Review

Non-Communicable Diseases: New Potential Therapeutic Application of n-3 Polyunsaturated Fatty Acids, Specialized Pro-Resolving Mediators and Prebiotics/Probiotics

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Non-Communicable Diseases: New Potential Therapeutic Application of n-3 Polyunsaturated Fatty Acids, Specialized Pro-Resolving Mediators and Prebiotics/Probiotics

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Abstract: There is overwhelming evidence of the anti-inflammatory effects of n-3 polyunsaturated fatty acids (n-3 PUFAs) and probiotics/prebiotics in different chronic non-communicable diseases (NCDs), such as metabolic syndrome, type 2 diabetes, hypertension, cardiovascular disease (CVD), non-infectious respiratory disease, chronic kidney disease, neurodegenerative and autoimmune diseases (i.e., rheumatoid arthritis), and various types of cancers. This review aims at describing and analysing the interplay among marine n-3 (PUFAs), gut microbiome and CVD. Furthermore, we discuss the beneficial role of marine n-3 PUFAs and/or probiotics/prebiotics in the treatment of CVD.

Keywords: Cardiovascular disease; inflammation; calcific aortic valve disease; microbiota; n-3 polyunsaturated fatty acids; specialized pro-resolving mediators; prebiotics; probiotics

1. Introduction

1.1. Atherosclerosis and Inflammation

Nowadays, two major pathways seem to be responsible for the development and progression of atherosclerosis, namely, high levels of low-density lipoprotein-cholesterol (LDL-C) and low-grade vascular inflammation [1,2]. Indeed, the accumulation of pro-inflammatory lipoproteins (mainly LDL) in the vessel wall predisposes the release of free cholesterol that can self-aggregate into crystalline forms, eventually triggering the activation/dysfunction of endothelial cells as well as the inflammatory process, leading to the early steps and progression of atherosclerosis [3,4]. Different studies have documented that the endothelial dysfunction is followed by the activation of NLRP3 (NACHT, leucin-rich repeat, and pyrin domain-containing protein 3) inflammasome and production of inflammasome-dependent cytokines, including interleukin (IL)-1beta and IL-18 [5]. IL-1beta locally promotes coagulation factors and platelet activation, thus inducing plaque rupture and thrombosis. While, systematically it stimulates IL-6 synthesis with hepatic production of C-reactive protein (CRP), that maintain a vicious cycle responsible for increasing cardiovascular (CV) events [6,2]. Conversely, IL-18 cooperates with IL-12 in stimulating the production of interferon (IFN)-γ from T and natural killer (NK) cells, eventually leading to NK cell activation, T helper (Th) 1 cell skewing and up-regulation of antigen presentation [7]. Several diseases are driven by elevated IL-18 levels, including multiple sclerosis, inflammatory bowel disease, and rheumatoid arthritis [8-10]. However, diverse studies suggest critical physiological functions for IL-18 in homeostasis. Therefore, IL-18 possesses both harmful and protective roles in inflammatory pathologies [11].

In this scenario, it is not surprising that cholesterol reduction is a seminal goal in preventive cardiology [12], whereas among secondary prevention patients taking high dose of statins, the CRP (hsCRP) concentration, mirroring low-grade systemic inflammation, is a more powerful determinant

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of recurrent CV events, death and all-cause mortality than LDL-C levels [13]. Recently, a collaborative analysis of three randomized clinical trials, PROMINENT, REDUCE-IT and STRENGTH, have been performed [13]. The patients enrolled in these studies were subjects with, or at high risk of, atherosclerotic disease, who were treated with statins [14,15] and with penafibrate (PROMINENT, n=9988) [16], AMR101 (icosapent ethyl) (REDUCE-IT, n=8179) [17] or Epanova [a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] (STRENGHT, n=13078) [18]. The authors documented that residual inflammatory risk (measured by hsCRP) was significantly associated with major CV events, CV and all-cause mortalities. On the contrary, the relationship of residual cholesterol risk (measured by LDL-C) was neutral for major CV events and not significant for CV and all-cause deaths [13]. Therefore, in the setting of secondary prevention, clinicians have to measure both CRP and LDL-C concentrations to better understand the true residual biological risk of their patients, aiming at the best "personalized medicine" [19,20].

Calcific aortic valve disease (CAVD) is the most common valve pathology worldwide, and in developed countries, following coronary heart disease and hypertension, is the third most prevalent CV disease (CVD) [21]. CAVD is the result of the transition from aortic valve sclerosis, characterized by thickening of the aortic valve and mild calcification, to aortic valve stenosis, where the aortic valve leaflet thickening and calcification progress, eventually leading to obstruction at the valve level [22]. Therefore, patients may experience life-threatening outcomes, such as, left ventricular hypertrophy, heart failure and premature mortality [23]. Epidemiological surveys have showed that different degrees of aortic valve sclerosis are present in 25% of individuals aged 65% years, with a prevalence rate of 54.4% among those aged 85% years old or older [24]. As a consequence, CAVD is emerging as an urgent global public health issue [25,26]. Similar to atherosclerosis, age, gender (male), body mass index, smoking, hypertension, dyslipidemia, diabetes, infections, and kidney disease are risk factors for this illness [27-29]. In addition, CAVD causes dramatic hemodynamic disturbance, aka shear stress, which may influence valve inflammation, immune cell function and disease progression [30]. This is not surprisingly based on the observation that CRP levels are elevated in CAVD patients [31]. In line with this data, a recent experimental study demonstrated a novel mechano-sensing mechanism of shear-inducing CRP dissociation, linking CAVD and inflammation [32]. Of note, statins do not effectively halt CAVD progression [33], and no established medical treatments are able to delay the advancement of this pathology in asymptomatic patients up to now [30].

Currently we have new therapeutic options consequently to the publication of randomized and placebo-controlled trials proving evidence that negative modulation of the NLRP3inflammasone/IL-1beta/IL-6 axis lowers CV events rates among patients already taking guideline-directed medical care. Specifically, within CANTOS study, the IL-1beta inhibitor canakinumab significantly decreased major adverse CV event rates by 15 and 17%, without a clear modification of LDL-C and apolipoprotein (apo)B levels, or blood pressure [34]. Oral low-dose colchicine (0.5 mg/d), a microtubule polymerization inhibitor, proved efficacy in lowering the rates of major CV events by 31% among patients with stable atherosclerosis (LoDoCo2) [35] and by 23% among those following recent myocardial infarction (COLCOT) [36]. Based on these positive results, the U.S. Food and Drug Administration (FDA) in 2023 approved low-dose colchicine as the first anti-inflammatory therapy to be used in combination with statins "to reduce the risk of myocardial infarction, stroke, coronary revascularization and CV death in adult patients with established atherosclerotic disease or with multiple risk factors for CVD" (Figure 1) [37]. In all the clinical studies, the colchicine was well tolerated and serious adverse effects were similar with those reported in the placebo groups. However, based on the pharmacokinetic and pharmaco-dynamic profile of the colchicine, this drug is contraindicated in patients with severe kidney or hepatic dysfunction and should be temporarily discontinued when taking medications that inhibit the CYP3A4 and P-glycoprotein metabolism pathways [34-36]. Therefore, it is relevant to "keep in mind" that before the above-mentioned clinical trials the only intervention that could be suggested to the patients with elevated CRP was a more dramatic lifestyle change. Altogether, these data strengthened the need of looking for dietary approaches, such as nutraceuticals and dietary supplements, to lower the residual inflammatory risk [38,39].

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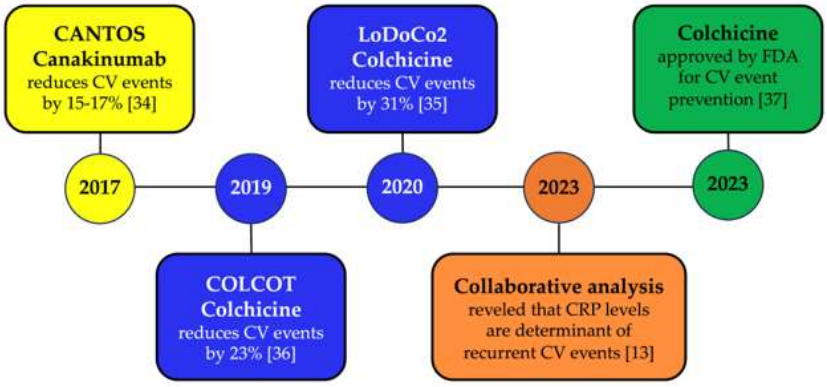

Figure 1. Flow chart representing the advances in atherosclerosis and cardiovascular disease therapies. CV—cardiovascular; FDA— U.S. Food and Drug Administration.

1.2. Gut Microbiota-Inflammation-Immunity Axis

The gastrointestinal tract hosts the largest population of microorganisms in the body, namely the gut microbiota (GM). This intestinal microbial community interacts with one another and with epithelial and mucosal immune cells, aiming at keeping immunological homeostasis, thus preventing the loss of immune tolerance, and maintaining healthy levels of inflammation [40]. In addition, GM is believed to be a virtual endocrine organ, producing molecules able at interacting with the host physiology and triggering responses at local and distant levels. The disruption of this equilibrium, whether due to genetic or environmental insults, results in critical and far-reaching alterations in intestinal and extra-intestinal organs, such as liver, lung, hearth and the central nervous system [41]. Indeed, GM dysbiosis, aka dramatic alterations in the amount and function of the intestinal microorganisms, has been associated with chronic low-grade inflammation and eventually with the aetiology of chronic non-communicable diseases (NCDs) [40]. Divergent metabolites drive the interplay between the host and its microbiome. Specifically, short-chain fatty acids (SCFAs), produced by bacteria from the fermentation of fibres, trimethylamine (TMA) derived from the bacteria' fermentation of L-carnitine and choline, bile acids produced in the liver and transformed by GM, and the tryptophan metabolites [42]. It has been documented that SCFAs influence several crucial functions for the eukaryotic host, ranging from being an energy source for intestinal epithelial cells to exerting anti-inflammatory properties on immune cells (neutrophils, macrophages and effector T cells) and promoting the differentiation of regulatory T cells (Treg), [42]. Moreover, the consumption of diets rich in meat (such as, the Western-type diet), which are a source of L-carnitine and choline, are directly correlated with the levels of TMA-N-oxide (TMAO), the product of the TMA's oxidation by the enzymatic activity of the liver flavin monooxygenase 3 (FMO3). Experimental and human studies have demonstrated that increasing TMAO levels are associated with enhance atherosclerosis development and major CV events, respectively [43-45]. Primary bile acids, released into the duodenum from the gall bladder, facilitate the absorption of dietary lipids and lipophilic vitamins. In the colon they are metabolized to secondary bile acids by GM, which encodes the enzymes involved in this unique microbial modification. Of note, primary and secondary bile acids act as signalling molecules by interacting with host bile receptors, farnesoid-X-receptor (FXR), vitamin D receptor and G protein-coupled bile acid receptor (TGR5), localized on monocytes, macrophages, dendritic and Kupffer cells (aka, hepatic macrophages). These activated receptors modulate the expression of pro-inflammatory genes through the nuclear factor kappa B (NF-kB) signalling pathway [42].

Tryptophan is an essential aromatic amino acid, recognized as a biosynthetic precursor of a large number of microbial and host metabolites [46]. Specifically, in the gastrointestinal tract dietary tryptophan can be directly transformed in indole and its derivates, which are ligands of the aryl

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hydrocarbon receptor (AhR) [47]. AhR signalling is considered a critical component of the immunity at barrier sites and is thus crucial for intestinal homeostasis, by modulating epithelial renewal, barrier integrity and many immune cell types [48]. In addition, GM influences the kynurenine-producing IDO (indoleamine 2,3-dioxygenase) pathway, which play a seminal role in inflammatory mechanisms, immune responses and neurobiological functions [49]. Finally, peripheral production of serotonin (5-HT) (more than 90% of the host serotonin) by enterochromaffin cells is under the control of the GM, specifically seems to be mediated by SCFA [50]. Gut-produced 5-HT is a pivotal gastrointestinal signalling molecule because regulates intestinal peristalsis and motility, secretion, vasodilatation and the absorption of nutrients [51,52].

In this scenario, it is not surprisingly that diet is considered as a relevant environmental factor which impacts on the GM composition and activity and, vice versa, the nutrition value of food is, at least in part, influenced by the composition of the host GM [40].

The Western lifestyle, including over-nutrition and sedentary behaviour, can lead to excess of fat deposition and cause lipid-engorged hypertrophic white adipocyte's expansion [53-55]. Altogether these events stimulate the secretion of pro-inflammatory cytokines, such as, tumour necrosis factor (TNF), IL-1beta, and IL-6, and mobilization of free fatty acids (FFAs), from adipose tissue into the circulation [56]. These high levels of circulating FFAs are responsible for the ectopic accumulation of lipids in the bone marrow and thymus, primary organ of the immune system [57]. Not surprisingly, this chronic exposure to an abnormal metabolic milieu leads to a dramatic imbalance of the innate and adaptive immunity, eventually producing a state of chronic low-grade inflammation. In adipose tissue and in peripheral blood leukocytes from obese subjects, higher levels of pro-inflammatory lipid mediators compared with those of specialized pro-resolving mediators (SPMs) were found [58]. Notably, it has been suggested that this pro-inflammatory state observe in obese individuals is driven by the GM dysbiosis [59], due to the consumption of diets rich in fat and sugar and low in fibres. In fact, these diets are associated with low SCFAs and *Bifidobacterium* amounts, and a decrease of the *Roseburia/Eubacterium rectale* group [60].

There is overwhelming evidence of the anti-inflammatory effects of n-3 polyunsaturated fatty acids (n-3 PUFAs) and probiotics/prebiotics in different chronic NCDs, such as metabolic syndrome, type 2 diabetes, hypertension, CVD, non-infectious respiratory disease, chronic kidney disease, neurodegenerative and autoimmune diseases (i.e., rheumatoid arthritis), and finally various cancer types [61].

This review aims at describing and analysing the interplay among marine n-3 (PUFAs), gut microbiome and CVD. Furthermore, we discuss the beneficial role of marine n-3 PUFAs and/or probiotics/prebiotics in the treatment of cardiovascular diseases.

2. Marine n-3 polyunsaturated Fatty Acids (n-3 PUFAs) and Specialized Pro-Resolving Mediators (SPMs)

Recent reviews have well summarized the pleiotropic effects of the marine n-3 PUFAs (mainly EPA and DHA) and those of the SPMs, endogenously synthesized from EPA, docosapentaenoic (DPA) and DHA [10,62]. Briefly, besides the fine documented triglyceride (TG)-lowering effect [63,64], n-3 PUFAs exert anti-inflammatory activities by inhibiting the cell-surface expression of adhesion molecules and the production of inflammatory cytokines (i.e., TNF-alpha, IL1-beta and IL-6) and cyclooxygenase (COX)-2 metabolites [65]. These effects are mediated by the n-3 PUFAs ability to dampen inflammatory signalling via NF-kB pathway [66]. Three diverse mechanisms have been suggested: 1) activation of peroxisome proliferator-activated receptor (PPAR)-gamma, which physically interacts with the dimeric form of NF-kB, preventing its nuclear translocation; 2) interfering with raft formation in the membrane of inflammatory cells; 3) binding to G-protein-coupled cell-membrane receptor (GPR120) [65].

In line with these data are the results obtained by the recent published randomized clinical trial RESPECT-EPA, designed to assess whether icosapent ethyl could impact on the recurrence of CV events in statin-treated patients who have low baseline EPA/AA (arachidonic acid) ratio [17]. Icosapent ethyl treatment decreased the cumulative primary end point, even though this effect did

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not reach the statistical significance. However, this treatment was significantly associated with a diminished risk of the secondary end point, such as sudden cardiac death, myocardial infarction, unstable angina, or coronary revascularization, and the sub-group of patients who responded to icosapent ethyl treatment, aka had an increase of the EPA/AA ratio, showed fewer events compared with the patients enrolled in the placebo group [17].

A systematic review and meta-analysis published in 2021 investigated the effectiveness and safety of n-3 PUFAs on fatal and non-fatal CV events [67]. The data documented a moderate efficacy of the n-3 PUFA treatment for reducing CV mortality and outcomes. Moreover, the studies considered in this meta-analysis underlined the existence of relevant differences on the effects exerted by EPA and DHA on membrane structure, inflammatory cascade, lipid oxidation, endothelial function and tissue distribution, associated with their divergent chemical structure [67]. These data were confirmed by a recent experimental study. Yu et al. showed that different ratio of DHA/EPA (3:1, 1.5:1, 1:1, 1:1.5, 1:3, respectively) supplements improved adipocyte dysfunction and lipid disorders in high-fat-diet-induced insulin resistance (IR) mice [68]. In this experimental setting, the 1.5:1 ratio exerted superior effects compared with the others ratios [68]. However, two major concerns still wait a clear answer from large well-designed randomized trials, that is, the non-neutral mineral oil comparator and the trend toward an increase of atrial fibrillation associated with EPA ethyl-ester monotherapy and mixed EPA-DHA formulations [69].

Finally, it is crucial to stress that marine oil contains other components besides n-3 PUFAs, such as astaxanthin, that could contribute to the beneficial observed effects. Indeed, krill oil proved higher efficacy in reducing adipocyte hypertrophy and hepatic steatosis compared with both DHA/EPA-phospholipid and DHA/EPA-TG forms [70,71]. The authors suggested that the interaction between n-3 PUFAs and astaxanthin may justify the observed differences [71]. This hypothesis was confirmed by Li et al. in a mouse model of atherosclerosis, namely, apoE-deficient mice (apoEKO) [72]. Mussel oil-treated apo EKO animals developed significantly smaller atherosclerotic plaque area, which was characterized by a lower lipid deposition and smooth muscle cells/macrophages content, compared with fish oil-treated mice. The major difference in the composition of the two oils resides in the amount of astaxanthin, that was superior in the mussel oil [72].

SPMs, produced by the action of COX, lipoxygenase (LOX) and cytochrome 450 mixed-function oxidase (CYP450) enzymes, are a family of molecules, comprising resolvins (Rvs), protectins (a.k.a. neuroprotectins, PD1/NPD1), maresins (MaRs), and the novel cysteinyl-SPMs (cys-SPMs) [73]. SPMs play a critical role in the "resolution phase" of the inflammatory response [73]. In detail, these mediators may: 1) limit granulocyte chemotaxis and infiltration; 2) stimulate the M2 macrophage polarization, phagocytosis and efferocytosis; 3) accelerate wound healing; 4) reduce the production of pro-inflammatory cytokines (TNF-alpha and IL-1beta) and lipid mediators (prostaglandins and leukotrienes); 5) promote the Treg response and release of IL-10; 6) diminish platelet aggregation and inflammasome formation [73,74].

Of note, in the presence of aspirin and statins (as occurred in the clinical studies of secondary CVD prevention [62]), an increased synthesis of some SPMs, such as lipoxins, Rvs and protectins, have been detected via acetylation or S-nitrosylation of the enzyme COX-2, respectively [75]. Eventually, this up-regulation of SPM pathway reduces numbers of polymorphonuclear neutrophils (PMN) as well as its recruitment into the exudate, to promote the resolution of inflammatory response [10]. Indeed, different experimental and clinical studies have demonstrated the capacity of aspirin and statins to promote SPMs synthesis together with reducing serum levels of pro-inflammatory cytokines, such as, IL-1beta and IL-6 [75]. Therefore, this could represent an additional mechanism to justify the anti-inflammatory and pro-resolving effects observed with aspirin and statins treatments.

These data together with an emerging body of experimental evidence strengthened the hypothesis that SPMs may exert protective roles in atherosclerosis and related CVD [76]. Administration of RvE1, an E-series resolvin derived from EPA, to apoE*3 Leiden mice fed a high-fat/high-cholesterol diet was associated with a significant reduction in atherosclerotic plaque development, together with a decreased gene expression of pro-inflammatory cytokines (e.g TNF and IFN-γ) [77]. D-series resolvins (namely, RvD1, RvD5$_{n\text{-}3\ DPA}$, and RvD2) and MaR1, biosynthesized

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from DHA, proved efficacy in promoting plaque stability, by reducing lesional macrophage numbers, necrotic cores, and thickening collagen caps, as well as in decreasing atherosclerotic lesion size and leukocyte/platelet activation in high-fat fed *Ldlr*-null [78,79] and apoEKO mice [80], respectively.

In addition, by using specific SPM or genetically modified mice [81] as well as animal models of CVD [82], it has been demonstrated that SPMs act through distinct G protein-coupled receptors (GPCRs), ALX/DRV1/GPR32 [83], DRV2/GPR18 [84], GPR37 [85], LGR6 [86], ERV1/ChemR23 and BLT1 [87]. In hyperlipidemic mice the lack of the receptor ERV1/ChemR23 was associated with proatherogenic signalling in macrophages, increased oxidized-LDL uptake, reduced phagocytosis, and larger atherosclerotic plaque volume and necrotic core formation compared with those observed in wild-type animals [88]. Moreover, analysing human atherosclerotic specimens, ERV1/ChemR23 expression was detected in a macrophages' subgroup located in the proximity of the necrotic, and its mRNA expression levels were found higher in lesions derived from statin users compared with nonusers [88] Since DRV2/GPR18 play a seminal role in the inflammatory "resolution phase" [84], being expressed in human leukocytes (PMN, monocytes and macrophages [89]), a new pro-resolving signalling axis, aka RvD2-GPR18, have been extensively investigated, aiming at developing a more tailored pro-resolution therapies for inflammatory-based pathologies [90,91]. However, translation of these experimental results into improving human health has been challenging. Intravenous or intraperitoneal administration of SPMs is not feasible for humans, as it is for rodents. Oral delivery of SPMs or dietary supplements containing SPMs precursor is not reasonable due to their relatively short half-life in biological fluids. In addition, data from patients affected by inflammatory-based pathologies, such as, diabetes, metabolic syndrome and inflammatory bowel diseases, suggested that the endogenous SPM-producing machinery may be dysfunctional under certain human illnesses [92].

In addition, both experimental and clinical studies have shown the ability of n-3 PUFAs to affect GM by 1) altering diversity and abundance of the its community (specifically, decreasing the *Firmicutes*/*Bacteroidetes* ratio and the levels of *Coprococcus* and *Faecalibacterium* and increasing the amount of butyrate-producing bacterial genera, i.e. *Bifidobacterium*, *Lachnospira*, *Roseburia* and *Lactobacillus*) [93,94] and 2) modulating levels of pro-inflammatory molecules, aka IL-17 and lipopolysaccharides (LPS) [95]. Djuricic et al reviewed the epidemiological studies and clinical data available that have investigated the role of n-3 PUFAs on prevention and/or incidence of cardiometabolic disease, focusing on the mechanism of actions. Altogether, these data suggest a beneficial effects of n-3 PUFAs ranging from improving blood lipids, glucose and insulin resistance, to promoting anti-inflammatory and pro-resolving effects and ending modulating GM composition [96]. The Figure 2 shows a schematic view of the inflammatory pathway modulation.

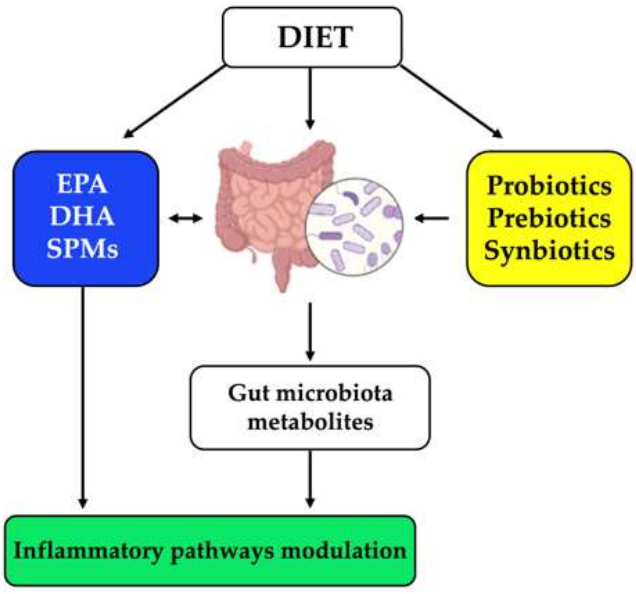

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Figure 2. The inflammation pathway modulation of diet, n-3 polyunsaturated fatty acids, prebiotics, probiotics, synbiotics,, and gut microbiota metabolites. DHA—docosahexaenoic acid; EPA—eicosapentaenoic acid; SPMs—specialized pro-resolving mediators.

3. Interplay Among n-3 PUFAs, Prebiotics/Probiotics, GM and CVD

Diverse studies have demonstrated that the consumption of prebiotics, probiotics, postbiotics and synbiotics (a combination of prebiotics and probiotics) proved efficacy on human health (Table 1) [97]. This is not surprisingly because the term "probiotic" refers to live microorganisms that confer a health benefit on the host who consumes them in adequate amounts [98]. For example, the probiotic bacteria *Lactobacilli* and *Bifidobacteria* have been associated with improved intestinal barrier function and integrity through diverse mechanisms, such as Toll-like receptor2 (TLR2) mediated-immune modulating and anti-inflammatory effects, promoting the production of butyrate and the expression of tight junction proteins, such as ZO-1 and occluding [99].

Conversely, the definition of prebiotic is "non-digestible food ingredients that beneficially influence the host by selectively stimulating the growth and/or the activity of one or a limited number of bacteria in the colon, thus improving host health" [100].

Finally, postbiotics include bioactive compounds (such as, microbial cells, cell constituents and metabolites) produced by food-grade microorganisms during a food fermentation process [101].

Experimental studies performed in rodents demonstrated that the consumption of *Bifidobacterium breve* CECT7263, *Lactobacillus fermentum* CECT5716 [102], the probiotic formulation composed of *L. fermentum* 139, 263 and 296 [103], and the combination between prebiotic inulin and probiotic *Lactobacillus casei* proved efficacy in preventing the CVD development (Table 1) [104]. This effect was associated with a reduction of the *Firumicutes*/*Bacteroidetes* ratio, an increase in the levels of *Lactobacillus* and *Akkermansia muciniphila*, these latter being beneficial bacteria for GM right balance, and a decrease of plasma TMAO amounts. Moreover, a significant increase in the butyrate levels was observed, suggesting the ability of these supplements of modulating oxidative stress and inflammatory response [104,105].

Table 1. Impact of Probiotics, Prebiotics, Synbiotics, and n-3 PUFAs on GM and CV health.

Study Type	Intervention	Effects	Ref.
Experimental (rats)	Probiotics	Improved intestinal barrier, prevent dysbiosis, endothelial dysfunction and high blood pressure	[102]
Experimental (rats)	Probiotics	Reduced inflammatory response and increased beneficial bacteria	[103]
Experimental (rats)	Synbiotics	Lower *Firmicutes*/*Bacteroidetes* ratio and TMAO, increase of *Lactobacillus* and *Akkermansia muciniphila*, and butyrate, modulated oxidative stress	[104]
Experimental (mice)	Prebiotics	Increase of *Allobaculum, S24-7* and*Akkermansia,* reduction of *Oscillospira* and *Ruminococcaceae*	[106]
Clinical trial	Synbiotic omega 3 (SynΩ3)	Increase of the SPM precursors levels (18-HEPE, 5-HEPE)	[110]
Clinical trial	Probiotics	Reducttion of FFAs in hypertriglyceridemic patients	[116]
Clinical trial	Probiotics	Improved n-3 PUFA and cytokine profile in breast milk	[117]
Clinical trial	Synbiotics	Reduction of hsCRP and increased n-3 PUFA levels	[118]

scGOS—short-chain galacto-oligosaccharide; lcFOS—long-chain fructo-oligosaccharide; SPMs—specialized pro-resolving mediators; FFAs—free fatty acids; EPA—eicosapentaenoic acid; DHA—docosahexaenoic acid; hsCRP—high-sensitivity C-reactive protein.

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A recent experimental study performed on healthy mice shown that early-life dietary interventions with a prebiotic, composed by a mixture of short-chain galacto-oligosaccharide (scGOS) and long-chain fructo-oligosaccharides (lcFOS), and/or n-3 PUFAs affected caecal content microbial profile [106]. In detail, the combination increased the relative abundance of *Allobaculum*, S24-7 Unclassified and *Akkermansia*, while reducing the abundance of the genera *Oscillospira* and *Ruminococcaceae* Unclassified. These data were also confirmed in clinical trials were the Mediterranean diet, rich in prebiotics, probiotics, n-3 PUFAs, polyphenols and fibres, has been associated with a reduction of the *Firumicutes*/*Bacteroidetes* ratio and eventually to an improvement of the cardiometabolic markers linked to a decreased incident of CV events [107-109].

Speckmann et al., aiming at overcoming the issues linked to the administration of SPMs and intrinsic (i.e., genetics, disease state, sex) and extrinsic (i.e., diet) determinant of body's SPM synthesis, developed a synbiotic approach based on the discovery that *Bacillus megaterium* strains are potent producers of SPMs, using a fish oil-derived n-3 PUFAs as a substrate [92]. A double-blind, randomized, placebo-controlled trial was then conducted in middle-aged, heathy but at-risk subjects [110]. In this 4-week intervention study the enrolled peoples received 1) the synbiotic omega 3 (SynΩ3) capsules, containing 1 billion colony-forming units of *Bacillus megaterium*, n-3 PUFAs lysine salt (83.3 mg EPA and 41,7 mg DHA) and 27.5 microg selenium in the form of L-selenomethionine; 2) fish oil capsules (containing 180 mg EPA and 120 DHA in triglyceride form, and 2.7 mg alpha-tocopherol); 3) cellulose powder capsules, as placebo. This study confirmed the ability of SynΩ3 to significantly increase the plasma concentrations of SPMs compared with the fish oil group [110]. These results strengthen the concept that an altered or limited metabolic capacity of the body to synthesize SPMs can be compensated by suitable microbes or synbiotics. Additionally, this strategy allows to use much smaller doses of n-3 PUFAs than typically administered, which may prevent potential side effects and eventually increase patient compliance [69,110].

It has been demonstrated that the synthesis of n-3 PUFAs by the foetus and placenta is very low [111]. Therefore, maternal supply of n-3 PUFAs is seminal, because n-3 PUFAs play a critical role in new-born neurodevelopment and may lower the risk of allergic disease [112-114]. Moreover, recent data highlighted the relevance of n-3 and n-6 PUFA status to maternal metabolic health, as FFAs levels have been related with the risk of gestational diabetes mellitus [115]. Preliminary evidence showed that probiotic may impact on the serum FFAs concentration. The administration of *Lactobacillus gasseri* SBT2055 proved efficacy in reducing the FFAs levels in hypertriglyceridemic patients [116]. In addition, the combination between dietary counselling and *Lactobacillus rhamnosus GG and Bifidobacterium lactis* Bb12 demonstrated the possibility of improving the profile of both the n-3 PUFAs and different cytokines in the breast milk of pregnant women [117]. A very recent randomised-controlled trial was conducted in pregnant women with overweight and obesity [118]. The study protocol aimed at investigating the impact of fish oil and probiotics, alone or in combination, on the serum concentration of n-3 PUFAs and the relationship between serum concentration of n-3 PUFAs and low-grade inflammation, evaluated as the hsCRP circulating levels. The authors documented that fish oil administered from early pregnancy onward significantly increased the serum concentration of n-3 PUFAs [118]. No differences were instead observed among the probiotic-treated groups in comparison with the fish oil-treated and the placebo groups. Of note, this study detected an inverse association between hsCRP (reflecting the low-grade inflammation status) and n-3 PUFA levels [118].

4. Materials and Methods

The usage of MeSH tool in PubMed allowed us to browse through NLM databases. Through this tool, we were able to refine our search and emphasize the relevant studies. The following search terms were combined: "fish oil" OR "marine n-3 polyunsaturated fatty acids" OR "krill oil" AND "mice" OR "mouse" OR "rat" OR "rodent" OR "clinical studies" OR "human studies" AND "LDL" OR "triglycerides" OR "HDL" OR "atherosclerosis" OR "cardiovascular disease" OR "calcific aortic valve disease" OR "diabetes" OR "inflammation" AND "gut microbiota" OR "microbiota

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composition" OR "gut microbiota diversity" OR "gut microbiota dysbiosis" AND "probiotics" OR "prebiotics" OR "synbiotics". The search was updated until December 2024.

5. Conclusions

Nowadays, high levels of LDL-C and low-grade vascular inflammation are the major determinant for the atherosclerosis development. Indeed, the accumulation of pro-inflammatory lipoproteins in the vessel wall (mainly LDL) triggers the activation/dysfunction of endothelial cells as well as the inflammatory process, leading to the early steps and progression of atherosclerosis. Different studies have demonstrated that the endothelial dysfunction is followed by the activation of NLRP3 inflammasome and production IL-1beta and IL-18. In addition, a collaborative analysis demonstrated that in patients taking high dose of statins, the CRP (hsCRP) concentration, reflecting low-grade systemic inflammation, is a more powerful determinant of recurrent CV events, death and all-cause mortality than LDL-C levels. CAVD is the most common valve pathology worldwide. Recent data have linked CAVD and inflammation. Of note, since no established medical treatments are able to delay the advancement/treat this pathology, these data can promote new therapeutic approaches.

Today we have new treatments' options to manage the patients in secondary prevention. In fact, LoDoCo2 and COLCOT are randomized and placebo-controlled trials proving evidence that negative modulation of the NLRP3inflammasone/IL-1beta/IL-6 axis lowers CV events rates among patients already taking guideline-directed medical care. Based on these clinical data, the U.S. FDA approved low-dose colchicine as the first anti-inflammatory therapy to be used in combination with statins. However, this drug is contraindicated in patients with severe kidney or hepatic dysfunction.

It is currently well documented that GM dysbiosis is associated with different inflammatory-based pathologies. Many studies have shown beneficial effects of probiotics/prebiotics on the GM dysbiosis, by modulating both inflammation and immunity. Moreover, several decades of research have documented that n-3 PUFAs exert TG-lowering and antithrombotic effects, and play a seminal role in the resolution of inflammatory processes, being the precursors of SPMs. Therefore, the hypothesis to improve the residual CVD risk with dietary interventions including n-3 PUFAs and prebiotics/probiotics has been preliminary validated in different experimental and clinical studies.

In conclusion, based on these premises, oncoming well-conducted and controlled clinical trials could be designed by adding functional food/nutraceuticals to the standardized therapeutical protocols, aiming at including all the patients at high risk of CV events (Figure 3) as well as aged peoples (Figure 4).

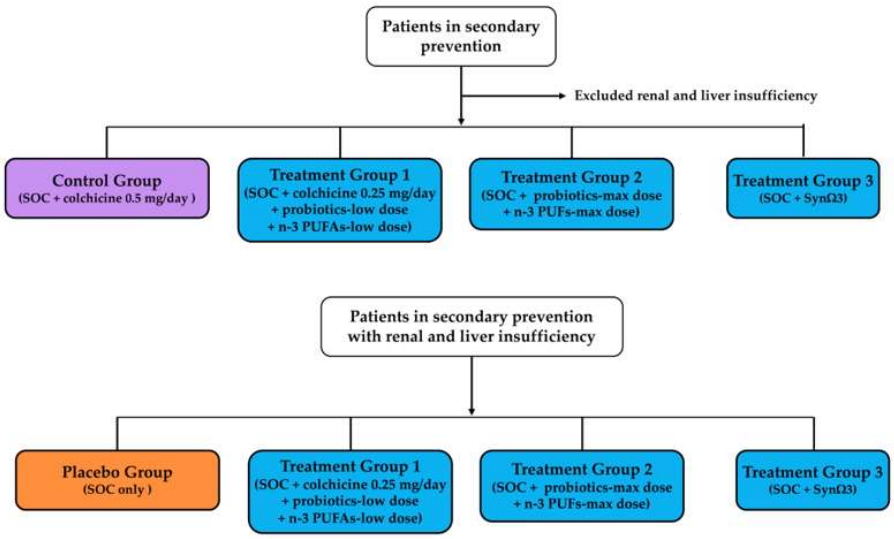

Figure 3. Patient Flow of two oncoming clinical trials to validate the anti-inflammatory effect of n-3 PUFA and probiotics. SOC—standard of care.

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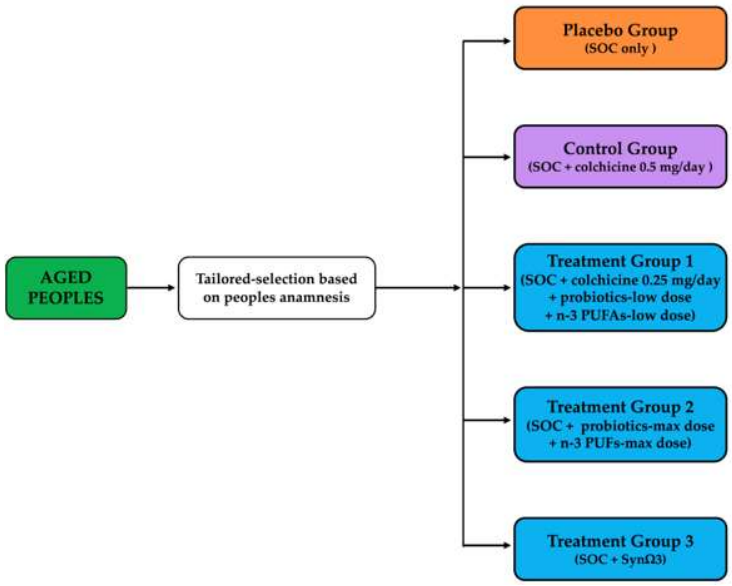

Figure 4. Patient Flow of an oncoming clinical trial to validate the anti-inflammatory effect of n-3 PUFA and probiotics. SOC—standard of care.

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Abbreviations

LDL-C	low-density lipoprotein-cholesterol
NLRP3	NACHT, leucin-rich repeat, and pyrin domain-containing protein 3
IL	interleukin
CRP	C-reactive protein
CV	cardiovascular
IFN	interferon
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
CAVD	calcific aortic valve disease
CVD	CV disease
Apo	apolipoprotein
FDA	Food and Drug Administration
GM	gut microbiota
NCDs	non-communicable diseases

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SCFAs	short-chain fatty acids
TMA	trimethylamine
Treg	regulatory T
TMAO	TMA-N-oxide
FMO3	flavin monooxygenase 3
FXR	farnesoid-X-receptor
TGR5	G protein-coupled bile acid receptor
NF-kB	nuclear factor kappa B
AhR	aryl hydrocarbon receptor
IDO	indoleamine 2,3-dioxygenase
5-HT	serotonin
TNF	tumour necrosis factor
FFAs	free fatty acids
SPMs	specialized pro-resolving mediators
n-3 PUFAs	n-3 polyunsaturated fatty acids
TG	triglyceride
COX	cyclooxygenase
PPAR	peroxisome proliferator-activated receptor
GPR120	G-protein-coupled cell-membrane receptor
AA	arachidonic acid
LOX	lipoxygenase
CYP450	cytochrome 450 mixed-function oxidase
Rvs	resolvins
MaRs	maresins
cys-SPMs	cysteinyl-SPMs
GPCRs	G protein-coupled receptors
LPS	lipopolysaccharides
TLR2	Toll-like receptor2
scGOS	short-chain galacto-oligosaccharide
lcFOS	long-chain fructo-oligosaccharides

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