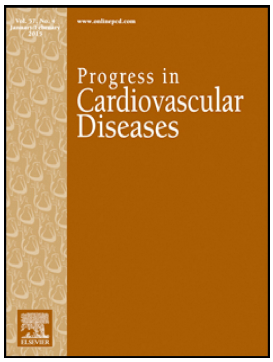

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Impact of Nutraceuticals on Markers of Systemic Inflammation: Potential Relevance to Cardiovascular Diseases – A Position Paper From The International Lipid Expert Panel (ILEP)

Massimiliano Ruscica[1], Peter E. Penson[2,3], Nicola Ferri[4], Cesare R. Sirtori[1], Matteo Pirro[5], G. B. John Mancini[6], Naveed Sattar[7], Peter P. Toth[8], Amirhossein Sahebkar[9], Carl J. Lavie[10], Nathan D. Wong[11], Maciej Banach[12,13*], on behalf of *the International Lipid Expert Panel* (ILEP)[#]

[1] Department of Pharmacology and Biomolecular Sciences, Università degli Studi di Milano, Milano, Italy; [2] School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK; [3]Liverpool Centre for Cardiovascular Science, Liverpool, UK; [4]Department of Pharmaceutical and Pharmacological Sciences, Università degli Studi di Padova, Padova, Italy; [5]Internal Medicine Section, Department of Medicine and Surgery, University of Perugia, Perugia, Italy; [6]Center for Cardiovascular Innovation, University of British Columbia, Vancouver, British Columbia, Canada; [7]Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom; [8]Cicarrone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [9]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran; [10]Department of Medicine, John Ochsner Medical Center, New Orleans, Louisiana, USA; [11]Heart Disease Prevention Program, Division of Cardiology, University of California Irvine, Irvine, California, USA; [12]Department of Hypertension, Medical University of Lodz (MUL), Lodz, Poland; [13]Cardiovascular Research Centre, University of Zielona Gora, Zielona Gora, Poland.

Running title: *Nutraceuticals and inflammation.*

**Corresponding Author:*

Prof. Maciej Banach, MD, PhD, FNLA, FAHA, FESC, FASA, President, the International Lipid Expert Panel (ILEP, ilep.eu); Department of Hypertension, Medical University of Lodz (MUL), Rzgowska 281/289; 93-338 Lodz, Poland. Phone: +48422711124; E-mail: maciej.banach@iczmp.edu.pl

ABSTRACT:

Inflammation is a marker of arterial disease stemming from cholesterol-dependent to -independent molecular mechanisms. In recent years, the role of inflammation in atherogenesis has been underpinned by pharmacological approaches targeting systemic inflammation that have led to a significant reduction in cardiovascular disease (CVD) risk. Although the use of nutraceuticals to prevent CVD has largely focused on lipid-lowering (*e.g,* red-yeast rice and omega-3 fatty acids), there is growing interest and need, especially now in the time of coronavirus pandemic, in the use of nutraceuticals to reduce inflammatory markers, and potentially the inflammatory CVD burden, however, there is still not enough evidence to confirm this. Indeed, diet is an important lifestyle determinant of health and can influence both systemic and vascular inflammation, to varying extents, according to the individual nutraceutical constituents. Thus, the aim of this Position Paper is to provide the first attempt at recommendations on the use of nutraceuticals with effective anti-inflammatory properties.

Keywords: cardiovascular disease, C-reactive protein, inflammation, nutraceuticals, omega-3, position paper, red-yeast rice.

ABBREVIATIONS:

ACS	acute coronary syndromes
ACE	angiotensin converting enzyme
ARA	arachidonic acid
ASCVD	atherosclerotic cardiovascular disease
BAPs	bioactive anti-inflammatory peptides
BCAA	branched-chain amino acids
BEO	Bergamot essential oil
CHD	coronary heart disease
COVID-19	coronarovirus diseases 2019
COX-1	cyclooxygenase-1
CRP	C-reactive protein
CVD	cardiovascular disease
DHA	docosahexaenoic acid
eNOS	endothelial nitric oxide synthase
EPA	eicosapentaenoic acid
FRLFE	flavanol-rich lychee fruit extract
HDL-C	high density lipoprotein cholesterol
HODEs	hydroxydecadienoic acids
HR	hazard ratio
ICAM-1	intercellular adhesion molecule-1
IL-1β	interleukin-1β
ILEP	International Lipid Expert Panel
LA	linoleic acid
LDL-C	low density lipoprotein cholesterol
LOX	lipoxygenase
MCP-1	monocyte chemoattractant protein-1
NAFLD	non-alcoholic fatty liver disease
NLRP3	NLR family pyrin domain containing 3
PAD	peripheral artery disease
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
RYR	red yeast rice
TET2	Tet methylcytosine dioxygenase 2
TG	triglycerides
TGFβ	transforming growth factor beta
TLR4	toll-like receptor-4
TMAO	trimethylamine-N-oxide
TNF-R	tumor necrosis factor receptor
VEGF-A	Vascular Endothelial Growth Factor-A

INTRODUCTION

Overactivation of the inflammation cascade is a well-established factor promoting tissue and organ disfunction in several disease conditions [1,2]. Increasing evidence demonstrates additional roles for inflammation in the development of arterial diseases [1,2]. Inflammation is, in fact, an obligatory marker of atherosclerotic cardiovascular disease (CVD; ASCVD), resulting from the inflammatory activity of cholesterol itself as well as from other well-established molecular mechanisms [3]. Clinical trials with anti-inflammatory drugs have led to the extensive evaluation of biomarkers, such as high sensitivity C-reactive protein (CRP; hsCRP) and interleukin (IL)-6, which are indicative of increased CVD risk [4]. The approach to the prevention of atherosclerosis increasingly encompasses the targeting of inflammation [5] and the increased use of agents targeting inflammatory pathways [6].

Since inflammation contributes to residual CVD risk after optimal preventive treatments with, e.g. statins, the mechanisms of the inflammatory process have been studied in detail. In terms of molecular mechanisms, cholesterol crystals in atherosclerotic lesions can promote plaque instability [7] by activation of NLR family pyrin domain containing 3 (NLRP3) (NACHT-, LRR- and pyrin domain-containing 3). NLRP3 nucleates the assembly of an inflammasome, leading to caspase 1-mediated activation of the interleukin-1β (IL-1β) family of cytokines, thus inducing inflammatory pyroptotic cell death [8]. More recently, the study of mechanisms related to myelopoiesis [9] has led to important contributions to the understanding of inflammatory mechanisms underlying acute coronary syndromes (ACS) and of potentially protective mechanisms, such as Tet methylcytosine dioxygenase 2 (TET2) production [10]. In addition to drugs specifically affecting this pathway (e.g. canakinumab and colchicine), anti-inflammatory actions of agents in general use in CVD prevention, *e.g.*, statins, have become widely known (11). In line with this evidence, there is also a growing interest in non-drug approaches involving natural products (nutraceuticals) to influence the inflammatory etiology of CVD [12]. The use of nutraceuticals to help to prevent CVD has largely focused on lipid-lowering to date, such as in the documents produced by the International Lipid Expert Panel (ILEP) [13]. This work, however, has highlighted the potential of these agents to effect inflammatory parameters, and as a consequence, their potential to play a supplemental role in the reduction of inflammation-related residual CVD risk.

OPENING STATEMENT

In order to provide an objective assessment of nutraceuticals with potential anti-inflammatory activity, the purpose of this Position Paper is to classify nutraceuticals by molecular type and mechanism of action. This will allow us to highlight the most important recent developments in this therapeutic area and to recommend the nutraceuticals with the greatest potential based on the available evidence.

To pursue this aim, the following search algorithm was used to search pubmed.gov (by 31 March 2021): *nutraceuticals* OR *nutraceutical approaches* OR *absorbable nutraceuticals* OR *non-absorbable nutraceuticals* AND *inflammation* AND *atherosclerosis* AND *cardiovascular disease*. Relevant *in vitro*, *in vivo* and clinical studies were included in this review.

The levels of evidence and the strength of recommendation have been weighed and graded according to predefined scales, as outlined in **Tables 1** and **2.** The experts of the recommendations, based on available data, extensively discussed each nutraceutical finally included in the Position Paper and discussed and agreed on the recommended levels. Due to the limited data, the experts did not decide to evaluate each selected nutraceutical with the class of the evidence. The experts of the writing and reviewing panels completed declaration of interest forms where real or potential sources of conflicts of interest might be perceived (see end of the paper).

Physicians and medical professionals of other specialties treating patients with inflammatory conditions are encouraged to consider the Position Paper in the process of evaluating the clinical status of their patients and to determine and implement medical strategies with the recommended nutraceuticals. However, the Position Paper does not override in any way the individual responsibility of physicians to make appropriate and accurate decisions taking into account the condition of a given patient and in consultation with that patient, and, where necessary, with the patient's guardian or caretaker. It is also the responsibility of health professionals to verify the doses, rules, and regulations applicable to drugs and devices at the time of their *prescription/use.*

DIETARY COMPONENTS, NUTRACEUTICALS AND ANTI-INFLAMMATORY PROPERTIES

Diet is an important lifestyle determinant of health and can influence inflammation, including vascular inflammation, to varying extents, according to the individual components of food [14].

Among food-components with a drug-like activity, commonly used nutraceuticals play a major role. A nutraceutical, as per the definition by De Felice (1989), "is a food or part of a food, providing a medical or health benefit. These products may range from isolated nutrients to dietary supplements and specific diets to genetically engineering designed foods, herbal products and processed foods". It has become customary, in daily practice, to distinguish between nutraceuticals with pharmaceutical-like formulations, in which the composition is standardized, and "functional foods", *i.e.*, foods with health benefits [13,14].

Omega- 6 Fatty Acids

Dietary fatty acids, in particular, omega-6 fatty acids, are major components of daily lipid intake. The predominant polyunsaturated fatty acid (PUFA) is linoleic acid (LA:18:2 n-6), whose intake has been associated, in a number of epidemiological and interventional studies, with reduced CVD risk [15, 16]. A recent assessment of omega-6 PUFA intake among adults in the UK indicated an intake of 10.9±4.7 g/day, most of which (at least 90%) being LA, and which was responsible for about 7% of daily energy intake. LA is converted, through a series of steps, to γ-linolenic acid, dihomo-γ-linolenic acid and to arachidonic acid (ARA) [17]. The latter is the major precursor of eicosanoids converted by cyclooxygenase-1 (COX-1) to prostaglandins/thromboxanes. Concentrations of ARA-derived eicosanoids are elevated in people with inflammatory conditions [18]. The pathway to ARA synthesis from LA is generally saturated in the presence of a high intake of LA in humans (likely to be around 10 g/d). Thus, raising LA intake will have no further effect on the promotion of ARA synthesis, and therefore will not alter ARA levels in circulating mononuclear cells (MCs) and inflammatory markers in individuals on a normal diet [19].

The major potential effect of LA itself on inflammation is *via* its metabolism to lipoxygenase (LOX) derivatives, such as the hydroxydecadienoic acids (HODEs) and further, to oxo-HODEs and epoxy-HODEs [20]. These compounds play a role in inflammation and have been detected in colonic mucosal biopsies of patients with ulcerative colitis without being significantly associated with the degree of inflammation [20].

Dietary LA intake was evaluated in a cross-sectional study in 405 healthy men and 454 healthy women and found not to be significantly associated with inflammatory markers, such as CRP, IL-6, soluble (s) tumor necrosis factor receptor (TNF-R) and sTNF-R2 [21]. An epidemiological study in Italy on 1123 subjects (aged 20-98 years) showed that those with the lowest intake of LA had the highest pro-inflammatory IL-6 and CRP [22]. However, when multivariable models were used,

omega-6 fatty acids were positively associated with IL-1 receptor antagonist (IL-1RA) and negatively with IL-10 and transforming growth factor beta (TGFβ), two powerful antiinflammatory cytokines. Similar conclusions were reached in 67 obese individuals randomly assigned to receive either 10-week isocaloric diet high in vegetable n-6 PUFA or SFA mainly from butter. n-6 PUFAs did not cause any signs of inflammation, but instead led to a reduction of IL-1RA and TNF-R2. No changes in CRP, IL-1β, IL-6 or IL-10 were found [23].

This and other studies have led to the conclusion that, despite a long-held belief to the contrary, available evidence does not support that high dietary intake or high plasma concentrations of LA raise tissue ARA or alter concentrations of inflammatory markers in humans. Since LA can limit the synthesis of eicosapentaenoic acid (EPA) from α-linolenic acid in humans, there is the possibility that low LA in the background diet might limit endogenous EPA synthesis, potentially creating a more inflammatory environment [24].

The lack of a significant anti-inflammatory effect of LA or omega-6 fatty acids in general does not rule out a beneficial action in CVD prevention. Such an effect is supported by the recent Consortium Evaluation of 30 prospective observational studies from 13 countries (follow up ranging between 2.5 to 31.9 years) [25], in which high levels of LA were significantly associated with a lower risk of total CVD (hazard ratio [HR]: 0.93; 95% CI, 0.88-0.99), CV mortality (HR: 0.78; 95% CI 0.70-0.85) and ischemic stroke (HR: 0.88; 95% CI 0.79-0.98). ARA levels were not associated with a high incidence of CVD outcomes. However, another recent meta-analysis has not confirmed these results, and Mendelian Randomization results suggested that individuals with genetically higher serum adrenic acid (AA; 22:4,n-6 - naturally occurring PUFA formed through a 2-carbon chain elongation of ARA), levels had a greater risk of coronary heart disease (CHD) events (inverse variance weighting [IVW]-Beta: 0.526, p=0.007), myocardial infarction (MI) (IVW=Beta: 0.606, p=0.017) and stroke (IVW=Beta: 1.694, p=0.009) [26].

Special members of the omega-6 fatty acid series are the conjugated linoleic acids (CLA), a group of positional and geometric isomers of LA (18:2 n-6). Present in meat and dairy products and synthesized endogenously, CLA can bind peroxisome proliferator-activated receptor alfa (PPARα), a nuclear receptor regulating fatty acid catabolism and inflammatory responses [27]. Of special interest for this widely consumed nutraceutical is its activity on neuroinflammation, potentially protective against Alzheimer disease [28]. However, the use of CLA, as well as all other omega-6 fatty acids, by patients, as a general anti-inflammatory awaits more convincing evidence (**Table 3, Figure 1**).

Omega-3 FattyAacids

Dietary intake of omega-3 fatty acids is essential for health since these PUFAs cannot be endogenously synthesized to a significant extent [29]. Omega-3 PUFAs are regarded as anti-inflammatory, exerting their activity *via* multiple mechanisms [29]. The basic mechanism is the incorporation of EPA and docosahexaenoic acid (DHA) into cell membranes at the expense of ARA, resulting in inhibited ARA metabolism and the consequent decreased expression of the *COX* gene and, as a final consequence, reduction of ARA derived eicosanoids [30]. Finally, partial inhibition of a number of aspects of inflammation, including leukocyte chemotaxis, adhesion molecule expression and leukocyte-endothelial adhesive interactions, production of inflammatory cytokines, and T-helper 1 lymphocyte reactivity have to be considered [30].

More recently, a major advancement in the field of PUFA and inflammation has been the discovery of the so-called pro-resolving lipid mediators produced from EPA and DHA. These mediators include resolvins from EPA (E-series) and DHA (D-series) and protectin and maresin from DHA. Their synthesis involves the COX and lipopxygenase (LOX) pathways operating in a transcellular manner. Early steps can occur in one cell type and the latter in another [31]. Resolvins and maresins can be found in humans after EPA or DHA intake [32] and have shown anti-inflammatory benefits *in vitro* and in animal models of inflammation [33]. By these mechanisms, omega-3 PUFAs, and especially DHA, decrease the expression of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) on the surface of endothelial and cells and monocyte cultures as well as of the scavenger receptor A in rats fed a high-fat fish oil diet [34] (**Figure 1**). Interesingly, these properties have now been used in studies on the potential role of omega-3 acids in coronavirus disease 2019 (COVID-19) [35].

The inhibitory activity of omega-3 fatty acids on the nuclear factor (NF)-κB is probably exerted by reduced translocation of the NF-κ dimer to the nucleus, where it binds to response elements, thus upregulating inflammatory gene expression. Exposure of macrophages to DHA lowers the ability of toll-like receptor-4 (TLR4) agonists to recruit co-stimulatory molecules, MHC class II, and to stimulate cytokine production [36].

A randomized controlled trial (RCT) in ageing adults with chronic venous leg ulcers given EPA+DHA therapy (2.5 g/d) reported reduced IL-6, IL-1β and TNF-α after 4 and 8 weeks of

treatment [37]. An ongoing trial will evaluate in 248 eligible adults (≥55 years) with chronic venous leg ulcers the effectiveness of EPA (1.87 g/day) + DHA (1.0 g/day) to target and to reduce excessive systemic and local activation of polymorphonuclear leukocytes [38].

A direct evaluation of the two fatty acids was carried out by Allaire *et al.* [39], testing in a double-blind fashion supplementation of EPA and DHA (both 2.7 g/d) *vs* corn oil (control group) for a period of 10 weeks. Compared with EPA, DHA appeared to lead to a larger reduction of IL-18 (-7.0 *vs* -0.5%), hsCRP (-7.9% *vs* -1.8%) and TNF-α (-14.8% *vs* -7.6%) and to increased adiponectin (+3.1% *vs* -1.2%) *vs* EPA; effects on IL-6 (-12.0% *vs* -13.4%) were similar. Interestingly DHA led to a more pronounced reduction of triglycerides (-13.3% *vs* -11.9%) and a greater increase in HDL-C (+7.6% *vs* -0.7%) and LDL-C (+6.9% *vs* +2.2%) *vs* EPA. Different conclusions were reached by Pisaniello *et al.* reporting that supplementation with EPA, more than DHA, ameliorates acute and chronic vascular inflammation. EPA (4 g/day) reduced the expression of C-C motif chemokine ligand 2 (CCL2) by 25% and vascular inflammation compared with placebo [40]. Additionally, available reports suggest that purified EPA may have an effect on red cell distribution width (RDW) and its association with chronic inflammation and red blood cell deformability [41,42].

These findings have gained interest after the positive outcome of the Reduction of Cardiovascular Events with Icosapent Ethyl - Intervention Trial (REDUCE-IT) using a high dose of highly purified EPA (icosapent ethyl, IPE 4 g/day) given to secondary prevention CVD patients or patients with diabetes and multiple risk factors on statin therapy, but with moderately elevated triglycerides (TG; 135-499 mg/dL) [43]. This intervention resulted in a primary CVD endpoint reduction of 25% in treated patients [43]. At five years, these patients had a median reduction in TG levels of -20% with a non-significant change in HDL-C. The lipid findings, particularly those pertaining to TG, were interpreted as not fully explaining the observed large CVD benefit. Interestingly, however, at the last visit, hsCRP levels were reduced by rougly 37%, thus probably adding to the CVD benefit of EPA intake [43]. In this context, it is worth recalling that prominent in this area were the previous results of the JELIS (Japan eicosapentaenoic acid (EPA) Lipid Intervention Study) trial, in which hypercholesterolemic patients were randomized to 1.8 g/day high-purity EPA *vs* placebo. The relative risk of major CHD events was reduced by 19% over a 4.6-year-mean follow-up [44]. The cardioprotective effects were also observed in a recent meta-analysis of 13 studies with 127,447 individuals, in which the authors showed a significant reduction of the CHD death risk (risk ratio [RR] 0.91, 95%CI 0.85-0.97), major vascular event (0.95,

95%CI 0.93-0.98), non-fatal MI (0.89, 95%CI 0.83-0.95), and all-cause mortality (0.95, 95%CI 0.92-0.99) with omega-3 intervention [45].

More recently, the REDUCE-IT findings were not confirmed in another secondary prevention trial, this time in patients given a pre-formulated mixture of EPA and DHA (4 g/day). The STRENGTH study did not result in CVD benefits (similarly to all previous studies and trials with the mixture of omega-3 acids) and was terminated early due to a lack of evident protective activity. hsCRP was reduced by -20.0% in the group receiving omega-3 carboxylic acid formulation *vs* −6.3% in the placebo arm [46]. Moreover, the EVOLVE (The EpanoVa fOr Lowering Very high triglyceridEs) study did not show significant reduction in the levels of hsCRP from baseline in patients with hypertriglyceridemia after administration of different daily doses of omega-3 fatty acid (2 g, 3 g or 4 g) *vs* olive oil (placebo) [47].

Debate on the differences between REDUCE-IT and STRENGTH, besides the different composition of the two formulations, also has to consider differences between the two placebos (mineral oil in REDUCE-IT and corn oil in) [48]. While some have argued whether the effect of mineral oil's on increasing hsCRP may have exaggerated the effects seen in REDUCE-IT, an analysis showed the reduction in REDUCE-IT was similar both in those whose hsCRP increased or not [48]. Neutral effects from omega-3 were also reported in earlier studies [49,50]. The ASCEND (A Study of Cardiovascular Events in Diabetes) trial evaluated the efficacy of EPA and DHA in doses recommended by the Nutrition Committee of the American Heart Association, *i.e.*, 460 and 380 mg, respectively. After a mean follow-up of 7.4 years, there was no significant differences between the treatment and placebo groups with respect to the occurrence of a composite MI, stroke, transient ischemic attack, or vascular death: HR of 0.97 (95%CI 0.87-1.08; p=0.55) [51]. The superiority *vs* placebo of similar doses of EPA/DHA to reduce MI, stroke, or CVD death in primary prevention was the objective of the VITAL (Vitamin D and Omega-3 Trial) study [52]. Over a median of 5.3 years of follow-up, the HR was 0.92 (95%CI, 0.80-1.06; p=0.24) [52] (**Table 3, Figure 1**). Additionally , a major recent meta-analysis of 40 studies in over 135,000 participants demonstrated the marked benefits of this therapy in reducing major CVD outcomes [53], as well as in an updated analysis in 42 studies of 149,000 participants that included the STRENGTH [54-56]. (**Table 3, Figure 1**).

Nutraceuticals as Non-Absorbable Agents

In addition to PUFAs, the evaluation of nutraceuticals extends from dietary components of common foods to non-absorbable and absorbable agents, with recognized anti-inflammatory activities, and to specific functional foods.

Among non-absorbable nutraceuticals, sterols/stanols, soluble fibers (β-glucan, psyllium, glucomannan and non-fiber chitosan) might demonstrate anti-inflammatory properties, among others, due to their clear lipid-lowering activity [13]. The beneficial impact of **dietary fiber** on circulating CRP levels has been also observed in a comprehensive meta-analysis of RCTs [57], however, these results are still limited and inconclusive. An anti-inflammatory action of non-absorbable nutraceuticals has been reported in obese patients with osteoarthritis [58], but observational studies have not been still supported by controlled investigations.

Plant Stanol Eters are widely available as rapeseed oil-based spreads, and other phytosterols are commonly-used nutraceuticals for moderate cholesterol reduction (-10-15%) [59,60]; however, potentially rare harmful effects have been observed. These molecules, which affect cholesterol absorption, may lead to hypercholesterolemia and elevated CVD risk in some rare genetic abnormalities of the ABCG5/ABCG8 transporters [61].

Recently an inflammation-like phenomenon appeared to be reduced by plant stanol supplementation (2-3 g/d). Patients with modest cholesterol elevations experienced a clear reduction of low-density lipoprotein (LDL) aggregation after treatment with stanol esters [62]. The decrease in aggregation was more extensive in participants with a body mass index (BMI) <25 kg/m^2. Decreased aggregation was associated with a reduced proportion of LDL sphingomyelines and increased LDL triglycerides (TGs). Since LDL particles are more susceptible to aggregation in individuals with established CVD, an aggregation prone-LDL may predict future ASCVD independent of conventional CVD risk factors [63]. Further studies are still necessary to confirm their direct and indirect effects on different inflammatory parameters.

Nutraceuticals as Absorbable Agents

Among absorbable nutraceuticals, **probiotics** can reduce cholesterol by modifying gut flora, in particular, by providing enzymes catalyzing the transformation of cholesterol into cholest-4-en-one, an intermediate in the conversion to coprostenol or coprostanol, directly excreted into faeces. Probiotics such as *Lactobacillus acidophilus, Bifidobacterium bifidum* or *bulgaricus* can reduce the enterohepatic circulation of cholesterol by activation of bile-salt hydrolase [64], consequently increasing excretion [65]. Probiotics may also help to reduce the lecithin/carnitine

derived trimethylamine-N-oxide (TMAO) and the consequent inflammatory changes [66]. The anti-inflammatory activity of probiotics appears to be linked to immune regulation. Activated regulatory T (Treg) cells are reduced by *L. reuteri* in pregnant women in the second half of pregnancy with treatment independent changes in lymphocytes and monocytes and in subpopulations of T-helper cells [67]. Interest in the clinical use of *L.* reuteri has grown after the positive clinical studies in inflammatory bowel disease [68].

Among absorbable nutraceuticals, **flavonoids** are enjoying a growing interest. These compounds are widely consumed components of food. Subclasses of flavonoids, including catechins and flavanols, present in cocoa and green tea, have received the most interest [69]. They exert powerful antioxidant properties, together with the ability to inhibit the secretion of pro-inflammatory cytokines and chemokines from activated endothelial cells. The anti-inflammatory effect of flavanols has been demonstrated in a few studies by the supplementation of FRLFE (flavanol-rich lychee fruit extract) [70]. In healthy individuals, during submaximal and maximal exercise workloads, FRLFE supplementation (100 mg/d for four weeks and two months) reduced the concentrations of the pro-inflammatory cytokines IL-1β and IL-6 as well as cortisol. The concentration of TGF-β was increased. Supplementation with FRLFE for 30 days in regular exercising males at maximal workloads also significantly increased time to exhaustion [71].

The anti-inflammatory activity of flavanols may work in harmony with potential vascular protective effects, in particular those exerted by cocoa flavanols [72]. This recognition has led to the indication of *black flavanol-rich chocolate in blood pressure control*, which also has the potential to improve cognitive performance in the elderly [73-75]. A large clinical study on the preventive activity of a flavanol-rich cocoa-equivalent in hypertensive patients is ongoing and will also evaluate inflammatory markers (COcoa Supplement and Multivitamin Outcomes Study (COSMOS) [76]. This has led to the identification of possible additional indications, such as peripheral artery disease (PAD). A six-month double-blind RCT in these patients evaluated cocoa (15 g cocoa and 75 mg epicatechin daily) *vs* placebo. An improvement in the 6-min walk distance at the 6-month follow up, by 42.6 m 2.5 h after the final study beverage and 18 m at 24 h, compared with placebo, was reported [77]. Data from muscle biopsies in treated patients were clearly indicative of an improvement in microvascular parameters, with significantly raised mitochondrial and capillary densities, possibly dependent on higher VEGF-A (Vascular Endothelial Growth Factor-A) levels [78]. The antioxidant activity of flavanols does not appear to be related to changes in nitrotyrosine and 4-HNE (hydroxynonenal) [78]. An additional anti-inflammatory

activity relates to the reduction of the pro-inflammatory cytokine IL1-β [79]. Large studies investigating the flavanol content and inflammatory consequences of a Mediterranean diet, such as the Prevención con Dieta Mediterránea (PREDIMED) study, detected a reduction of inflammatory markers together with a clear CVD benefit [80] (**Table 3, Figure 2**).

Curcumin is a dietary polyphenol derived from the root of *Curcuma longa,* commonly known as turmeric. Curcuma contains approximately 5% curcuminoids by weight. Curcumin has traditionally been used for chemopreventive and antioxidant properties. Potential health benefit in metabolic syndrome has been reported, resulting in a significant decrement in serum concentrations of TNF-α, IL-6, TGF-β and monocyte chemoattractant protein-1 (MCP-1) [81]. Whilst curcumin exerts a modest lipid-lowering effect, potentiating the effects of phytosterols [82], it also exerts definite antioxidant and anti-inflammatory effects [83]. Potential mechanisms underlying this effect are thought to relate to inhibition of NF-κB and TLR-4 signalling and activation of the PPARγ pathway [84]. More recently, potential up-regulation of mir-126, leading to inhibition of PI3K/AKT and JAK2/STAT5 signalling pathways, has been reported [85]. These anti-inflammatory actions have been exploited to ameliorate symptoms and reduce the burden of clinical inflammation in several diseases (e.g., inflammatory bowel disease, psoriasis, etc.); these properties of curcumin are also currently under investigation in a variety of other clinical conditions in the ongoing studies [34,86,87]. A significant reduction of circulating IL-6 (standardized mean difference [SMD] -2.08) and CRP levels (SMD -0.65) was reported in a recent meta-analysis of 15 RCTs [88]. A previous meta-analysis of 6 trials testing the impact of curcuminoids on circulating CRP revealed that the overall significant anti-inflammatory effect of curcuminoids was dependent on the bioavailability of the different preparations [89].

The bioavailability of curcumin is low following oral use, and a number of reports have investigated if the use of novel formulations and absorption ehancers could boost the pharmacological effects [90]. Recently, a phospholipid-curcumin complex was found to be better absorbed and to provide higher benefit at a 250 mg/day dosage (equivalent to 50 mg of curcumin) in conditions such as non-alcoholic fatty liver disease (NAFLD). In a double-blind study, positive changes in the liver proteome were reported after 8 weeks of administration [90]. Moreover, several studies have shown that co-administration of curcumin with the alkaloid piperine might be effective in enhancing the bioavailability of the former; the anti-inflammatory effects of this combination has been reported in RCTs [91]. A prodrug hypothesis has been very recently proposed in order the explain the anti-inflammatory activity of curcumin in the absence of

adequate bioavailability [92]. Curcumin can undergo extensive glucuronidation in plasma and curcumin glucuronide may act as an inflammation responsive natural prodrug, being later converted back to curcumin in inflamed target tissues. By this mechanism, curcumin would act as a direct anti-inflammatory and potentially anti-tumoral agent [92] (**Table 3, Figure 2**).

Bergamot is the common name of the fruit *Citrus bergami, Risso.* It differs from other Citrus fruits in composition and richness in flavonoids. Bergamot essential oil (BEO) and bergamot juice (BJ) contain up to 93-96% volatile compounds such as monoterpenes (mainly limonene) and 4-7% nonvolatile compounds, such as pigments, waxes, coumarins, and psoralens [93]. Some Bergamot fractions were found to have statin-like actions, inhibiting HMG-CoA reductase [94], indicating that bergamot (generally at the dose of 1000 mg/day) can lower total and LDL-cholesterol in patients, in addition to reducing oxidized LDL [95]. Its lipid-lowering potential and safety has led to the recommendations of bergamot in statin intolerant patients (IIa B) in the ILEP Position Paper in 2018 [96].

The anti-inflammatory activity of bergamot might be associated with a reduction in pro-inflammatory cytokines [97], the mechanism occurring via sirtuin-1 (SIRT-1)-mediated NF-κB inhibition in THP1 monocytes. An *in vitro* protective effect of bergamot peel extract on endothelial cells exposed to tumour TNF-α was found to be associated with reduced intracellular levels of malondialdehyde/4-hydroxynonenal and raised oxidized glutathione and superoxide dismutase activities [98]. The anti-inflammatory activity of bergamot could be of potential clinical interest, as reported in experimental *periodontal disease*, where bergamot reduced tissue injury and several markers of gingival inflammation, including nuclear NF-κB translocation, cytokine expression, myeloperoxidase activity and adhesion molecules such as ICAM and P-selectin [99]. In inflammatory bowel disease, administration of bergamot was found to reduce the release of pro-inflammatory cytokines and decrease apoptosis, with an increase of antiapoptotic BCL-2 in a model of ischemia-reperfusion injury [100]. Bergamot appears not to exert any serious adverse effects, and interest in the potential use in dental and cardiological patients remains active, however more clinical data on the potential anti-inflammatory activities of bargamot is still necessary (**Table 3, Figure 2**).

Garlic (*Allium sativum*) has been traditionally believed to be endowed with numerous beneficial properties, including lipid-lowering and antihypertensive actions. While many of these actions have not been definitively confirmed, a number of studies have reported potential activity of garlic in allergic conditions and dermatitis [13]. Garlic contains the non-protein aminoacid

allicin, characterized by the content of hydrogen sulphide (H_2S), a potential nitric oxide (NO) agonist [13]. Recently a large meta-analysis of 16 RCTs [101] reported that garlic doses ranging from 1200 to 3600 mg/d for a duration of 2 to 52 weeks significantly reduced CRP (-0.61 mg/L), IL-6 (0.73 ng/L) and TNF-α (-0.26 ng/L), with no activity on adiponectin and leptin, thus indicating that a potential mechanism on inflammatory and CVD disorders needs still to be evaluated. A further activity of potential clinical interest is the antagonism of the pro-inflammatory adipocytokines resistin and TNF-α by garlic supplementation leading to reduced severity of pain in overweight and obese women with knee osteoarthritis in a RCT [102] (**Table 3, Figure 2**).

Berberine is a quinolone alkaloid found in various medicinal plants, including *Coptis chinensis* and *Berberis aristata*. In addition to the many traditional activities described in the old literature, recent years have provided evidence of significant stimulatory activity on LDL receptors (with the class IA in the ILEP recommendations) [13,103]. This experimental observation was later supported by numerous studies in hyperlipidemia and diabetes. Berberine also appears to have a unique mechanism, *i.e.*, that of reducing peripheral branched-chain amino acids (BCAA); by this mechanism, it can improve insulin resistance in experimental models and in humans [104]. This mechanism may be potentially associated with direct anti-inflammatory effects described in animal models such as *apo* $E^{-/-}$ mice [105], thus suggesting the potential to reduce atheroma plaque size, vulnerability, inflammation and oxidative stress. Unfortunately, the bioavailability of berberine is poor, but clinical use in European countries in combination with red yeast rice (RYR) has found wide support [106]. An unexpected activity of berberine was recently observed in a model of experimental NAFLD, i.e. the reduction of the inflammatory response by way of SIRT3-mediated long-chain acyl CoA dehydrogenase (LCAD) deacetylation [106]. In NAFLD induced by a high-fat diet in mice, pro-inflammatory cytokines (CCL2, TNF-α) are increased, as is the infiltration of inflammatory cells (CCR2), hepatic mRNA and levels of angiopoietin-like 2 (Angptl2), NF-κB and forkhead box protein O1 (Foxo1). Following berberine treatment, liver tissue pathology, biochemical data, and the Angptl2 pathway-related genes are significantly ameliorated [107].

Despite a lipid-lowering potential and available experimental studies with berberine on its antiinflammatory properties, there are still limited clinical data on the potential role of berberine on the inflammatory parameters. The meta-analysis of 5 RCTs showed that serum levels of CRP were significantly decreased after berberine supplementation (-0.64 mg/L). Based on these results, the authors concluded that especially CVD and diabetic patients are two important groups, which might benefit from berberine supplementation, however further well-designed, longer

studies with larger samples are needed to ascertain the effects of berberine on chronic inflammation [108] (**Table 3, Figure 2**).

RYR is a prodrug derived from a contaminant of rice containing the yeast *Monascus purpureus*, from which statins were originally extracted. RYR contains monacolin K, chemically identical to lovastatin, in concentrations around 2%. A number of studies have evaluated RYR by itself or as purified derivatives enriched with monacolin K. The cholesterol-lowering activity has been well described and is comparable with that of lovastatin [109]. In the last several years, there has been a substantial debate on RYR safety, however, recent raports, including postmarketing nutrivigilance reports (based on data from 2.3 million consumers), clearly confirmed its safety, even in patients with statin intolerance [110-112].

A raw extract of RYR, xuezhikang, given in doses of 1200 to 1400 mg/day, was associated with a 45% reduction in CHD events over 4.5 years, as well as significant reductions in CVD and total mortality in a large controlled secondary prevention study [113]. In CHD patients, xuezhikang (1200 mg/day) given for six weeks also led to a 50% reduction in fasting hsCRP reduction compared with placebo. This decrement was correlated with improved preprandial and postprandial flow-mediated dilatation (FMD) an index of endothelial function [114]. Similar conclusions were reached when patients with stable angina were considered. After 14 days, xuezhikang (1200 or 2400 mg/day) reduced the levels of hsCRP by roughly 28% from baseline values, an effect irrespective of the dose [115].

A number of specifically targeted studies of RYR in inflammation have been published recently, potentially indicating an improvement of endothelial dysfunction. Monacolin K promotes and stabilizes the expression of endothelial nitric oxide synthase (eNOS) and uncouples tetrahydrobiopterin (BH4) [116]. The anti-inflammatory mechanism of RYR is quite similar to that of statins, *i.e.*, suppression of NF-kB binding to cells and inhibition of the IP3K/AKT/nGOR pathway and histone deacetylase 1 [117]. This may lead to the inhibition of mitogen-activated protein kinases (MAPKs) participating in inflammation through various subfamilies (JNK, ERK 1/2 and p38 kinase). Inflammation occurring atherosclerosis induced by a high-fat diet is suppressed by RYR *via* the blocking of MAPK signalling pathways [118]. RYR may thus reduce the expression of pro-inflammatory mediators through the PK signalling pathway and inhibited NO release, thereby ameliorating inflammation-linked diseases mediated by excessive and/or prolonged activation of immune cells [119] (**Figure 2**). In *in vitro* conditions RYR reduced TNFα by down-regulating the NF-κB activatity and reducing the intracellular production of reactive oxygen species (ROS) in aortic

smooth muscle cells (SMC) [120], thus supporting the conclusion that the anti-inflammatory effect may be similar to that of statins and may be of potential benefit in CVD prevention [121,122] **(Table 3).**

Dietary Plant Proteins

Dietary plant proteins have been associated, in a number of recent epidemiological studies, with a significant protective effect against CVD [123]. Dietary studies with the use of specific proteins have largely focused on soy and lupin. The use of soy proteins for the treatment of hypercholesterolemia dates back several decades [124,125]. In recent years, this type of dietary approach to severe hypercholesterolemia has been utilized to a far lesser extent, mainly because of the commercial availability of statins, which have dramatic activity on upregulating the LDL receptor on hepatocytes.

Among the consequences of frequent use of this diet among normocholesterolemic or moderately hypercholesterolemic individuals, a number of erroneous conclusions were drawn. The first is that soy proteins do not possess a hypocholesterolemic activity: this was contradicted by the observation that soy proteins and components such as the 7S globulin markedly activate LDL-R expression in animals [126] and in patients with familial hypercholesterolemia [127]. The second erroneous conclusion is that other components such as phytoestrogens present to a variable extent in commercial soy preparations but absent, *e.g.* in lupin, may be responsible. Phytoestrogens do not exert any significant hypocholesterolemic activity [128, 129].

The anti-inflammatory activity of soy and lupin proteins is again likely dependent in both cases on the protein component [130], but the presence in soy of other non-protein moieties may perhaps contribute to some extent to the anti-inflammatory activity without having any effect on cholesterol.

Soy Proteins. Dietary soy proteins are available as a mixture of proteins and peptides, with additional components, including fibers and phytoestrogens. Phytoestrogens may be of some benefit in the relief of symptoms in post-menopausal women. However, the results of the studies are not conclusive [131]. Some clinical benefit on inflammatory markers was reported in women with metabolic syndrome [132]. In this last study, consumption of soy-nut was compared with that of soy proteins and red meat. Soy-nut exerted a clearly better anti-inflammatory activity

compared with soy proteins and red meat. In particular, IL-18 was reduced by -9.2% by soy-nuts compared with meat, but soy proteins had no activity. With respect to CRP, the difference from the red meat diet was significant (-8.9%) on the soy-nut diet and -1.6% on the soy protein diet [132]. While in this study, phytoestrogen intake may have played an important role, more recent studies have been focused on the protein components themselves. Detailed investigations have described bioactive anti-inflammatory peptides (BAPs) released from dietary proteins by enzymatic digestion in the intestine. BAPs, at concentrations of 200-1,000 μM, inhibit inflammation by the MAPK or NFK-β pathways [133]. This type of antagonism to inflammatory cytokine expression can also be exerted by soybean derived dipeptides and tripeptides [134].

Contradictory and inconclusive findings have been reported in two meta-analyses evaluating the effect of soy supplementation on inflammatory biomarkers. The first meta-analysis comprising 36 studies published before December 2016 showed a non-significant 0.19 mg/dL reduction in the levels of hsCRP after consumption of soy products [135]. Subgroup analysis highlighted that this effect was mainly driven by natural soy products in comparison with other sources of isoflavones, being the levels of the latter significantly correlated with serum hsCRP [135]. A second meta-analysis comprising 51 RCT reported that supplementation with soy products led to a significant reduction of hsCRP (-0.27 mg/L; 95%CI -0.51, -0.02) but not IL-6 and TNF-α. However, the effect became significant when studies with a long-term design (≥12 weeks) and low dose isoflavone (<100 mg/day) were chosen [136].

The soy diet has been shown to result in remarkably reduced colon inflammation in pigs with dextran-sulphate induced colitis [134]. Furthermore, clear evidence has now been provided that these small molecules can be transported from the intestine into the bloodstream of humans or animals by the peptide transporter (hPepT1) system [137], thus indicating the potential for soybean proteins to affect generalized inflammatory diseases such as atherosclerosis and hypertension [138]. The potential of soy protein diets to exert lipid-lowering effects in hypercholesterolemic individuals, and to affect inflammation, may lead to advances in the prevention of ASCVD and the development of protein or peptide fractions with improved activity (**Table 3, Figure 2**).

Lupin Proteins. Proteins from white lupin seed are essentially phytoestrogen free and exert a similar activity to soy on cholesterolemia in rodents [139,140]. This occurs *via* stimulation of the activity of LDL-R. Proteins from lupin have been investigated to a lesser extent than soy in the clinical treatment of hypercholesterolemia, but results have been encouraging [141]. Some lupin

proteins have been demonstrated to have anti-inflammatory activity. The most active is γ-conglutin, a small protein that is associated with improvements in insulin resistance *in vitro* [142]. This protein has been extensively studied for a potential hypoglycemic activity [143], but in addition, it has been shown to have a potential role in the regulation of blood pressure by inhibiting the activity of angiotensin converting enzyme (ACE) [144]. Peptides with inhibitory activity against ACE can be obtained by direct enzymatic hydrolysis of lupin [145]. These peptides appear to provide a range of potential activities besides those on lipids and blood pressure. Specifically, the anti-inflammatory activity [146], in addition to the lipid-lowering mechanism, may offer an important tool for CVD prevention. Lupin peptides were recently investigated for their anti-inflammatory activity on RAW264.7 cells (cell line origin: mouse monocyte macrophage) [147]. Among peptides isolated from the gastroduodenal digests of extruded lupin, the lupine peptide monomer IQDKEGIPPDQQR was the most promising, significantly inhibiting lipoprotein polysaccharide (LPS) induced activation of TNF-α, IL-6, IL-1β and MCP-1 production by 40-50% at a concentration of 10 μM [147]. Lupin proteins appears not to exert any serious adverse effects, however clinical data on their potential anti-inflammatory activities is mandatory (**Table 3, Figure 2**).

CONCLUSIONS

Increased recognition of the problem of residual CVD risk in optimally drug-treated patients has led to more intensive evaluation of non-drug approaches, in particular nutraceuticals. Most available data relates to the effect of nutraceuticals on selected inflammatory parameters, and we must strongly emphasize the fact that nutraceuticals cannot replace pharmacological treatment. Neverthess, they might be useful, especially given the currently limited range of options for therapeutic antiinflammatory agents, particulatly at the present time when optimal therapy is necessary during the COVID-19 pandemic.

Indeed, as has been reviewed elsewhere [12], not all recent drug-based anti-inflammatory interventions aimed at reducing CVD burden have been successful. While in the CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial, the use of canakinumab (anti-IL1β) led to a 15% reduction in CVD events, and a similar outcome occurred in the COLCOT (Colchicine Cardiovascular Outcomes Trial) study with colchicine (-13%), a neutral effect was described in the CIRT (Cardiovascular Inflammation Reduction Trial) study with methotrexate (HR 1.01; 95% CI 0.82-1.25). Furthermore, in an Australian trial enrolling patients with acute coronary

syndromes, the addition of colchicine to standard medical therapy did not significantly affect CVD outcomes at 12 months and was associated with a higher rate of mortality [148]. Irrespective, of these findings, none of these drugs is yet available on the market to treat inflammatory-linked CVD residual risk. Only colchicine seems likely to enter clinical practice in the near future, and only in patients with strictly limited indications [149,150].

This detailed overview of nutraceuticals addresses their effects on inflammatory parameters and offers a promising insight into the role of natural molecules or functional foods with the potential to reduce the inflammatory burden associated with CVD. These are the first recommendations that provide a clear message on the nutraceuticals with the potential to reduce inflammation. These generally well-tolerated products are increasingly used [112] in the community and may provide, due to their multiple properties (lipid-lowering, anti-inflammatory, anti-oxidant, hypoglycemic, etc.), some benefits in conditions of raised CVD risk, which is not fully addressed by currently available pharmacological treatments.

In addition to the effectiveness of selected nutraceuticals to reduce inflammatory parameters levels, equally important (despite currently insufficient data), is that these therapies appear to be safe and well tolerated. However, further studies in individuals with inflammatory conditions, especially in those with residual CVD risk due to inflammation (with a suitably large group of patients and longer follow-up), are still necessary to confirm the effectiveness and safety of nutraceuticals (at a specific dosage), to prove that they maintain their efficacy in the long-term, as well as to answer the question of whether these therapies might have a positive effect on CVD outcomes.

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Table 1. Classes of recommendation.

Classes of Recommendations	Definition	Suggested Wording to Use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/ is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2. Level of evidence.

Level of evidence	Definition
A	Data derived from multiple randomized clinical trials or their meta-analysis
B	Data derived from single randomized clinical trial or large non-randomized studies
C	Data from preclinical or *in vitro* studies

Table 3. ILEP recommendations on the effect of nutraceuticals on inflammatory parameters.

	Class	Level		
Omega- 6 fatty acids	IIb	B	No inhibition of CRP, IL-6, soluble (s)TNF-R and sTNF-R2	[21]
			Positively associated with IL-1RA and negatively with IL-10 and TGF-β, anti-inflammatory cytokines	[22]
			Reduction of IL-1RA and TNF-R2. No changes in CRP, IL-1β, IL-6 and IL-10	[23]
Omega- 3 fatty acids[1]	I	A	EPA+DHA therapy (2.5 g/d) reduced IL-6, IL-1β and TNF-alfa	[37]
			Compared with EPA, DHA led to a greater reduction of IL-18 (-7.0% *vs* -0.5%), hs-CRP (-7.9% vs -1.8%) and TNF alfa (-8% *vs* -7.6%). Reductions of IL-6 were similar (-12.0% *vs* -13.4%)	[39]
			Purified EPA may have effect on red cell distribution width (RDW) and its association with chronic inflammation and red blood cells deformability	[41,42]
			EVOLVE study (omega-3 free fatty acid 2, 3 or 4 g/day) no significant changes in hs-CRP from baseline (-0.3 mg/L) compared with placebo (-0.2 mg/L)	[47]
			REDUCE-IT study (icosapent ethyl 4 g/day) hsCRP: -37.6% (between group difference)	[43]
			STRENGTH study (carboxylic acid formulation of EPA and DHA) hs-CRP: -20.0% in the group receiving omega-3 carboxylic acid formulation *vs* −6.3% in the placebo	[45]

			arm.	
Flavonoids	IIa	B	Reduction in IL-1β and IL-10	[75]
Curcumin	IIa	B	A significant decrement in serum concentrations of TNF-α, IL-6, TGF-β and MCP-1	[77]
			TNF-α, -4.69 pg/mL	[79]
Bergamot	III	C	*In vitro*: decrement in intracellular levels of malondialdehyde/4-hydroxynonenal	[94]
			Preclinical periodontal disease: reduced tissue injury and several markers of gingival inflammation In inflammatory bowel disease: reduce the release of pro-inflammatory cytokines	[95] [96]
Garlic	IIb	B	Doses ranging from 1200 to 3600 mg/d for a duration of 2 to 12 weeks significantly reduced CRP (-0.61 mg/L), IL-6 (0.73 ng/L) and TNF-α (-0.26 ng/L)	[97]
Berberine	IIb	B	Berberine might attenuate the liver inflammatory response in the livers of rats with high-fat diet-induced NAFLD	[103]
			In the meta-analysis of 5 RCTs showed that serum levels of CRP were significantly decreased after barberine supplementation (-0.64 mg/L).	[104]
RYR^{2}	I	A	hsCRP: -50%	[110]
			hsCRP: -28%	[111]
Soy	IIa	A	CRP: soy-nut diet led to a -8.9% compared with red meat diet.	[128]

			IL-18: soy-nuts diet led to -9.2% compared with red meat diet.	
			Meta-analysis: a non-significant 0.19 mg/dL reduction in the levels of hsCRP upon consumption of soy products	[131]
			Meta-analysis: significant reduction of hsCRP (-0.27 mg/L; 95%CI -0.51, -0.02) but not IL-6 and TNF-α	[132]
Lupin	III	C	*In vitro* data: IQDKEGIPPDQQR was the most promising, significantly inhibiting lipoprotein polysaccharide (LPS) induced activation of TNF-α, IL-6, IL-1β and MCP-1 production by 40-50% at a concentration of 10 µM.	[143]

ABBREVIATIONS: hsCRP, high-sensitivity C-reactive protein; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; NAFLD, non-alcoholic fatty liver disease; TGF-β, transforming growth factor; TNF-α, tumor necrosis factor alfa; EVOLVE, Epanova® for Lowering Very High Triglycerides; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; STRENGTH, Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia.

[1]*There are some safety concerns based on the available studies. In the REDUCE-IT trial, an increase in the rate of hospitalization for atrial fibrillation (AF) and peripheral edema in the IPE vs placebo group (5.3% vs 3.9%, p=0.003, and 6.5% vs 5.0%, p=0.002, respectively), were observed.*

[2]*There are some safety concerns on RYR- related muscle adverse events. Based on the European Food Safety Authority (EFSA) Scientific Opinion from 2018, RYR is not available in all countries (e.g. in Switzerland). A new EU/EFSA Regulation is expected on its permissible dosage and safety.*

FIGURE LEGENDS:

Figure 1. Role of omega-6 and omega-3 fatty acids on inflammatory pathways.

LA, EPA and DHA are incorporated into the phospholipids of cell membranes at the expense of ARA. LA can also be converted, through a series of steps, to γ-linolenic acid, dihomo-γ-linolenic acid and to ARA) which is also incorporated into phospholipids of cell membranes. Phospholipase A2 catalyzes the release of LA, ARA, EPA and DHA which undergo intracellular metabolism. LA is converted to proinflammatory mediators oxo-HODEs and epoxy-HODEs while ARA to PGG2 and PPGH2. LA consumption is negatively associated with IL-1RA, IL-10, TGF-β and TNF-R2. EPA and DHA are metabolized by CYP450, 15-lipoxygenase, 12-lipoxygenase and 5-lipoxygenase leading to the formation of the pro-resolving lipid mediators, such as resolvins, protectin, and maresins. These molecules have been shown to reduce the expression of profinflammatory cytokines IL-1β, IL-6, IL-18 and TNF-α. EPA and DHA have been shown to reduce hs-CRP plasma levels. The anti-inflammatory effect may affect neutrophil activation, diapedesis and ROS synthesis. Reduced expression of adhesion molecules, pro-inflammatory cytokines and ROS production may be observed in endothelial cells. Finally, reduced dendritic cell migration and IL-12 may also be predicted.

Abbreviations: *Arachidonic acid (ARA); Docosahexaenoic acid (DHA); Eicosapentaenoic acid (EPA); High-sensitivity C-reactive protein (hsCRP); Interleukin (IL); Linoleic acid (LA); Phospholipase A2 (PLA2); Prostaglandin G2 (PGG2); Prostaglandin H2 (PGH2); Reactive oxygen species synthesis (ROS); Tumor necrosis factor (TNF); Tumor necrosis factor receptor (TNF-R).*

Figure 2. Basic mechanism for the anti-inflammatory effect of absorbable agents.

Accumulation of cholesterol in the atherosclerotic plaque determines the recruitment of macrophages and the activation of the inflammasome system. NLRP3 induces caspase-1 activation which, in turn, cleaves pro-IL-1β and pro-IL-18 to their active counterparts that induce IL-6. In the liver, IL-6 induces CRP synthesis, a clinically proven biomarker of inflammatory status and cardiovascular risk. The effect of different nutraceuticals on pro-inflammatory and anti-inflammatory mediators are depicted.

Abbreviations: *C-reactive protein (CRP); Interleukin (IL); β-Hydroxy β-methylglutaryl-CoA (HMG-CoA); NACHT-, LRR- and pyrin domain-containing 3 (NLRP3).*

#International Lipid Expert Panel Experts (alphabetically):

Julio Acosta (Cátedra de Cardiología Clínica de la Escuela Médica Razetti de la Universidad Central de Venezuela, Caracas, Venezuela); *Mutaz Al-Khnifsawi* (Al-Qadisiyah University, Faculty of Medicine, Department of Internal Medicine, Diwaniya City, Iraq); *Fahad Alnouri* (Cardiovascular Prevention Unit, Adult Cardiology Department. Prince Sultan Cardiac Centre Riyadh, Saudi Arabia), *Fahma Amar* (Unit of Diabetes & Metabolism, Alexandria University, Alexandria, Egypt), *Atanas G. Atanasov* (Institute of Genetics and Animal Biotechnology of the Polish Academy of Sciences, Jastrzebiec, Poland; Department of Pharmacognosy, University of Vienna, Vienna, Austria; Ludwig Boltzmann Institute for Digital Health and Patient Safety, Medical University of Vienna, Vienna, Austria), *Gani Bajraktari* (Institute of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; Clinic of Cardiology, University Clinical Centre of Kosovo, Prishtina, Kosovo; Medical Faculty, University of Prishtina, Prishtina, Kosovo), *Maciej Banach* (Department of Hypertension, Medical University of Lodz, Poland; Cardiovascular Research Centre, University of Zielona-Gora, Zielona-Gora, Poland), *Sonu Bhaskar* (Department of Neurology & Neurophysiology, Liverpool Hospital and South Western Sydney Local Health District, Sydney, NSW, Australia); *Bojko Bjelakovic* (Clinic of Pediatrics, Clinical Center, Nis, Faculty of Medicine, University of Nis, Serbia), *Eric Bruckert* (Pitié-Salpetrière Hospital and Sorbonne University, Cardio metabolic Institute, Paris, France), *Richard Ceska* (Third Department of Medicine - Department of Endocrinology and Metabolism of the First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic), *Arrigo F.G. Cicero* (IRCCS Policlinico S.Orsola-Malpighi, University of Bologna, Italy), *Xavier Collet* (Institute of Metabolic and Cardiovascular Diseases, Inserm, Toulouse, France), *Olivier Descamps* (Department of Internal Medicine, Centres Hospitaliers Jolimont, Haine Saint Paul, Belgium; Department of Cardiology, Cliniques Universitaires Saint-Luc, Bruxells, Belgium), *Dragan Djuric* (Institute of Medical Physiology "Richard Burian" Faculty of Medicine, University of Belgrade, Belgrade, Serbia), *Ronen Durst* (Cardiology Department, Hadassah Hebrew University Medical Center, Ein Kerem, Jerusalem, Israel), *Marat V. Ezhov* (National Medical Research Center of Cardiology, Moscow, Russia), *Zlatko Fras* (Preventive Cardiology Unit, Department of Vascular Medicine, Division of Medicine, University Medical Centre Ljubljana, Slovenia; Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia), *Dan Gaita* (Institutul de Boli Cardiovasculare, Universitatea de Medicina si Farmacie Victor Babes din Timisoara, Romania), *Adrian V. Hernandez* (Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, Storrs, CT, USA; Vicerrectorado de Investigación, Universidad San Ignacio de Loyola (USIL), Lima, Peru), *Steven R. Jones* (the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD, USA), *Jacek Jozwiak* (Department of Family Medicine and Public Health Faculty of Medicine University of Opole, Opole, Poland), *Nona Kakauridze* (Department of Internal Medicine, Faculty of Medicine, Tbilisi State Medical University, Tbilisi, Georgia), *Amani Kallel* (University of Tunis El Manar, Faculty of Medicine of Tunis, Tunis, Tunisia); *Niki Katsiki* (Diabetes Center, Division of Endocrinology and Metabolism, First Department of Internal Medicine, AHEPA University Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece), *Amit Khera* (Department of Cardiology, UT Southwestern Medical Center, Dallas, TX, USA), *Karam Kostner* (Mater Hospital, University of Queensland, St Lucia, QLD, Australia), *Raimondas Kubilius* (Department of Rehabilitation, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania), *Gustavs Latkovskis* (Institute of Cardiology and Regenerative Medicine, Faculty of Medicine, University of Latvia, Riga, Latvia; Pauls Stradins Clinical University Hospital, Riga, Latvia), *G.B. John Mancini* (Department of Medicine, Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada), *A. David Marais* (Chemical Pathology Division of the Department of Pathology, University of Cape Town Health Science Faculty, Cape Town, South Africa), *Seth S. Martin* (Ciccarone Center for Prevention of Heart Disease, Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA), *Julio Acosta Martinez* (Medico Cardiologo de la Policlinica Metropolitana, Carcass, Venezuela), *Mohsen Mazidi* (Department of Twin Research and Genetic Epidemiology, King's College London, St Thomas' Hospital, Strand, London, UK), *Dimitri P. Mikhailidis* (Department of Clinical Biochemistry, Royal Free Campus, University College London Medical School, University College London (UCL), London, UK), *Erkin Mirrakhimov* (Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan), *Andre R. Miserez* (diagene Research Institute, Reinach, Switzerland; University of Basel, Basel, Switzerland), *Olena Mitchenko* (Dyslipidaemia Department, Institute of Cardiology AMS of Ukraine,

Ukraine), *Natalya P. Mitkovskaya* (Belarusian State Medical Univer- sity, Minsk, Republic of Belarus), *Patrick M. Moriarty* (Division of Clinical Pharmacology, Division of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas, USA), *Seyed Mohammad Nabavi* (Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran), *Devaki Nair* (Department of Clinical Biochemistry, the Royal Free London NHS Foundation Trust, Pond Street, London, UK), *Demosthenes B. Panagiotakos* (School of Health Science and Education, Department of Nutrition and Dietetics, Harokopio University of Athens, Athens, Greece), *György Paragh* (Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary), *Daniel Pella* (1st Department of Internal Medicine, Faculty of Medicine, Pavol Jozef Safarik University, Košice, Slovakia), *Peter E. Penson* (School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK), *Zaneta Petrulioniene* (Vilnius University Faculty of Medicine, Vilnius, Lithuania; Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania), *Matteo Pirro* (Department of Medicine, University of Perugia, Perugia, Italy), *Arman Postadzhiyan* (Bulgarian Society of Cardiology, Medical University of Sofia, Sofia, Bulgaria), *Raman Puri* (I P Apollo Hospital, New Delhi, India), *Ashraf Reda* (Menoufia University, President of EAVA), *Željko Reiner* (University Hospital Center Zagreb, Department of Internal Medicine, School of Medicine, University of Zagreb, Zagreb, Croatia), *Dina Radenkovic* (Health Longevity Performance Optimisation Institute, Cambridge, UK), *Michał Rakowski* (International Lipid Expert Panel, Poland; The Bio-Med-Chem Doctoral School of the University of Lodz and Lodz Institutes of the Polish Academy of Sciences / University of Lodz, Faculty of Biology and Environmental Protection, Department of Molecular Biophysics, University of Lodz, Lodz, Poland); *Jemaa Riadh* (Laboratory of Biochemistry, Faculty of Medicine of Tunis, Rabta Hospital, University of Tunis El Manar, Tunis, Tunisia), *Dimitri Richter* (Cardiac Department, Euroclinic, Athens, Greece), *Manfredi Rizzo* (Biomedical Department of Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy), *Massimiliano Ruscica* (Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy), *Amirhossein Sahebkar* (Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran), *Naveed Sattar* (Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK), *Maria-Corina Serban* (Department of Functional Sciences, Discipline of Pathophysiology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania), *Abdulla M.A Shehab* (Medical Education Department, United Arab Emirates University, Al Ain, United Arab Emirates), *Aleksandr B. Shek* (Department of Ischemic Heart Disease and Atherosclerosis, Republican Specialised Center of Cardiology, Tashkent, Uzbekistan), *Cesare R. Sirtori* (Dipartimento di Scienze Farmacologiche e Biomolecolari, Università di Milano Centro Dislipidemie, Grande Ospedale Metropolitano, Niguarda Ca'Granda President, Fondazione Carlo Sirtori), *Claudia Stefanutti* (Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy), *Tomasz Tomasik* (Department of Family Medicine, Jagiellonian University Medical College, Krakow, Poland), *Peter P. Toth* (The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD, USA), *Margus Viigimaa* (Tallinn University of Technology, North Estonia Medical Centre, Tallinn, Estonia), *Pedro Valdivielso* (Catedrático de Medicina, Departamento de Medicina y Dermatología, Universidad de Málaga, España), *Dragos Vinereanu* (Cardiology Department, University and Emergency Hospital, Bucharest, Romania, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania), *Branislav Vohnout* (Institute of Nutrition, Faculty of Nursing and Health Professional Studies and Coordination Centre for Familial Hyperlipoproteinemias, Slovak Medical University in Bratislava, Bratislava, Slovakia; Institute of Epidemiology, School of Medicine, Comenius University, Bratislava, Slovakia), *Stephan von Haehling* (Department of Cardiology and Pneumology, Heart Center Göttingen, University of Göttingen Medical Center, Georg-August-University, Göttingen, Germany), *Michal Vrablik* (1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic), *Nathan D. Wong* (Department of Medicine, School of Medicine University of California, Irvine, CA, USA; Heart Disease Prevention Program, Division of Cardiology, University of California, Irvine, California, USA), *Hung-I Yeh* (Department of Medicine, Mackay Medical College, Taipei, Taiwan; Cardiovascular Division, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan), *Jiang Zhisheng* (Institute of Cardiovascular Disease, University of South China, Hengyang, Hunan, China), *Andreas Zirlik* (University Heart Centre Freiburg University, Department of Cardiology and Angiology I, Faculty of Medicine, University of Freiburg, Freiburg, Germany).

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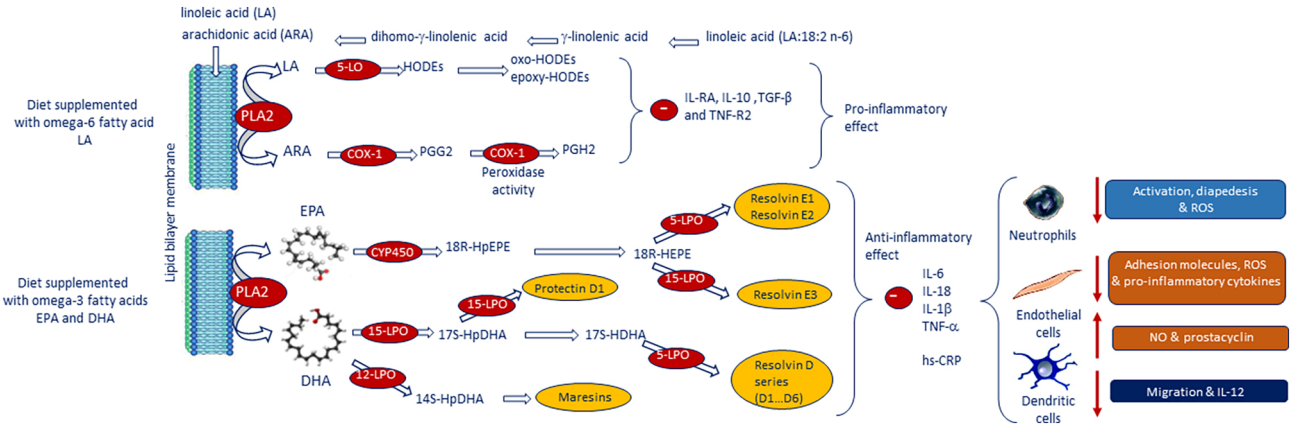
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arachidonic acid (ARA)
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Diet supplemented with omega-3 fatty acids EPA and DHA
Lipid bilayer membrane
PLA2
LA
ARA
5-LO
HODEs
oxo-HODEs
epoxy-HODEs
COX-1
PGG2
PGH2
Peroxidase activity
IL-RA, IL-10 ,TGF-β and TNF-R2
Pro-inflammatory effect
EPA
DHA
CYP450
18R-HpEPE
18R-HEPE
5-LPO
15-LPO
Resolvin E1
Resolvin E2
Resolvin E3
Protectin D1
17S-HpDPHA
17S-HDHA
12-LPO
14S-HpDHA
Maresins
Resolvin D series (D1...D6)
Anti-inflammatory effect
IL-6
IL-18
IL-1β
TNF-α
hs-CRP
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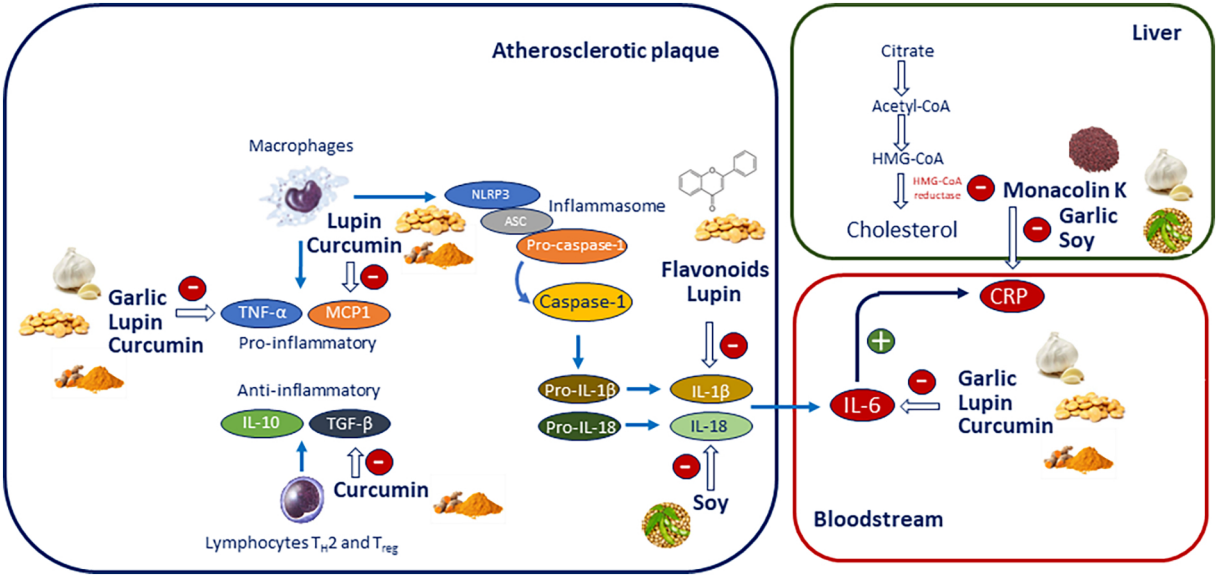
Endothelial cells
Dendritic cells
Activation, diapedesis & ROS
Adhesion molecules, ROS & pro-inflammatory cytokines
NO & prostacyclin
Migration & IL-12

Figure 1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IL-1β
IL-18
Anti-inflammatory
IL-10
TGF-β
Curcumin
Soy
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Liver
Citrate
Acetyl-CoA
HMG-CoA
HMG-CoA reductase
Cholesterol
Monacolin K
Garlic
Soy
CRP
IL-6
Garlic
Lupin
Curcumin
Bloodstream

Figure 2