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Bioactive compounds with effects on inflammation markers in humans

FLÁVIA TRONCON ROSA[1], M. ÁNGELES ZULET[2], JULIO SÉRGIO MARCHINI[1], & J. ALFREDO MARTÍNEZ[2]

[1]*Division of Clinical Nutrition, Department of Internal Medicine, Faculty of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil, and* [2]*Department of Nutrition and Food Sciences, Physiology and Toxicology, University of Navarra, Pamplona, Spain*

Abstract
Obesity and other chronic diseases are accompanied by adipose tissue, liver, pancreas, muscle and brain low-grade chronic inflammation. Indeed, the obese condition and metabolic syndrome are characterized by an increased expression of inflammatory cytokines and infiltration of immune cells in adipocytes. The inflammatory response promotes the activation of transcriptional factors and pro-inflammatory cytokines, which can lead to an unresolved inflammatory response associated with an inhibition of insulin signalling and high risk for cardiovascular events. Epidemiological and intervention studies have been carried out to find out dietary patterns, foods and bioactive compounds with protective anti-inflammatory actions. The most studied compounds are polyphenols, especially isoflavone and anthocyanin, but quercertin, catechin and resveratrol have also been investigated. Furthermore, some studies have reported the effects of milk peptides, plant sterol and stanol, L-carnitine and α-lipoic acid on inflammatory processes. This review aimed to collect and discuss those relevant studies reported in the scientific literature following a systematic scientific search about the effect of such bioactive compounds on inflammation in humans.

Keywords: *inflammation, bioactive compounds, functional foods, polyphenols, bioactive peptides, review*

Introduction

Obesity is often associated with a low-grade chronic inflammation that occurs in tissues such as adipose tissue, liver, pancreas, muscle and brain (De Souza et al. 2005; Ehses et al. 2007; Zulet et al. 2007). The mechanisms that initiate the inflammatory signalling in obesity are partly unknown, but some hypotheses and theories have arisen (Gregor and Hotamisligil 2011). One concept is that the nutrients themselves are inflammatory and so a physiological slight immune response is activated while they are metabolized (Wellen et al. 2007; Gregor and Hotamisligil 2011). Alternatively, it has been suggested that the nutrient *per se* is not inflammatory, but an overfeeding or high fat intake could be wrongly identified as an external factor/pathogen that can trigger an inflammatory response by increasing the expression of Toll-like receptors (Shi et al. 2006). Another claimed possibility is that the increased adipocyte death in obese tissue recruits macrophages to clear away dead cells and repair tissue function eliciting a pro-inflammatory phenomenon (Cinti et al. 2005; Baker et al. 2011). Finally, the increased intestinal permeability that occurs after feeding is greater in obese subjects and may facilitate the entrance of a more constant inflammatory signal with nutrients (Gregor and Hotamisligil 2011).

The inflammatory trigger could be a variety of stimuli [tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1), T-cell activation signals, reactive oxygen intermediates, etc.], which promotes the activation of nuclear factor *kappa* B (NF-κB), the central regulator of inflammation (Baeuerle and Henkel 1994; May and Ghosh 1998). Indeed, NF-κB is a transcription factor located at the cytoplasm of unstimulated immune cells being bound to an inhibitory protein IκB (IκBα and IκBβ).

Correspondence: J. Alfredo Martínez, Edificio de Investigación, Universidad de Navarra, Calle Irunlarrea, 1, 31008 Pamplona, Navarra, Spain. Tel.: + 34 948 425600 Ext. 6424. Fax + 34 948 425740. E-mail: jalfmtz@unav.es

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The stimulation of these cells induces IκB phosphorylation by the cellular kinase complex IκB kinase (IKK), resulting in the degradation of IκB and translocation of subunits of NF-κB (p50/p65) to nucleus (Alkalay et al. 1995; Li et al. 1999). Another transcription factor that acts in assistance to NF-κB in the regulation of the synthesis and intra-cellular signalling of inflammation mediators is the mitogen-activated protein kinase (MAPK; Santangelo et al. 2007). The MAPK functions involve the regulation of cellular processes such as proliferation, differentiation, motility and survival (Chang and Karin 2001). It occurs by a cascade of serine/threonine protein kinases and the p38 proteins (p38 MAPK) and the Jun N-terminal kinases (JNK) pathways have been shown to exhibit anti-inflammatory effects (Chang and Karin 2001; Kaminska 2005). These transcription factors bind to the promoter regions of genes encoding for immune and inflammatory responses such as TNF-α, monocyte chemoattractant protein-1 (MCP-1), IL-8, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), plasminogen activator inhibitor-1 (PAI-1) as described elsewhere (May and Ghosh 1998; Gregor and Hotamisligil 2011). The increased expression of inflammatory cytokines and infiltration of immune cells such as macrophages, mast cells and natural killer cells in adipocytes and metabolic tissues can lead to an unresolved inflammatory response, inhibition of insulin signalling and a higher risk of cardiovascular disease (CVD; Hermsdorff et al. 2010a; Baker et al. 2011).

Besides cytokines, chemokines and vascular adhesion molecules, another class of inflammation mediators is the lipids that include eicosanoids, omega-3 fatty acid derivatives, phospholipid mediators, sphingolipid derivatives and oxidized lipids (Ouchi et al. 2011). They are derived from different pathways and also contribute to the pathophysiology of diseases that originate with an inflammation process (Nomikos et al. 2007).

Cell culture experiments, epidemiological surveys and intervention studies in animals and humans have been carried out to find and characterize dietary patterns, foods and bioactive compounds that could be applied to prevent or counteract the inflammation-mediated metabolic diseases (Hermsdorff et al. 2009, 2010c, 2011a; Ramel et al. 2010; Vincent et al. 2010). Thus, the aim of this systematic review was to report and critically discuss recent and relevant studies from the scientific literature about the effects of some bioactive compounds on inflammation in humans.

Methods

The scientific database used was the US National Library of Medicine PUBMED. The search was limited to the human studies typed as Clinical Trial, Randomized-Controlled Trial, Controlled Clinical Trial and Multicenter Study published from January 2000 to June 2011, with adults as subjects. The keywords applied were combinations of 'inflammation' and 'anti-inflammatory' with words that could encompass bioactive compounds such as 'nutrient', 'food', 'bioactive compounds' and 'functional food'. This search found 637 articles from which 99 referred to bioactive compounds. The identified compounds were recombined with the words 'inflammation' and 'anti-inflammatory' and resulted in 9 articles about quercetin, 20 about isoflavone, 13 about anthocyanin, 14 about resveratrol, 10 about cathechin and proanthocyanidin, 4 about bioactive milk peptides, 7 about L-carnitine, 9 about plant sterol and plant stanol and 5 about α-lipoic acid. From these, acute response studies and those without placebo or control group were excluded. Also, studies that were not indexed by 'inflammation' in the database, but those that were referred by original articles and evaluated any marker of inflammation were also included. Animal and *in vitro* studies were included solely as supportive information to elucidate the mechanism of action of the compounds.

The articles included in this review are all classified in the levels I and II-1 of the hierarchy of research design previously proposed by the Task Force (Harris et al. 2001). Based on the criteria for grading the internal validity of individual studies (Harris et al. 2001) and other selected criteria such as sample size, diet control, biomarkers analysed and discussion of the results, the most relevant studies were discriminated and given in the Tables.

Results and discussion

Flavonol: quercetin

Quercetin is a flavonoid of the subclass of flavonols, which is widely present in vegetable sources such as onion, apple, broccoli and lettuce, but the quantity consumed in a daily diet is generally low (Manach et al. 2005). The benefits of quercetin supplementation in humans are a relatively new issue in the health area. Concerning inflammation, a number of studies evaluated the effects of quercetin supplementation on different health conditions, age and sex (Table I).

A suggested mechanism by which quercetin could reduce inflammation processes as well as gene expression and production of TNF-α involves the modulation of IκB phosphorylation and NF-κB signal transduction (Nair et al. 2006). The authors, through an *in vitro* study, demonstrated that quercetin decreased the phosphorylation of IκB and inhibited the NF-κB gene expression in peripheral mononuclear blood cells (Nair et al. 2006) that is subsequently involved in the downregulation of endogenous TNF-α, IL-1β, IL-6 and inducible nitric oxide synthase (iNOS) expression (Cho et al. 2003; Comalada et al. 2005; Nair et al. 2006).

Table I. Trials investigating the effects of quercetin supplementation on inflammation markers in human.

Authors	Subjects and characteristics	Intervention design/groups	Period (wk)	Results/outcomes
Egert et al. (2008)	$n = 36$ men and women BMI 19–25 kg/m^2 19–40 years	Groups: A (50-mg/d quercetin), B (100 mg/d quercetin) and C (150 mg/d quercetin). Crossover trial with 2-wk wash-out period.	2	No significant changes on TNF-α.
Bae et al. (2009)	$n = 20$ rheumatoid arthritis patients BMI 22.3 ± 3.1 kg/m^2 52.1 ± 10.3 years	Groups: quercetin (498 + 399 mg vitamin C/d); lipoic acid (900 mg/d) or placebo. Crossover trial with 2-wk wash-out period.	4	No significant changes were observed for IL-6, IL-1β, TNF-α and CRP.
Egert et al. (2009)⋆	$n = 93$ men and women BMI 25–35 kg/m^2 25–65 years	Groups: 150-mg quercetin/d, or placebo. Crossover trial with 5-wk wash-out period.	6	No significant decrease in hs-CRP and hs-TNF-α compared to placebo.
Heinz et al. (2010)⋆	$n = 120$ healthy women BMI 26.6 ± 1.2 kg/m^2 30–79 years	Groups: 500-mg quercetin/d (Q-500), 1000-mg quercetin/d (Q-1000) or placebo.	12	No significant changes on IL-6 and TNF-α and total leucocytes, lymphocytes and neutrophil counts.
Egert et al. (2010)⋆	$n = 93$ men and women BMI 25–35 kg/m^2 25–65 years	Groups: 150-mg quercetin/d or placebo. Crossover trial with 5-wk wash-out period. Individuals were classified into the following three genotypes: (1) apo E2 group, (2) apo E3 group and (3) apo E4.	6	Decrease in serum TNF-α, in apo E3 and E4 subgroups, but no effects on serum CRP.
Knab et al. (2011)⋆	$n = 1.023$ men and women BMI 18.5–24.9 kg/m^2 18–85 years	Groups: Q-500 (500-mg quercetin, 125-mg vitamin C, 5-mg niacin/d), Q-1000 (1000-mg quercetin, 250-mg vitamin C and 10-mg niacin/d) or placebo.	12	No significant changes on IL-6, IL-10, granulocyte colony-stimulating factor, MCP-1, TNF-α and CRP.

Notes: wk, weeks; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; IL-1β, interleukin-1β; CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein-1.
⋆The asterisk denotes those more relevant studies.

Despite the number of human intervention studies that have evaluated quercetin as an anti-inflammatory supplement, almost all of them did not observe beneficial effects (Table I). Thus, Knab et al. (2011) proposed a high dose of quercetin (500 and 1000 mg) associated with vitamin C and niacin, but they did not find improvements on inflammation markers.

Egert et al. (2009) were also not able to demonstrate marked different responses in hs-TNF-α in overweight/obese subjects, with traits of metabolic syndrome after a 150 mg of quercetin/day (d) supplementation. On the other hand, these authors made a second analysis with the same group, by distributing the subjects according to their most frequent ApoE allele and showed significant reductions on hs-TNF-α by quercetin in ϵ3 and ϵ4 allele carriers, but no changes on hs-C-reactive protein (hs-CRP; Egert et al. 2010). ApoE is an important protein involved in the lipoprotein metabolism and several studies indicate that subjects carrying the ϵ4 alleles present higher oxidative stress and pro-inflammatory state (Jofre-Monseny et al. 2007a, b; Vitek et al. 2009).

Although quercetin supplementation has shown anti-inflammatory effects on animals (Dias et al. 2005; Stewart et al. 2008) and *in vitro* experiments (Cho et al. 2003; Comalada et al. 2005), the results have not yet been reproduced in humans. An important issue is the bioavailability of quercetin. The intestinal and hepatic metabolization of quercetin results in glucuronidated, sulphated and methylated derivatives (Day et al. 2001). Decreased TNF-α mRNA levels, TNF-α secretion, mRNA and protein levels of iNOS as well as IL-1β, IL-6 and MIP-1α mRNA levels and inhibition of NF-κB transactivation were observed after quercetin and isorhamnetin treatment of lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages, but not after quercetin-3-glucuronide (Boesch-Saadatmandi et al. 2011). In humans, Egert et al. (2011) found that quercetin from enriched cereal bars was more bioavailable than quercetin powder-filled capsules because of the higher production of methylated metabolites (isorhamnetin and tamarixetin) after the intake of cereal bars. The methylation instead of glucuronidation of quercetin is associated with greater effects (Boesch-Saadatmandi et al. 2011).

Besides, the volunteers of such studies were, predominantly, healthy (Egert et al. 2009, 2010). Thus, future studies must be designed to investigate the quercetin effects in patients with elevated levels of inflammation and oxidative stress markers.

Isoflavones: genistein and daidzein

Isoflavones are compounds structurally similar to estradiol and thereafter have been classified as phytoestrogens (Rostagno et al. 2009). Three forms of this polyphenol are genistein, daidzein and glycitein. The high-binding affinity of these compounds to estrogen receptor makes them promising substances to

exert putative hormone properties. This alternative therapeutic approach based on isoflavone supplementation has been considered because important studies demonstrated an early increased risk of hormone replacement therapy (HRT) on coronary artery events (Hulley et al. 1998; Manson et al. 2003). Moreover, some studies have associated the use of hormone replacement therapy (HRT) with increased levels of C-reactive protein (CRP; Cushman et al. 1999; Pradhan et al. 2002; Lakoski et al. 2005).

The application of isoflavone was evaluated by Huang et al. (2005) in humans and *in vitro* monocyte culture cells. The authors demonstrated the inhibition of LPS-stimulated increase in TNF-α by up to 65.7% in the presence of daidzein and genistein and the inhibition was stronger with lower (10 nM) than higher (1000 nM) concentrations. The researchers also investigated the consumption of soymilk by healthy post-menopausal women for 16 weeks and found reductions in the serum levels of TNF-α and IL-1α as well as decreased proportion of monocytes (14%) in blood without affecting white blood cell count. They suggest that these reductions are associated with the estrogenic action of genistein and daidzein. However, isoflavone did not seem to decrease or increase inflammation markers (Table II) exerting neutral effect on vascular health (Nikander et al. 2003).

The controversial results related to cell adhesion molecules may be influenced by the time of supplementation and/or dose offered (Greany et al. 2008). A 2-year supplementation to osteopenic women with 54 mg of genistein resulted in the significant reductions of VCAM and ICAM compared to placebo, besides improvements in fasting glycemia, fasting insulin, homeostatic model assessment (HOMA) index and F2-isoprostane, a marker of oxidative stress (Atteritano et al. 2007).

The bioavailability of isoflavone can also influence the variability of results (Greany et al. 2008). Equol is a gut metabolite of daidzein considered to present higher affinity to estrogen receptor than other subtypes of isoflavones and the ability to produce equol seems to vary from person to person (Rowland et al. 2000). However, Hall et al. (2005) did not find differences in inflammatory response to isoflavone or placebo supplementation comparing equol producers (24-h urinary excretion >0.45 mg/d) or non-equol producers. On the other hand, Nikander et al. (2003) found significant reductions in the levels of E-selectin in subjects who presented changes in plasma daidzein and genistein higher than 861 and 363 nmol/l, respectively. E-selectin is a product of endothelial cells whose lower levels could be beneficial for vascular health. Almost all studies in humans use the soy protein or soymilk as matrix, but the isolated isoflavone genistein and daidzein could show better results.

Genotypic variation on estrogen receptor gene ERβ *Alu*I showed different responses to isoflavone intake (Hall et al. 2005). Women with the variant AA genotype presented reductions on VCAM-1 levels after isoflavone supplementation compared to homozygous wild type (GG) or heterozygous (GA) genotypes.

The lack of positive results on inflammation markers is also considered to be due to the healthy and relatively normal body weight of women profile (Charles et al. 2009). The effects seem to be greater in persons with hyperlipidaemia consuming suboptimal diets with low antioxidant sources such as fruits and vegetables (Steinberg et al. 2003).

Anthocyanin

Other subclasses of flavonoids are the anthocyanins found in berry fruits such as cranberries, chokeberries and blueberries as a red and blue pigment. These fruits have been studied due to the high content of these flavonoids and because their compositions may have antioxidant and anti-inflammatory actions (Naruszewicz et al. 2007; Basu et al. 2010a, 2011a). The chokeberry fruit has great content of anthocyanins, procyanidin, phenolic acids, as well as quercetin contents (Oszmianski and Wojdylo 2005), which rise the interest to study it in post-myocardial infarction (Naruszewicz et al. 2007). In this experiment, the patients were supplemented with an extract of the *Aronia melanocarpa* species with a mean composition of 25% anthocyanins, 50% monomeric and olygomeric procyanidins and 9% phenolic acids. The treatment group showed mean reductions of 30% on hsIL-6 and 23% on hs-CRP levels besides the lowered levels of SCAM, MCP-1 and increased adiponectin. The authors suggested that these results are due to the antioxidant property as demonstrated by a significant 38% reduction of 8-isoprostans and 29% of oxidized forms of low density lipoprotein (LDL) (Naruszewicz et al. 2007).

Another study (Karlsen 2007) investigated the supplementation of purified anthocyanins isolated from bilberry (*Vaccinium myrtillus*) and blackcurrant (*Ribes nigrum*). The consumption by healthy adults of 300 mg/d, approximately equivalent to 100 g of fresh bilberries, decreased some NF-κB-related inflammatory chemokines [IL-8 and regulated upon activation, normal T-cell expressed and secreted (RANTES)] and some inducers of NF-κB activation [interferon-α (IFN-α), IL-4 and IL-13]. The researchers also found lowered levels of CRP, IL-6, IL-15 and monokine inducible by IFN-γ (MIG), but increased levels of TNF-α in volunteers at an increased risk of CVD, after 4 weeks of supplementation with 330 mL/d of bilberry juice (Karlsen et al. 2010).

Basu et al. (2010b) evaluated cell adhesion molecules as markers of inflammation after 8 weeks of strawberry beverage supplementation, and found decreased levels of VCAM but no differences on ICAM compared to control. On the other hand, the same authors did not demonstrate significant changes on the markers of inflammation after consumption of

Table II. Trials investigating the effects of isoflavone supplementation on inflammation markers in human.

Authors	Subjects and characteristics	Intervention design/groups	Period	Results/outcomes
Jenkins et al. (2002)	$n = 21$ men and women BMI 25.3 ± 0.5 kg/m^2 62 ± 2 years	Groups: control diet, low-isoflavone soy food phase (10 mg/d of isoflavone), and high-isoflavone soy food phase (73 mg/d). Crossover trial with 2-wk wash-out period.	1 m	No differences in CRP and TNF-α, but an increase in IL-6 at high isoflavone compared to control.
Blum et al. (2003)	$n = 24$ hypercholesterolaemic post-menopausal women 55 ± 5 years	Groups: supplemented with 25 g of soy protein isolated isoflavones or total milk protein. Crossover trial with 1-m wash-out period.	6 wk	No reductions in vascular markers of inflammation ICAM, VCAM, E-selectin, P-selectin and sIL-2R.
Steinberg et al. (2003)*	$n = 28$ post-menopausal women BMI ~24.5 kg/m^2 ~ 55 years	Groups: 25 g/d of isolated soy protein, 107.67 mg of isoflavone (55-mg genistein, 47-mg daidzein, 5-mg glycitein); stanol washed isolated soy protein, 1.82 mg of isoflavone and milk protein. Crossover trial with 4-wk wash-out period.	6 wk	No differences were observed for endothelin-1, VCAM-1 and ICAM-1, E-selectin or NOx among the treatment groups.
Nikander et al. (2003)	$n = 56$ post breast cancer treatment women BMI 21.2–33.6 kg/m^2 35–69 years	Groups: tablets of 114 mg of isoflavone/d (33 mg of glycitein, 21 mg of daidzein and 3 mg of genistein) or placebo. Crossover trial with 2-m wash-out period.	3 wk	No effects on CRP, E-selectin and NOx levels.
Teede et al. (2004)	$n = 50$ post-menopausal women BMI ~25 kg/m^2 50–75 years	Groups: supplemented with 40-g powdered soy protein isolate (118-mg isoflavone/d) or placebo.	3 wk	No changes in CRP compared to placebo group.
Hall et al. (2005)*	$n = 117$ post-menopausal women BMI 20–32 kg/m^2 45–70 years	Groups: supplemented with 2 cereal bars/d enriched with 50 mg of isoflavone extract (genistein-to-daidzein ratio of 2:1) or placebo. Crossover trial with 8-wk wash-out period.	8 wk	No effects on plasma VCAM-1, ICAM-1, E-selectin, MCP-1, endothelin-1 and vWF concentrations.
Hilpert et al. (2005)	$n = 32$ men and post-menopausal women BMI 20–32 kg/m^2 45–70 years	Groups: diet containing 25-g/d soy proteins isolate (90-mg/d isoflavones) or 25-g/d milk protein isolate. Crossover trial with 2-wk wash-out period. Individuals were also classified as CRP status defined as high (>3.5 mg/L) or low (<3.5 mg/L).	6 wk	CRP and IL-6 concentrations did not differ between the groups even in the high CRP group.
Ryan-Borchers et al. (2005)*	$n = 52$ post-menopausal women BMI ~27 kg/m^2 50–65 years	Groups: cow milk plus placebo; soy milk plus placebo (~71-mg isoflavones/d); or cow milk and isoflavone tablets (~70-mg isoflavones/d).	16 wk	No significant influences on the concentrations of IFN-γ, IL-2, or TNF-α and CRP.
Atteritano et al. (2007)*	$n = 389$ osteopenic post-menopausal women BMI ~ 25 kg/m^2 49–67 years	Groups: supplemented with 54 mg of genistein/d in tablets or placebo.	24 m	Significant reductions in VCAM and ICAM compared to placebo.
Törmälä et al. (2008)*	$n = 36$ post-menopausal women on tibolone treatment BMI < 33 kg/m^2 47–68 years	Groups: 52 g of soy protein powder (63-mg genistein, 43-mg daidzein, 6-mg glycitein and 112-mg isoflavones) or milk protein powder. Crossover trial with 4-wk wash-out period. Women were classified for high or low equol producer (four-fold rise in serum equol after 1-wk consumption of a soy drink).	8 wk	No reductions in levels of CRP, ICAM or VCAM but significant decrease in P-selectin after soy supplement in equol producers.
Greany et al. (2008)*	$n = 34$ post-menopausal women BMI 18–36 kg/m^2 47–69 years	Groups: supplemented with 0.38 g of soy protein isolate/kg weight containing 1.16-mg isoflavones/g powder (57% genistein, 34% daidzein and 9% glycitein) or milk protein isolate. Crossover trial with 2-wk wash-out period.	6 wk	Hcy, CRP, sE-selectin, VCAM-1 and ICAM-1 were not different between soy and milk treatments.
Charles et al. (2009)*	$n = 75$ healthy post-menopausal women ~ 57 years	Groups: supplemented with 20 g of soy protein powder containing 160 mg of isoflavones (genistein 64 mg, daidzein 63 mg and glycitein 34 mg) or placebo.	12 wk	No effects on leptin, resistin, IL-6 and TNF-α, but small increase in adiponectin levels.

TABLE II – *continued*

Authors	Subjects and characteristics	Intervention design/groups	Period	Results/outcomes
Beavers et al. (2009)*	$n = 31$ post-menopausal women BMI 19–35 kg/m^2 40–60 years	Groups: supplemented with three servings of soy milk (~90 mg of isoflavone) or dairy milk. Crossover trial with 4-wk wash-out period.	4 wk	No effects on IL-1β, IL-6 and TNF-α levels.
Napora et al. (2011)	$n = 33$ men undergoing medical or surgical ADT BMI ~ 29 kg/m^2 > 21 years	Groups: supplemented with 20 g of soy protein powder containing 160 mg of isoflavones (genistein 64 mg, daidzein 63 mg and glycitein 34 mg) or placebo.	12 wk	No changes in IL-6, IL-6R, TNF-α, sTNF-α RI, sTNF-α RII, and CRP or on leptin, resistin and adiponectin.

Notes: wk, weeks; m, months; CRP, C-reactive protein; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; ICAM, intercellular cell adhesion molecule; VCAM, vascular cell adhesion molecule; sIL-2R, interleukin-2 receptor; NOx, nitric oxide-derived products (nitrite and nitrato); MCP-1, monocyte chemoattractant protein-1; vWF, von Willebrand factor; IFN-γ, interferon-γ; IL-2, interleukin-2; Hcy, homocystein; IL-6R, interleukin-6 receptor (sp130); sTNF-α RI and sTNF-α RII, TNF-α receptor I and receptor II; ADT, androgen deprivation therapy.
*The asterisk denotes those more relevant studies.

50 g of freeze-dried blueberry (approximately 350 g of fresh fruit) by obese subjects during 8 weeks (Basu et al. 2010a).

Although controversial results were observed when freeze-dried fruits are supplemented (Table III), reductions in some markers of inflammation and of endothelial function were observed when the compound was offered as an extract of the fruit or isolate anthocyanin.

Also, the different food sources (blueberry, bilberry, chokeberry, elderberry, black rice pigment, etc.) could be an explanation to the controversial results as well as the periods of exposure to anthocyanin foods in each study and baseline inflammation status of the volunteers. Anthocyanin seems to be a promising substance to be applied even to prevent or to counteract inflammation process, since results were found in healthy people (Karlsen 2007; Kaspar et al. 2011) and also in patients with metabolic syndrome (Basu et al. 2010b) and CVD (Naruszewicz et al. 2007; Wang et al. 2007; Karlsen 2010).

Stilbenes: resveratrol

Resveratrol, a polyphenol from the stilbene class, is one of the many phenols of red wine to which the beneficial effects have been attributed (Vang et al. 2011).

Some epidemiological studies have found a lower CVD risk after moderate consumption of some alcohol beverages (Klatsky et al. 1986; Gaziano et al. 1993). Intervention studies found effects on blood lipids, especially increasing high density lipoprotein (HDL) cholesterol (Badia et al. 2004; Sacanella et al. 2007); on fibrinolytic activity and decreasing platelet aggregation (Gaziano et al. 1993); as well as anti-inflammatory actions (Estruch et al. 2004; Blanco-Colio et al. 2007; Sacanella 2007) after alcoholic drink intake. Human intervention studies compared the consumption of red wine and other alcohol beverages with the low content of polyphenols (white wine, brandy, rum and gin) or no content of polyphenol (vodka) and found better results after red wine consumption followed by those beverages with the low content of polyphenols (Badia et al. 2004; Estruch et al. 2004; Sacanella 2007).

Sacanella et al. (2007) explored whether 20 g of alcohol/d as red or white wine (equivalent to two cups of 100 mL) has the same beneficial effects in healthy women. The authors found significant reductions in inflammation markers by both red and white wine consumption with greater reductions in VCAM and E-selectin. Also, red wine intake prevented monocyte adhesion to TNF-α stimulated endothelial cells. Compared to baseline, red wine intake promoted a decrease in the adhesion of 89% monocytes, while white wine promoted 51%. Furthermore, Zern et al. (2005) investigated the effect of lyophilized grape powder (LGP) on the inflammation markers of pre- and post-menopausal women and observed reductions in TNF-α, but not in IL-6 and CRP levels. Even the

Table III. Trials investigating the effects of anthocyanin supplementation on inflammation markers in human.

Authors	Subjects and characteristics	Intervention design/groups	Period	Results/outcomes
Karlsen et al. (2007)*	$n = 118$ healthy men and women BMI 17–35 kg/m^2 40–74 years	Groups: supplemented with four capsules of 75-mg/d corresponding to 300-mg anthocyanins/d or placebo.	3 wk	Reductions in IL-8, RANTES, IFN-α, IL-4 and IL-13 compared to placebo group. CRP did not differ between the groups.
Naruszewicz et al. (2007)*	$n = 44$ men and women in statin therapy after MI BMI ~26.5 kg/m^2 ~ 66 years	Groups: supplemented 3 × 85 mg/d chokeberry flavonoid extract (anthocyans 25%, monomeric and olygomeric procyanidins 50% and phenolic acids 9%) or placebo.	6 wk	Lowering effect on ICAM, VCAM, MCP-1, hsIL-6 and hs-CRP.
Wang et al. (2007)*	$n = 60$ men and women with CHD BMI ~24 kg/m^2 45–75 years	Groups: 30 g/d of BRF powder (10-g BRF, 12-g starch and 8-g sucrose) or WRF (10-g WRF, 12-g starch and 8-g sucrose).	6 m	Significant reductions of VCAM-1, sCD40L and hs-CRP in the BRF group.
Curtis et al. (2009)*	$n = 57$ post-menopausal women BMI 20–32 kg/m^2 < 70 years	Groups: supplemented with 4 capsules/d of elderberry extract containing a total of 500 mg/d of anthocyanin or placebo.	12 wk	No changes were observed on CRP, TNF-α, IL-6, TNF-α RI and RII and RANTES.
Stull et al. (2010)	$n = 32$ obese and insulin resistant men and women BMI 32–45 kg/m^2 ≥ 20 years	Groups: supplemented with 45 g/d of freeze-dried highbush blueberry powder (668 mg of anthocyanins) or placebo.	6 wk	No changes in hs-CRP, TNF-α and MCP-1.
Basu et al. (2010a)	$n = 48$ metabolic syndrome men and women BMI ~37.5 kg/m^2 50 ± 3 years	Groups: supplemented with 50 g of freeze-dried blueberry (742 mg of anthocyanin) + 960 mL of water to be consumed twice daily and control group (960 mL of water).	8 wk	No changes in plasma CRP, IL-6, MPO, ICAM-1, VCAM-1, and adiponectin between the groups.
Basu et al. (2010b)	$n = 27$ men and women with metabolic syndrome BMI 37.5 ± 2.15 kg/m^2 47 ± 3 years	Groups: supplemented with two cups of strawberry beverage (25 g of freeze-dried strawberry powder – 154-mg anthocyanin) and two cups of water/d or control four cups of water/d.	8 wk	Decreased plasma levels of VCAM but no effects on ICAM.
Karlsen et al. (2010)	$n = 62$ men and women with high risk for CVD BMI 18–32 kg/m^2 22–55 years	Groups: bilberry juice (330 mL/d diluted to 1 L water) and water.	4 wk	Concentrations of CRP, IL-6, IL-15, and MIG decreased and TNF-α increased in the bilberry group.
Jim et al. (2010)*	$n = 117$ healthy men and women 22–55 years	Groups: FV (fruit and vegetable juice powder concentrate); FVB (FV with added berry powder) and placebo.	60 d	FV and FVB reduced serum levels of the MCP-1, MIP-1β, and RANTES compared to placebo.
Kaspar et al. (2011)*	$n = 36$ healthy men BMI 19.5–32.2 kg/m^2 18–40 years	Groups: supplemented with 150 g/d of cooked white (WP), yellow (58 mg of carotenoids and 0.3 g of anthocyanin/kg), and purple (1.3 mg of carotenoids and 6.2 g of anthocyanin/kg) potato cultivars.	6 wk	Significant decrease in CRP in purple potato group. No changes in plasma IL-1α, IL-1β, IL-2, IL-4, IL-8, IL-10, IFN-γ or TNF-α.

Notes: wk, weeks; d, days; IL-8, interleukin-8; RANTES, regulated upon activation, normal T-cell expressed and secreted (chemokine ligand 5); IFN-γ, interferon γ; CRP, C-reactive protein; ICAM, intercellular cell adhesion molecule; VCAM, vascular cell adhesion molecule; MCP-1, monocyte chemoattractant protein-1; sCD40L, soluble CD40 ligand; BRF, black rice pigment fraction; WRF, white rice pigment fraction; TNF-α, tumour necrosis factor-α; sTNF-α RI and TNF-α RII, TNF-α receptor I and receptor II; MPO, myeloperoxidase; MIG, monokine inducible by IFN-γ; MIP-1β, macrophage inflammatory protein-1β; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.
* The asterisk denotes those more relevant studies.

red and white wines as well as LGP contain different quantities of resveratrol, but also different quantities of anthocyanin and total polyphenols which hamper to render definitive conclusions of the efficiency of resveratrol alone.

In another study, an extract of *Polygonum cuspidatum* containing 40 mg of resveratrol was supplemented to healthy subjects for 6 weeks and the results showed the suppression of the pro-inflammatory kinases JNK-1, IKKβ and the intra-nuclear binding of NF-κB, reduction in the expression of TNF-α and IL-6 in mononuclear cells (MNCs) and TNF-α and CRP plasma concentrations. The content of resveratrol was 20% of the total extract but the doubt about the exclusive effects of this compound still remain (Ghanim et al. 2010). *P. cuspidatum* is a traditional Chinese medicine product and besides resveratrol other components are anthraglycoside B, emodin and physcion (Chu et al. 2005).

Similar to quercetin, resveratrol metabolization results in conjugates such as resveratrol monoglucuronides, resveratrol-3-*O*-sulfate, resveratrol disulphate and resveratrol sulfate glucuronide. The concentrations of these metabolites in plasma are detected in greater quantities than resveratrol that is always found at, or below, the limit of quantitation (Patel et al. 2010). However, it is still unknown whether this resveratrol conjugates can achieve target human tissues and reproduce *in vitro* observations (Baur and Sinclair 2006; Patel et al. 2010).

In this review, no articles in humans were found evaluating the anti-inflammatory effects of an extract containing, exclusively, resveratrol (Table IV). The water insoluble structure of resveratrol might render its applicability as a supplement difficult (Lee et al. 2011). On the other hand, Fragopoulou et al. (2007) studied the antithrombotic effects of acetylated forms of resveratrol by the inhibition of platelet-activating factor, a potent phospholipid mediator of inflammation. The authors found that monoacetylated and triacetylated derivatives presented similar inhibition of rabbit platelet aggregation as resveratrol, and diacetylated form presented a more potent inhibitory activity. This option could be an alternative to the use of resveratrol as a supplement.

Flavanols: proanthocyanidin and catechin

The proanthocyanidins are found as oligomers or polymers in the flavanol subgroup (de la Iglesia et al. 2010). These compounds are also known as condensed tannins and they are mostly present in fruits, especially cranberry, chokeberry and grape seeds (Gu et al. 2004). Although the beneficial effects of these compounds on cancer, diabetes, bacterial infections and also CVD are known (de la Iglesia et al. 2010), few intervention studies on inflammation were found in humans. One of these is a randomized crossover-blinded study in obese type 2 diabetes patients (Kar et al. 2009). The subjects received 300 mg of grapeseed extract twice daily for 4 weeks or placebo with a 2-week wash-out period. The authors observed a 40% decrease in CRP concentrations compared to placebo. Future studies must evaluate other markers of inflammation in addition to CRP to confirm this outcome.

Together with the proanthocyanidins are the catechins and flavonoids that also belong to the flavanol subclass (Williamson and Manach 2005). The consumption of tea has been associated with metabolic health and the benefits have been attributed mainly to this compound (De Bacquer et al. 2006; Wolfram 2007). This substance is present in both black and green tea, and the effect on reducing inflammation markers has been investigated (de Maat et al. 2000; Steptoe et al. 2007; Basu et al. 2011b). In this context, there were reductions in CRP when a 6-week crossover study was compared with the intake of 1050 mg of black tea extracts with placebo (Steptoe et al. 2007). On the other hand, the great majority of the studies compiled did not show reductions in the inflammatory markers after the consumption of catechins even by black or green tea or green tea extracts (de Maat et al. 2000; Widlansky et al. 2005; Basu et al. 2011b).

A recent study evaluated a range of inflammation markers that included CRP, IL-6, IL-1β, ICAM, VCAM, adiponectin and leptin (Basu et al. 2011b). The authors also did not find effects in obese subjects after the intake of 4 cups/d of green tea or 2 capsules/d of green tea extract, but demonstrated significant reduction in serum amyloid alfa (SAA) concentrations. SAA is an acute phase protein expressed by hepatocytes in early stages of inflammation shown to have chemoattractant role and to regulate release of cytokines, such as IL-1β (Patel et al. 1998). These results corroborate those of Nantz et al. (2009) who compared the intake of a 2 capsules/d of a decaffeinated mixture of L-theanine and catechin green tea extract (*Camelia sinensis*) or placebo by healthy subjects for 3 months. The authors found a significant reduction in SAA (−42%) in subjects taking the green tea extracts, but no differences in CRP or IL-6 levels. The interpretation of this selective effect on reducing SAA, but no other inflammation markers, is still to be determined.

Bioactive milk-derived peptides

In humans, the investigation of the effects of bioactive peptides on inflammation is recent. The angiotensin I-converting enzyme (ACE) inhibiting the activity of the peptides from both whey (also named lactokinins) and casein (casokinins) proteins (Mullally et al. 1997; FitzGerald and Meisel 1999) awakened the interest in studying the anti-inflammatory actions, since some ACE-inhibitor medicines also present the lowering effects on inflammation markers (Lee et al. 2007).

Table IV. Trials investigating the effects of resveratrol supplementation on inflammation markers in human.

Authors	Subjects and characteristics	Intervention design/groups	Period	Results/outcomes
Estruch et al. (2004)*	$n = 40$ healthy men 30–50 years	Groups: supplemented with 30 g of ethanol as red wine (320 mL) or gin (100 mL). Crossover trial with 15-days wash-out period.	2 wk	Reduced expression of VLA-4 in T-lymphocytes, LFA-1, Mac-1, VLA-4, MCP-1 in monocytes and plasma VCAM-1, ICAM-1 and hs-CRP after red wine. No changes in TNF-α and MCP-1.
Badia et al. (2004)*	$n = 16$ healthy men 30–50 years	Groups: supplemented with 30 g of ethanol as red wine (320 mL) or gin (100 mL). Crossover trial with 2-wk wash-out period.	4 wk	Reduced expression of VLA-4 on monocytes after red wine, but no changes in LFA-1, Mac-1 or MCP-1. Greater decrease in monocyte adhesion to endothelial cell after red wine.
Zern et al. (2005)	$n = 24$ and 20 in pre- and post-menopausal women, respectively BMI $\sim 31\ kg/m^2$	Groups: 36 g/d of LGP and placebo. Crossover trial with 3-wk wash-out period.	4 wk	LGP decreased TNF-α concentration but had no effect on CRP and IL-6 in both the groups compared to placebo.
Sacanella et al. (2007)*	$n = 35$ healthy women BMI $23.9 \pm 3.8\ kg/m^2$ 20–50 years	Groups: supplemented with 20-g alcohol/d as red wine (12.8 mg/L of resveratrol) or white wine (1.3 mg/L of resveratrol). Crossover trial with 4-wk wash-out period.	4 wk	Decreased hs-CRP, IL-6, ICAM-1 and CD40L in both the groups, but VCAM-1, E-selectin, P-selectin only after red wine. Reduced expression of Mac-1, VLA-4, MCP-1 and CD40 on monocyte in both the groups.
Blanco-Colio et al. (2007)	$n = 16$ healthy men and women 22–29 years	Groups: red wine or vodka or brandy or rum or control without alcohol, all groups accompanied by a fat-enriched diet (44%). Crossover trial with 2-wk wash-out period.	5 d	Red wine, brandy and rum decreased NF-κB activation. Red wine decreased plasma MCP-1.
Ghanim et al. (2010)*	$n = 20$ healthy subjects BMI $21.8 \pm 0.5\ kg/m^2$ 36 ± 5 years	Groups: supplemented with 200 mg of *P. cuspidatum* extract (equivalent to 40-mg/d *trans*-resveratrol) or placebo.	6 wk	Reduced intra-nuclear NF-κB DNA binding in MNCs; TNF-α and IL-6 mRNA expression in MNCs; and plasma TNF-α and CRP, JNK-1, IKκB mRNA expression compared to placebo.

Notes: wk, weeks; d, days; VLA-4, very late activation antigen-4; LFA-1, lymphocyte function-associated antigen-1; Mac-1, macrophage-1 antigen; MCP-1, monocyte chemoattractant protein-1; VCAM, vascular cell adhesion molecule; ICAM, intercellular cell adhesion molecule; CRP, C-reactive protein; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; sCD40L, soluble CD40 ligand; NF-κB, nuclear factor-kappa B; MNC, mononuclear cell; JNK-1, Jun-N-terminal kinase; IKκB, inhibitor of κB-kinase.
*The asterisk denotes those more relevant studies.

Lee et al. (2007) performed a 12-week intervention with whey powder (2.6 g) offered in a base of skimmed milk or placebo in mild hypertensive subjects and did not find changes on IL-6, CRP and PAI-1. These findings are in agreement with the results of Pal and Ellis (2010, 2011), which did not show significant reductions in IL-6, CRP and TNF-α level in overweight and obese subjects after neither chronic nor acute supplementation of whey protein isolate or sodium caseinate compared to control. Lee et al. (2007) suggested a possible degradation of the peptides by intestinal or plasma peptidases as an explanation for the absence of effects.

Contrary wise, a 180-day supplementation with the capsules of 125 mg of a ribonuclease-enriched lactoferrin, a milk protein-based peptide, resulted in the improvement of the inflammatory status of post-menopausal women (Bharadwaj et al. 2010). The authors observed a significant decrease in TNF-α, IL-6 and CRP levels, and increase in IL-12. Also, an increase in the anti-inflammatory cytokine IL-10 was demonstrated.

At this moment, it is too early to ensure whether whey or casein peptides are anti-inflammatory compounds and more studies are needed to prove it.

L-Carnitine

L-Carnitine is a substance that is mainly obtained from dietary sources, especially animal products, but the regulation/formation of this compound in the body occurs by a relation of intake/absorption, kidney reabsorption and endogenous synthesis by methylation of lysine, mainly in liver (Steiber et al. 2004). The effects of carnitine on inflammation markers have been studied especially in haemodialysis patients (Table V) since this treatment can promote its loss and consequently deficiency (Hakeshzadeh et al. 2010; Shakeri et al. 2010).

Indeed, significant reductions in CRP (Hakeshzadeh et al. 2010), IL-6 (Shakeri et al. 2010) and SAA (Tabibi et al. 2011) levels were observed after 3 months of 1000 mg/d of oral supplementation. Also, CRP was reduced after 6 months of infusions of 20 mg/kg three times weekly (Savica et al. 2005; Duranay et al. 2006). The mechanisms by which L-carnitine reduces inflammation in haemodialysis are still unknown (Shakeri et al. 2010).

Besides renal disease, animal experiments have shown decreased concentration of intramuscular free carnitine in animal models of ageing, genetic diabetes or diet-induced obesity compared to control animals (Noland et al. 2009). These conditions could also be beneficiated by carnitine supplementation and deserve more studies.

Phytosterol: plant stanol and sterol

The consumption of 2 g/d of plant stanol/sterol has been recommended by the NCEP/ATPIII as

Table V. Trials investigating the effects of L-carnitine supplementation on inflammation markers in human.

Authors	Subjects and characteristics	Intervention design/groups	Period	Results/outcomes
Savica et al. (2005)	$n = 113$ haemodialysis men and women BMI ~ 21 kg/m^2	Groups: infusion of 20 mg/kg of L-carnitine or placebo three times weekly.	6 m	Reductions in CRP levels compared to placebo group.
Duranay et al. (2006)	$n = 42$ haemodialysis men and women ~ 44 ± 13 years	Groups: infusion of 20 mg/kg of L-carnitine or placebo three times weekly.	6 m	Reductions in CRP levels compared to placebo group.
Kumar et al. (2007)	$n = 58$ CHF men and women	Groups: supplemented with 9 softgel of 270 mg of ubiquinone and 2250 mg of L-carnitine or 9 matching placebo.	12 wk	Both treatments reduced IL-6 and TNF-α levels but carnitine promoted greater reductions compared to placebo.
Derosa et al. (2010)	$n = 227$ type 2 diabetic men and women BMI ≥ 30 kg/m^2 ≥ 18 years	Groups: supplemented with orlistat 120 mg three times a day plus 2 g of L-carnitine once a day or orlistat 120 mg three times a day as placebo.	12 wk	Both treatments reduced CRP, RBP-4 and resistin levels but the combination with carnitine promoted faster reductions, with 6 or 9 months of treatment.
Hakeshzadeh et al. (2010)	$n = 36$ haemodialysis men and women 20–74 years	Groups: supplemented with 1000 mg/d oral L-carnitine or placebo.	12 wk	Reductions in CRP compared to placebo but no differences for PAI-1.
Shakeri et al. (2010)	$n = 36$ haemodialysis men and women 24–80 years	Groups: supplemented with 1000 mg/d oral L-carnitine or control.	12 wk	Reductions in CRP and IL-6 compared to control but no differences in IL-1β and TNF-α.
Tabibi et al. (2011)*	$n = 36$ haemodialysis men and women	Groups: supplemented with 1000 mg/d oral L-carnitine or placebo.	12 wk	Reductions in SAA compared to placebo, but no changes on VCAM, ICAM, E-selectin and P-selectin.

Notes: wk, weeks; m, months; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; RBP-4, retinol-binding protein; PAI-1, plasminogen activator inhibitor; IL-1β, interleukin-1-β; SAA, serum amyloid alfa; VCAM, vascular cell adhesion molecule; ICAM, intercellular cell adhesion molecule.
*The asterisk denotes those more relevant studies.

a therapeutic dietary option to reduce LDL cholesterol (NCEP 2002; EFSA 2008). The most common forms are β-sitosterol, campesterol and stigmasterol; and due to their structural similarity to cholesterol, they present reducing cholesterol absorption properties (Berger et al. 2004).

The effects on reducing hypercholesterolemia increased the interest on plant sterol/stanol as an anti-inflammatory compound (Table VI).

It was observed that plant sterols associated with *n*-3 polyunsaturated fatty acids (PUFAs) improved the anti-inflammatory effects compared to *n*-3 PUFA alone (Micallef and Garg 2009) or corn oil (Bitzur et al. 2010). The authors speculate that the greater effects are due to a possible conversion of C18:3n-3 to C22:6n-3 since the plant sterols were offered in conjunction to 1.5 g of C18:3n-3 (Micallef and Garg 2009). The results of the studies about the effects of plant sterols/stanols on inflammation are inconsistent, and the mechanisms by which these compounds could exert its anti-inflammatory effects are still unknown.

α-Lipoic acid

Lipoic acid is present in some foods such as meat, liver, heart and in less quantities in spinach and cabbages, but the body supply comes mainly by its synthesis from octanoic acid in mitochondria (Prieto-Hontoria et al. 2011). Animal and *in vitro* studies have shown positive results of lipoic acid as mitochondrial antioxidant (Valdecantos et al. 2010) and about its protective effect on weight gain by reducing the feed efficiency (Prieto-Hontoria et al. 2009). Besides these effects, Sola et al. (2005) found significant reductions on IL-6 and PAI-1 in metabolic syndrome patients after 4 weeks of supplementation of lipoic acid (300 mg/d) or lipoic acid plus ibersartan. On the other hand, studies that offered 600 mg/d of lipoic acid for 3 months (Vincent et al. 2007) and 400 mg/d during 4 weeks did not produce changes on CRP.

Deiuliis et al. (2011), from the data observed in visceral adipose tissue of obese insulin resistance mice, suggest that the anti-inflammatory effects of lipoic acid are related to its ability to prevent NF-κB activation. More intervention studies must be designed to determine whether the effects are reproduced in humans.

Particular considerations

Specific foods and dietary patterns have been shown to influence the inflammatory response process. The most studied compounds with action on inflammation markers in human were polyphenols, especially the isoflavone and anthocyanin, but quercertin, catechin and resveratrol have been evaluated. Furthermore, some human intervention studies were found about the effects of other compounds such as bioactive milk peptides, plant sterol and stanol, L-carnitine and α-lipoic acid.

The great majority of intervention studies in humans investigated the effects of some bioactive compounds on plasma levels of TNF-α, IL-6, IL-1, PAI-1 and others. However, the question whether reductions on a singular cytokine are sufficient to improve a metabolic disease remains unanswered (Gregor and Hotamisligil 2011). Long-term randomized-controlled trials in a large number of subjects are still needed and should focus on the mechanisms of activation of IKK/NF-κB and MAPK pathways and gene interactions. Moreover, none of the human interventions discussed here measured lipid mediators as the markers of inflammation and it would be interesting to figure out the mechanisms of actions of each anti-inflammatory bioactive compound.

The Mediterranean diet consumption, based on high intake of grains, fruits, legumes, nuts and fish; low intake of meat and moderate intake of milk and derivatives produced reductions on RBP4, C3 complement, TNF-α, IL-6 and CRP in subjects with higher adherence (Hermsdorff et al. 2009). Besides the high content of fibre, monounsaturated fatty acids and PUFAs; low saturated fatty acid and adequate micronutrients composition, the health benefits must also be associated with the many bioactive compounds existing in these diet patterns (Abete et al. 2011).

Few studies were found specifically investigating the effects of an isolated bioactive compound as a supplement, but often studied fresh, dried or frozen food sources. The food matrix is accompanied by other polyphenols or substances that can exert additional synergistic functions and limits the conclusions about the compounds that really prevent or improve inflammatory response. Anthocyanin and resveratrol seem to be the most promising compounds. However, the food sources that showed positive results on inflammation markers, such as chokeberry, red grape or red wine, also present other compounds in the composition. One of these compounds is the proanthocyanins (Williamson and Manach 2005) that have been less studied until now but deserve more attention.

Other possible questions to be investigated are the doses, the form of supplementation and the bioavailability to exert its function in target tissues. As an example, the composition of polyphenols of grape seeds can decrease according to variety, the area of production (Prieur et al. 1994) and maturity of fruits (Santos-Buelga et al. 1995) and can lead to different results. Moreover, the diet technique to prepare a food or drink and the addition or not of other components can alter the efficacy of bioactive compounds action, so it must also be considered in intervention studies and in clinical practice (Ryan and Petit 2010; Hermsdorff et al. 2011b).

The studies compiled here included those applied either in health, overweight and obese subjects

Table VI. Trials investigating the effects of plant stanol and plant sterol supplementation on inflammation markers in human.

Authors	Subjects and characteristics	Intervention design/groups	Period	Results/outcomes
Devaraj et al. (2006)*	$n = 72$ healthy men and women BMI $\sim 25\,kg/m^2$ 19–74 years	Groups: 240-mL sterol orange juice beverage (2-g sterol/d equivalent to 40% β-sitosterol, 25% campesterol and 20% stigmasterol) or 240-mL placebo orange juice beverage twice daily.	8 wk	Reductions of 12% in CRP concentration compared to placebo.
AbuMweis et al. (2006)	$n = 30$ men and women BMI $22–34\,kg/m^2$ 40–85 years	Groups: free plant sterols; plant sterols esterified to sunflower oil; plant sterols esterified to (*n*-3) PUFA from fish oil; free plant sterols in combination with (*n*-3) PUFA from fish oil or control margarine. Plant sterols were given at a dose of 22 mg/kg. Crossover trial with 2–4-wk wash-out period.	29 d	No changes in CRP.
De Jong et al. (2008)	$n = 43$ men and women in statin treatment BMI $\leq 32\,kg/m^2$ 18–65 years	Groups: placebo group consumed 30 g/d of margarine (40% fat); sterol group consumed a plant sterol-enriched margarine (2.5 g of sterol) and stanol group consumed a plant stanol-enriched margarine.	16 wk	No effects on plasma ICAM, VCAM, E-selectin, MCP-1 and CRP compared to placebo.
Micallef and Garg 2009*	$n = 60$ hyperlipidaemic men and women BMI $26.9 \pm 0.5\,kg/m^2$ 35–70 years	Groups: SO, 4-g placebo capsules of sunola oil per day; SOP, SO plus 2-g/d plant sterols; FO, 4-g tuna oil capsules and FOP, FO plus 2 g/d plant sterols.	3 wk	Reduced hs-CRP and TNF-α in the FO group and hs-CRP, TNF-α, IL-6 and LTB_4 in the FOP group compared to baseline. Changes of hs-CRP in FO and FOP differed from placebo.
Plat et al. (2009)*	$n = 36$ metabolic syndrome men and women BMI $\sim 30\,kg/m^2$ 45–70 years (men) or 55–70 years (women)	Groups: stanol group, low-fat yoghurt plus 2 g of free plant stanols/d and placebo tablets; statin group, placebo yoghurt plus 10-mg simvastatin; combination group, low-fat yoghurt plus 2 g of free plant stanols/d and 10-mg simvastatin and placebo group received placebo yoghurt and placebo tablets.	8 wk	No changes in hs-CRP, SAA, sE-selectin, ICAM, VCAM-1, MCP-1, IL-6, matrix metallopeptidase-9 and CD40 ligand concentrations.
Theuwissen et al. (2009)*	$n = 42$ slightly hypercholesterolaemic men and women BMI $25 \pm 3\,kg/m^2$ 52 ± 11 years	Groups: control muesli (4.8-g control fibre), β-glucan muesli (4.8-g oat β-glucan) or combination muesli (4.8-g oat β-glucan plus 1.4-g plant stanols as PSE). Crossover trial with 2-wk wash-out period.	4 wk	No differences in plasma hs-CRP, and production of TNF-α, IL-6 and IL-8 by PBMC and platelet-poor plasma between the groups.
Gagliardi et al. (2010)	$n = 53$ metabolic syndrome men and women	Groups: butter group (18 g/d); no-trans-fat margarine group (36 g/d) and plant sterol margarine group (30 g/d, 2.4 g of plant sterol), all provided ~ 12.7 g/d of total lipids.	35 d	No changes in CRP, E-selectin, IL-6 or CD-40L.
Bitzur et al. (2010)*	$n = 84$ hyperlipidaemic men and women 18–70 years	Groups: four 1-g capsules, providing the equivalent of 1.6-g free plant sterols and 1.3-g EPA + DHA or 4-g corn oil per day.	12 wk	Reductions in hs-CRP compared to placebo.
Athyros et al. (2011)	$n = 150$ mild hypercholesterolaemic men and women BMI $\sim 27\,kg/m^2$ $\sim$ 55 years	Groups: placebo spread, plant stanol ester spread (2 g/d) and Mediterranean diet.	16 wk	Reductions in hs-CRP compared to placebo. No changes in fibrinogen and PAI-1.

Notes: wk, weeks; d, days; CRP, C-reactive protein; VCAM, vascular cell adhesion molecule; ICAM, intercellular cell adhesion molecule; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; LTB_4, leukotriene B_4; SAA, serum amyloid alfa; sCD40L, soluble CD40 ligand; PBMC, peripheral blood mononuclear cell; (*n*-3) PUFA, long-chain (*n*-3) polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PAI-1, plasminogen activator inhibitor.

*The asterisk denotes those more relevant studies.

associated or not with other diseases. It was not possible to select only articles evaluating obese group because of the still short number of studies related to this group and the bioactive compounds. Besides that, the differences in the study design, the source and dosage of supplement and the biomarkers evaluated impaired comparisons between them. The increasing interest in this topic will soon make it possible to infer conclusions for the use of these compounds in obesity treatment.

Conclusion

Finally, the use of anti-inflammatory bioactive compounds is a promising area of investigation (Garcia-Lafuente et al. 2009) but, nowadays, it is not possible to firmly state neither the exact component or components nor dosages of supplements that would be effective on reducing inflammation markers in humans (Abete et al. 2011). The knowledge about the most beneficial compounds would allow the combination of food sources that favour them to exert the maximal activity.

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