabetic subjects Experimental group ( $n=40$ ) Placebo group ( $n=40$ )	↓ Blood CRP, CRP:IL-6 ratio, and MDA	[214]
Cinnamon	RCT	3 g/day or placebo for 8 weeks	Adult patients with T2DM Experimental group ( $n=20$ ) Placebo group ( $n=19$ )	NS effects on reduction of SIRT1, IL-6, CRP, and TNF- $\alpha$ levels ↓ Plasma NF- $\kappa$ B	[215]
Cinnamon	RCT	3 glasses/day of black tea plus either 3 g/day of cardamom (group 1); 3 g/day cinnamon (group 2); 3 g/day ginger (group 3); 3 g/day of saffron (group 4); or control (only 3 glasses of black tea) for 8 weeks	Adult patients with TD2M Group 1 ( $n=42$ ) Group 2 ( $n=40$ ) Group 3 ( $n=41$ ) Group 4 ( $n=42$ ) Control ( $n=39$ )	NS effects on serum CRP (groups 1, 2, 3, and 4 vs. control)	[216]
Cinnamon	RCT	3 g/day of cinnamon (group 1); 3 g/day of ginger (group 2); or placebo for 6 weeks	Iranian female athletes ( $n=60$ )	NS effects on plasma IL-6 (groups 1 and 2 vs. placebo)	[217]
Cinnamon	RCT	2 capsules/day (each capsule contain 750 mg of cinnamon) or placebo for 12 weeks	Patients with NAFLD Experimental group ( $n=23$ ) Placebo group ( $n=22$ )	↓ Serum CRP	[218]
Cinnamon powder	RCT	4 capsules/day of 500 mg of cinnamon powder or placebo for 8 weeks	Women with rheumatoid arthritis Experimental group ( $n=18$ ) Placebo group ( $n=18$ )	↓ Blood CRP and TNF- $\alpha$	[219]
Cinnamon powder	RCT	3 capsules/day (each containing 600 mg of cinnamon) or placebo	Patients with migraine Experimental group ( $n=21$ ) Placebo group ( $n=22$ )	↓ Blood IL-6 and nitric oxide	[220]
Clove buds	RCT	1 capsule/day (250 mg of clovinox) or placebo for 2 weeks	Male social drinkers Experimental group ( $n=8$ ) Placebo group ( $n=8$ )	↓ Serum CRP, IL-6, and lipid peroxidation	[221]
Cumin essential oil	RCT	75-mg cumin essential oil or placebo thrice daily for 8 weeks	Patients with metabolic syndrome Experimental group ( $n=22$ ) Placebo group ( $n=22$ )	↓ Blood MDA NS effects on CRP and TNF- $\alpha$	[222]
Garlic extracts	RCT	3.6 g/day or placebo for 6 weeks	Healthy adults with obesity Experimental group ( $n=24$ ) Placebo group ( $n=24$ )	↓ Blood IL-6 and TNF- $\alpha$ (borderline)	[223]

**Table 4** (continued)

Spice/ingredient	Study design	Dose/duration	Population	Main finding	Reference
Garlic extracts	RCT	400 mg twice a day or placebo for 8 weeks	Peritoneal dialysis patients Experimental group ( <i>n</i> = 19) Placebo group ( <i>n</i> = 21)	↓ Serum IL-6, CRP, and ESR	[224]
Garlic powder	RCT	2.1 g/day or placebo for 3 months	Overweight and smoking subjects Experimental group ( <i>n</i> = 28) Placebo group ( <i>n</i> = 26)	NS effects on serum TNF- $\alpha$ and CRP	[225]
Garlic powder	RCT	300 mg/day or placebo for 8 weeks	Hemodialysis patients Experimental group ( <i>n</i> = 70) Placebo group ( <i>n</i> = 70)	↓ Plasma homocysteine and oxLDL	[226]
Garlic powder	RCT	400 mg/day or placebo for 15 weeks	Patients with NAFLD Experimental group ( <i>n</i> = 47) Placebo group ( <i>n</i> = 51)	↓ Blood CRP	[227]
Ginger	RCT	2 tablets/day (1 g ginger in each) or placebo for 2 months	Adult patients with T2DM Experimental group ( <i>n</i> = 32) Placebo group ( <i>n</i> = 32)	↓ Blood CRP and TNF- $\alpha$ NS effects on serum IL-6	[228]
Ginger	RCT	4 tablets 500 mg (2 g) ginger or placebo twice a day for 8 weeks	Adult patients with T2DM and chronic periodontitis Experimental group ( <i>n</i> = 21) Placebo group ( <i>n</i> = 21)	↓ Plasma CRP, IL-6, and TNF- $\alpha$	[229]
Green cardamom	RCT	Two 500 mg capsules three times/day or placebo for 3 months	Overweight or obese patients with NAFLD Experimental group ( <i>n</i> = 43) Placebo group ( <i>n</i> = 44)	↓ Serum CRP, TNF- $\alpha$ , IL-6, and Sirt1	[230]
green cardamom plus low-calorie diet	RCT	3 g/day plus low-calorie diet or placebo (only low-calorie diet) during 16 weeks	Obese women with PCOS Experimental group ( <i>n</i> = 99) Placebo group ( <i>n</i> = 95)	↓ Serum CRP, TNF- $\alpha$ , and IL-6 ↓ Expression levels of <i>TNF-<math>\alpha</math></i> and <i>CRP</i> genes	[231]
Green cumin essential oil	RCT	50 mg/day (group 1); 100 mg/day (group 2); or placebo for 8 weeks	Adult patients with type 2 diabetes Group 1 ( <i>n</i> = 33) Group 2 ( <i>n</i> = 33) Placebo group ( <i>n</i> = 33)	NS effects on blood CRP, TNF- $\alpha$ , and adiponectin (groups 1 and 2 vs. placebo)	[232]
Herbal formulation	RCT	Curcumin (300 mg), gingerols (7.5 mg), and piperine (3.75 mg) or naproxen twice a day for 4 weeks	Patients with knee osteoarthritis Herbal formulation ( <i>n</i> = 30) Naproxen ( <i>n</i> = 30)	NS effects on plasma prostaglandin E2 levels	[233]
Onion	RCT	1 capsule of peel extracts (100 mg quercetin/day) or placebo for 12 weeks	Healthy overweight and obese women Experimental group ( <i>n</i> = 18) Placebo group ( <i>n</i> = 19)	NS effects on plasma leptin, TNF- $\alpha$ , IL-4, and visfatin	[234]
Turmeric (curcumin)	RCT	1 g/day or placebo for 4 weeks	Sulfur mustard-exposed patients Experimental group ( <i>n</i> = 46) Placebo group ( <i>n</i> = 50)	↓ Serum IL-8 and CRP NS effects on IL-6	[235]
Turmeric (curcumin)	RCT	2 g/day or placebo for 8 weeks	Patients with NAFLD Experimental group ( <i>n</i> = 32) Placebo group ( <i>n</i> = 32)	↓ Plasma MDA	[236]

**Table 4** (continued)

Spice/ingredient	Study design	Dose/duration	Population	Main finding	Reference
Turmeric (curcumin)	RCT	500 mg/day or placebo for 8 weeks	Women with moderate physical activity levels Experimental group (n=32) Placebo group (n=33)	↓ Blood MDA, CRP, and LDH	[237]
Turmeric (curcumin)	RCT	500 mg/day or placebo for 10 weeks	Overweight and obese adolescent girls Experimental group (n=30) Placebo group (n=30)	↓ Serum IL-6 and CRP	[238]
Turmeric (curcumin)	RCT	1500 mg/day plus lifestyle or placebo (only lifestyle) for 12 weeks	Patients with NAFLD Experimental group (n=25) Placebo group (n=25)	NS effects on NF-kB activity	[239]

RCT randomized controlled trial, NS no significant, T2DM type 2 diabetes mellitus, NAFLD non-alcoholic fatty liver disease, PCOS polycystic ovary syndrome, MDA malondialdehyde, NF-kB transcription nuclear factor kappa B, CRP C-reactive protein, IL-6 interleukin 6, TNF- $\alpha$  tumor necrosis factor alpha, IL-8 interleukin 8, IL-4 interleukin 4, IL-10 interleukin 10, SIRT1 sirtuin 1, ESR erythrocyte sedimentation rate, oxLDL oxidized LDL, LDH lactate dehydrogenase

### Westernized Diets and Ultra-processed/Discretionary Foods

Overall, the adoption of Western-type diets (WTD), with high contents of unhealthy fats, refined grains, sugars, and salt, evokes a state of chronic metabolic inflammation [264]. In this regard, a WTD showed positive associations with markers of inflammation and endothelial dysfunction in women from the Nurses' Health Study I cohort [265]. Also, a comparable WTD score positively correlated with CRP and IL-6 pro-inflammatory markers among Iranian women [266].

Interestingly, positive associations were found between the consumption of ultra-processed foods (UPF), which contain high amounts of free sugars, total fats, SFA, TFA, and sodium, and serum CRP levels among Brazilian women [267]. Likewise, Brazilian adolescents in the upper tertile of UPF ( $\geq 30\%$  of total energy) had increased circulating IL-8 concentrations when compared with adolescents in tertile 1 ( $\leq 15.9\%$  of total energy) of UPF [268].

Furthermore, a poor diet quality (considering habitual discretionary food consumption such as sweets, cakes, soft drinks, and fried potatoes) was associated with increased inflammation measured as plasma CRP and erythrocyte sedimentation rates in Swedish patients with rheumatoid arthritis [269].

### Chrononutrition Patterns

Recent progress in the analysis of circadian rhythms and nutrition (referred as "chrononutrition") has revealed that the time of day when food is consumed may affect metabolic homeostasis and immune function [270]. In this context, a significant association between breakfast skipping and

elevated serum CRP concentrations was reported in Chinese adults with poor diet quality [271]. In a randomized controlled crossover trial, breakfast skipping induced a higher activation of the NLRP3 inflammasome in human peripheral blood mononuclear cells and monocytes [272].

Intermittent fasting (IF), where individuals fast on consecutive or alternate days, has improved systemic inflammation in males with obesity [273]. Nevertheless, a transient elevation of biomarkers of macrophage infiltration in adipose tissue (CD40+) and skeletal muscle (CD163+) were found after IF in women with overweight or obesity [274].

Available evidence suggests that time-restricted eating (TRE), an alternative chrononutritional approach based on the consolidation of the total calorie intake during the active phase of the day, may modulate a variety of metabolic disease risk factors including exacerbated inflammation [275]. Indeed, it has been postulated that TRE as part of a periodized nutrition plan could be beneficial for reducing inflammation and induce a protective effect on some components of the immune system [276].

Interestingly, greater reductions in blood CRP levels were found in patients with metabolic syndrome after following an alternate day fasting (ADF), which consists of a "fast day," where caloric intake is limited, alternating with a "feed day," where food is consumed ad libitum [277]. Moreover, ADF reduced the plasma levels of sICAM-1 (an age-associated inflammatory marker) in healthy non-obese subjects [278].

Additionally, it has been reported that late eating, which refers to delay in the timing of meals (commonly the main meal of the day or the dinner) may increase the risk for developing cardiometabolic diseases [279]. In fact, late eating was associated with abdominal obesity, inflammatory

biomarkers such as IL-6 and CRP, and circadian-related disturbances in children [280].

### Personalized Anti-inflammatory Nutritional Strategies

The integrative analysis of precision variables (age, sex, body phenotype, habitual dietary intake, physical activity levels, and lifestyle) together with personalized issues (genetic background, epigenetic signatures, microbiota composition, gene expression profiles, and metabolomic fingerprints) may contribute to the prescription of more personalized treatments seeking to improve the nutritional and medical management of inflammation (Fig. 2). For example, there is evidence that genetic variation may predispose to inflammatory conditions through interactions with environmental factors, such as diet, modulating the individual susceptibility to developing inflammation-related chronic and acute diseases [281]. Also, epigenetic signatures (including DNA methylation, miRNA expression, and histone modifications) play a fundamental role in inflammatory gene transcription [282]. Of note, a microbiota-based regression model has been able to predict the obesity-related inflammatory status in humans, which could be a useful tool in the precision management of inflammobesity [283]. Moreover, the expressions of genes with pro- and anti-inflammatory effects ultimately determine the outcome of inflammation [284]. Furthermore, metabolomics is an integrative approach that can be used to dissect the local and systemic metabolic consequences of inflammation, providing novel insights into the regulation of inflammatory diseases [285]. The application of these instruments are helping to elucidate unique and specific inflammo-metabotypes, expanding our understanding of the complexity and diversity of human metabolism [286]. Overall, these novel scientific insights are leading to the design and implementation of precision medicine/nutrition strategies for the prevention and control of prevalent chronic diseases with an inflammatory background [287].

### Concluding Remarks

Nutrition is critical for life and well-being not only by contributing to disease prevention, health maintenance, and morbid conditions management, but also as a defense against endogenous and exogenous harmful factors including inflammation/oxidative stress or immune system dysfunctions. On the one hand, pro-inflammatory nutritional factors include the high consumption of foods rich in simple carbohydrates (fructose), SFA, TFA, cholesterol, and animal protein as well as habitually skipping breakfast and late overeating. On the other hand, potential anti-inflammatory

compounds encompass MUFA, PUFA, antioxidant vitamins and minerals, bioactive molecules (polyphenols), specific foods (dairy products, whole-grains, fish, oilseeds, fruits and vegetables, edible insects, legumes, green tea, and coffee), culinary spices (cinnamon, ginger, black cumin, garlic, and turmeric) and some chrononutrition features including intermittent fasting and time-restricted eating (Fig. 1). Because inconsistencies and discrepancies between studies exist, further research in this field is still required, taking into account critical aspects of heterogeneity including type of population (ancestry), minimum and maximum levels and adverse effects, cooking methods, physiopathological status, and times of intervention. However, current evidence is contributing to the understanding of the relationship between nutrition and meta-inflammation, providing novel insights and potential targets for the control and management of communicable and non-communicable diseases.

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### Declarations

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