Polyphenols and omega-3 as nutriceuticals

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The adequate combination of the well-recognized individual nutraceutical properties of polyphenols and omega-3 polyunsaturated fatty acids from fish oils (eicosapentaenoic and docosahexaenoic acids), particularlly their single antioxidant and anti-inflammatory properties, may offer a powerful tool for the design of successfully nutritional interventions for the prevention and palliation of a plethora of human diseases, often diet-related, whose etiology and progression are characterized by redox homeostasis disturbances and a low-grade of chronic inflammation. However, the certain mechanisms behind their biological activities, in vivo interaction (both between them and other food compounds), and their optimal doses and consumption are not well-known yet. Therefore, we review here the recent accumulated evidence in both preclinical and clinical trials, of the cooperative action between polyphenols and fish oils as nutraceuticals on human health, focusing on the mechanisms and pathways described and the effects reported. The final objective is to provide useful information for developing effective strategies of personalized nutrition based on the combined used of these bioactive food compounds.

eicosapentaenoic acid docosahexaenoic acid omega-3 polyunsaturated fatty acids plant bioactives oxidative stress inflammation metabolic disorders nutraceuticals

1. Introduction

Nutraceuticals, defined as “any substance that is food or part of a food and provide medical or health benefits, including the prevention and treatment of disease” [1], are currently considered a viable strategy for the prevention and palliation of several human diseases, including those related to the widespread “obesogenic” lifestyle.

The “obesogenic” lifestyle have notably increased the prevalence of metabolic alterations such as the so-called Metabolic Syndrome (MetS) [2], a pathological condition defined by the simultaneous presence of different combinations of three or more of the following metabolic alterations: abdominal obesity, blood hypertension, hyperglycemia, and serum dyslipidemia [3]. MetS is considered a risk factor for noncommunicable diseases such as type 2 diabetes and cardiovascular diseases (CVD) [4]. Other main chronic illnesses promoted by obesity are cancer and neurodegenerative pathologies [5]. Interestingly, all these pathologies are characterized by an increase in oxidative stress and a proinflammatory status [6]. For this reason, bioactive compounds naturally present in food with antioxidant and/or anti-inflammatory properties have attracted the attention of the scientific community for the development of successful nutritional interventions. Among those, dietary polyphenols are often considered because they are one of the most important groups of natural antioxidants and anti-inflammatory agents found in human diets, including fruits, vegetables, grains, tea, essential oils, and their derived foods and beverages [7]. On

the other hand, regular intake of fish-derived omega-3, i.e., eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, has also been reported to be involved in the prevention of several of those metabolic alterations and diseases [8], because of their biological functions and bioactivities. Interestingly, EPA and DHA play an important role in anti-inflammatory processes because they are substrates for cyclooxygenase, lipoxygenase, cytochrome P450, and several other enzymes [9]. As a result, numerous lipid mediators involved in inflammatory processes are generated, including specialized pro-resolving lipid mediators (SPMs), which actively resolve inflammation [10].

Several studies have pointed out that fish oils can also improve the antioxidant defense, mainly via nuclear factor erythroid 2 (Nrf2)-dependent mechanisms [11][12][13][14]. However, the influence of highly unsaturated fatty acids on redox homeostasis remains controversial. The high consumption of these omega-3 causes an enriched in PUFAs of cell membranes and tissues, which could make them more vulnerable to suffering from lipid peroxidation under oxidative stress insults, because of the presence of those high unsaturated structures carrying many “fragile” double bonds [15]. Therefore, a good strategy for preventing potentially detrimental health effects of the high PUFAs intake regarding oxidation may be the simultaneous consumption of omega-3 PUFAs and polyphenols. Nevertheless, it is necessary to unequivocally identify the molecular processes and biochemical pathways that can be modulated by the combination of those nutrients, determine the optimal consumption in the context of several metabolic alterations and describe potential adverse or antagonist effects, that could exist, among other concerns.

Therefore, we review the recent preclinical and clinical evidence that supports the combined use of fish-derived omega-3 PUFAs and polyphenols as nutraceuticals, for the prevention and treatment of metabolic disturbances governed by high oxidative stress and inflammation. We aim to provide solid scientific evidence for the optimum design of nutritional strategies. The studies that have addressed this topic during the last decade are summarized in Table 1 and will be discussed more in detail in the following sections.

Table 1. Summary of the researches from the last ten years that have studied the effect of the combination between polyphenols and fish oils for improving MetS features, neurodegenerative pathologies, cancer, and other health effects.

Bioactive´s Combination	Model	Health Effects of the Combination	Reference
MetS features			
• **In vitro studies**			
Epigallocatechin-3-gallate (EGCG) and DHA (50 µM; 1 h)	FaO cells (H4-11-E-C3 rat	Less lipid peroxidation levels; more GSH/GSSG and less	[16]

	hepatoma).	catalase; EGCG impairs DHA-related Nrf2 nuclear translocation and decreases HO-1 protein levels.	
Resveratrol (2·5 mg/mL) and EPA (30 mM); 19 h	RAW 264.7 murine macrophage.	Enhanced anti-inflammatory effect ,decreased NO levels; modulating P-SAPK/JNK;down-regulation of proinflammatory; genes (IL, chemokines, transcription factors); Up-regulation antioxidant genes.	[17]
Resveratrol (25 ?mol/L) and EPA (20 ?mol/L)	Human peripheral blood leukocytes (PBLs) and normal human articular chondrocytes from knee (NHAC-kn).	Synergistic effects on CCL5/RANTES; additive effects on IL-6 or CXCL8/IL-8.	[18]

- **In vivo studies**

Resveratrol (20 mg/kg/day) and fish oil (0.4 g (54% EPA, 10% DHA)/kg/day); 2 months.	Obese male Wistar rats.	Activation of the Nrf2/Keap1 pathway; increases survival of obese rats because of less oxidative stress in the aorta and myocardium.	[19]
Proanthocyanidin rich grape seed extract (0.8 g/kg feed) and	Prediabetic female Wistar–	Both additive and synergistic effects on total and specific	[20]

EPA/DHA 1:1 (16.6 g /kg feed); 24-weeks.	Kyoto rats.	protein carbonylation in liver;effects strongly depended on the background diet; results correlated with improved insulin sensitivity and antioxidant status.	
Proanthocyanidin rich grape seed extract (25 mg/kg body weight) and oil-rich DHA (500 mg (38.8% DHA)/kg body weight); 21 days.	Obese male Wistar rats.	Activation of muscle β-oxidation; more mitochondrial functionality and oxidative capacity; up-regulation of AMPK phosphorylation, PPARα and Ucp2.	[21]
1.5% apple polyphenol and 10% fish oil (27% EPA, 11% DHA); 4 weeks.	Male Sprague–Dawley rats.	Synergistic effects: lower posterior abdominal fat wall and testicle peripheral fat;additive effects: lower cholesterol and FFA; lower adiponectin than in fish oil and more than in polyphenols; less oxidative stress than in polyphenols but more than in fish oil.	[22]
Proanthocyanidin rich grape seed extract (0.8 g/kg feed) and EPA/DHA 1:1 (16.6 g /kg feed); 24-weeks.	Prediabetic female Wistar–Kyoto rats.	Complementary effects: Lower omega-6/-3 ratio; Lower production of ARA proinflammatory lipid mediators; Up-regulation desaturases towards omega-3. Additive effects: Down-regulation Δ5D and COX activities on ARA; Enhancing the antioxidant enzymes decreasing total FFA in plasma.	[23]

Proanthocyanidin rich grape seed extract (0.8 g/kg feed) and EPA/DHA 1:1 (16.6 g /kg feed); 24-weeks.	Prediabetic female Wistar–Kyoto rats.	Synergistic effect of GPx activity; higher amount of MUFA and PUFA-containing DAG and long-chain fatty acid-containing ceramides.	[24]
Proanthocyanidin rich grape seed extract (0.8 g/kg feed) and EPA/DHA 1:1 (16.6 g /kg feed); 24-weeks.	Prediabetic female Wistar–Kyoto rats.	Additive effects on the regulation of proteins involved in insulin signaling, glycolysis, fatty acid beta-oxidation, and endoplasmic reticulum stress.	[25]
Proanthocyanidin rich grape seed extract (0.8 g/kg feed) and EPA/DHA 1:1 (16.6 g /kg feed); 24-weeks.	Prediabetic female Wistar–Kyoto rats.	Additive effect on insulin, leptin, and triglycerides levels in prediabetic rats.	[26]
Salmon oil (1365 mg/kg body weight/day) supplemented tocopherols, cholecalciferol, retinol, lignans, coumarins and dicyclo esters at 1365, 2730 to 5460 mg/kg body weight; 21 days.	Male Balb/c mice.	Synergistic antioxidant effect as free radical scavengers; better immunomodulatory activity at highest plant extract doses without any toxicity.	[27]
Brown seaweed lipids (0.5% or 2.0%); 4 weeks.	Female KK-Ay mice.	Less lipid peroxidation in the liver; hepatic enrichment in DHA and ARA.	[28]
Biologically active substances-enriched (BASE) diet (polyphenols, b-carotene, probiotics, and salmon fat);;14 months.	Adult male Sprague–Dawley rats.	Regulation of gonadotrope cell activation pathway and guanylate cyclase pathway, mast cell activation, gap junction	[29]

		regulation, melanogenesis, and apoptosis.	
Anti-inflammatory dietary mixture (AIDM) (resveratrol, lycopene, catechin, vitamins E and C, and fish oil); 6 weeks.	Female ApoE*3Leiden transgenic mice.	Decreased CRP and fibrinogen expression; decreased plasma cholesterol, TG, serum amyloid Aβ, vascular inflammation markers, and adhesion molecules	[30]
Salmon oil/motherwort oil extract in 8:2(2340 and 1170 mg/day/kg body weight); 14 days.	Rats.	Increased left ventricular pressure after ischemia; normalized contraction/relaxation of left ventricle; decreased aspartate amino transferase and creatine kinase activity; cardioprotective effect without any toxicity.	[31]
• **Human studies**			
Diet naturally rich/or not in fish omega-3 PUFAs (4 g/day) and/or polyphenols (2.861 mg/day); 8 weeks	Humans at high metabolic risk.	Reduction of the postprandial lipid VLDL; increases IDL;LDL richer and HDL poorer in TG.	[32]
Diet naturally rich/or not in fish omega-3 PUFAs (4 g/day) and/or polyphenols (2.861 mg/day); 8 weeks	Humans at high metabolic risk.	Additive effects of polyphenols (less TG, large VLDL, and urinary 8-isoprostanes) and of fish oils (less postprandial chylomicron cholesterol and VLDL apolipoprotein B-48); correlation lipoprotein changes and 8-isoprostanes.	[33]

Diet naturally rich/or not in fish omega-3 PUFAs (4 g/day) and/or polyphenols (2.861 mg/day); 8 weeks	Humans at high metabolic risk.	Additive effects of polyphenols (less plasma glucose and increased early insulin secretion) and of omega-3 (reduced beta-cell function and GLP-1).	[34]
Diet naturally rich/or not in fish omega-3 PUFAs (4 g/day) and/or polyphenols (2.861 mg/day); 8 weeks	Humans at high metabolic risk.	Lipid rearrangements (in phospholipids fatty acid profiles of HDL).	[35]
Cranberry polyphenols (200 mL) and 1 g capsule EPA (180 mg) and DHA (120 mg) twice daily; 8 weeks.	Humans with diabetes and periodontal disease.	Decreased glycated hemoglobin; increased HDL-C;improve periodontal status.	[36]
Diet naturally rich/or not in fish omega-3 PUFAs (4 g/day) and/or polyphenols (2.861 mg/day); Blood samples taken before and up to 6 h after the test meal.	Humans at high metabolic risk.	Change in levels of chylomicron cholesterol and triglycerides due to omega-3; response to nutraceuticals depends on acute or chronic supplementation.	[37]
Diet rich in polyphenols and omega-3 (retrospective study from June 2017 to December 2018, Łódź, Poland).	Middle-age patients after percutaneous coronary intervention.	PLR and NLR depending on the omega-6/omega-3 ratio.	[38]
Diet naturally rich/or not in fish omega-3 PUFAs (4 g/day) and/or polyphenols (2.861 mg/day); 8 weeks	Human at high metabolic risk.	Change in gut microbiota associated with changes in glucose/lipid metabolism.	[39]

Fish oil (1.7 g EPA + DHA/day) and chocolate containing plant sterols (2.2 g/day) and green tea (two sachets/day); 6 weeks.	Patients suffering from type 2 diabetes.	Both nutraceuticals combined with statin therapy significantly reduced LDL-C and CRP.	[40]
PROG plan daily; 13 weeks.	Healthy overweight people with cardiometabolic syndrome.	Less body and fat mass; improved plasma lipid profiles and inflammation markers.	[41]
Nutraceutical cocktail (polyphenols, omega-3 fatty acids, vitamin E, and selenium) daily; 10–20 days.	People with sedentary behaviors and fructose overfeeding.	Less alterations on lipid metabolism; no effect in preventing insulin resistance.	[42]
Aterofisiol®;1 tablet every 24 h starting 30 days before the surgery and stopping 5 days before it.	Patients with carotid stenosis who underwent endarterectomy.	Alteration of atherosclerotic plaque composition; more prevention from neurological events associated.	[43]

Neurodegenerative Diseases

- **In vitro studies**

EPA (0.125 μM), lyc-O-mato (0.1 μM), carnosic acid (0.2 μM) and lutein (0.2 μM).	BV-2 immortalized murine microglial cell line.	Synergistic inhibition of the production of proinflammatory mediators: inhibition redox-sensitive NF-κB activation; inhibition of superoxide production; upregulation COX-2 and iNOS; more release of PGE2	[44]

		and NO; attenuation IL-6 and CD40.	
Resveratrol, quercetin, and apigenin (1.5 to 6.25 µM), α-ALA, EPA, DHA, and OA (6.25 to 50 µM) and α-Tocopherol.	N2a Neuronal cells.	Cytoprotective against 7-Ketocholesterol-induced neurotoxicity.	[45]

- **In vivo studies**

Resveratrol and DHA (50 mg/kg/day); 6 weeks.	Adult C57Bl/6 mice.	Modulation of steroid hormone biosynthesis, JAK-STAT signaling pathway, ribosome, graft-versus-host disease pathways in the hippocampus; Decreased IL-6 and Apolipoprotien E (ApoE) expression.	[46]
LMN diet; 5 months.	Tg2576 male and female mice as a model of AD.	Delays the Aβ plaque formation and decreases $A\beta_{1-40}$ and $A\beta_{1-42}$ plasma levels in adult mice.	[47]
LMN diet; 10, 20, 30, or 40 days.	129S1/SvImJ adult male mice.	Enhancement of cholinergic and catecholaminergic transmissions; Nrf2 activation and increased protein levels of SOD-1 and GPx.	[48]
Multivitamins, zinc, polyphenols, omega-3 fatty acids, and probiotics mixture; 48 days.	Crickets.	A combination of multivitamins, zinc, and omega-3 fatty acids was the most effective for	[49]

		improving memory and cognitive performance.	
Resveratrol (50 mg/L drinking water) and DHA (300 g) and prebiotics (100 g) of prebiotic in powdered food; from post-natal day 21 to 43.	Adolescent male and female Sprague–Dawley rats suffering from mild traumatic brain injury.	Modify premorbid characteristics; prevented injury-related deficits in longer-term behavior measures, medial prefrontal cortex spine density, and levels of *Aqp4, Gfap, Igf1, Nfl,* and *Sirt1* expression in the prefrontal cortex.	[50]
• **Human studies**			
Smartfish® (200 mL/day) ; 4–17 months.	Patients with minor cognitive impairment (MCI), with pre-MCI, or with Alzheimer disease (AD).	Increase amyloid-β phagocytosis and resolvin D1 in patients with MCI.	[51]
Smartfish® (200 mL/day); 6 months.	Older adults (68–83 years) without any specific pathology.	Limited beneficial effects improving cognitive function.	[52]
NEWSUP; 23 weeks.	Children aged 15 months to 7 years; primary population: children younger than 4.	Increased working memory, hemoglobin concentration among children with anemia, decreased body mass index z score gainm, and increased lean tissue accretion with less fat; increased index of cerebral blood flow (CBFi).	[53]

Cancer			
• **In vivo studies**			
Curcumin (1% *w*/*w*) and menhaden fish oil (4% *w*/*w*); 3 weeks.	Lgr5-EGFP-IRES^{creERT2} knock-in mice.	Only fish oils+curcumin reduced nuclear β-catenin in aberrant crypt foci and synergistically increased targeted apoptosis in DNA damaged Lgr5+ stem cells; only fish oils+curcumin up-regulated p53 signaling in Lgr5+ stem cells from mice exposed to a carcinogen.	[54]
• **Human studies**			
PureVida™ (3 capsules/day); 1 month.	Post-menopausal breast cancer patients.	Decrease in CRP; reduction of pain from aromatase inhibitors of hormonal therapies.	[55]
Mediterranean-type dietary pattern (population-based case–control study, January 2015 to December 2016, Catania, Italy).	Prostate cancer (PCa) cases and controls.	High adherence to diet inversely associated with the likelihood of prostate cancer: PCa cases consume a lower amount of vegetables, legumes, and fish.	[56]
Exercise and physical activity			

• **In vivo studies**			
5% fish oil (13.2% EPA, 8.6% DHA, 4.9%DPA) and 1% curcumin in diet;10 days.	C57Bl/6 mice.	Decreased loss of muscle cross-sectional area; an enhanced abundance of HSP70 and anabolic signaling (Akt phosphorylation, p70S6K phosphorylation) while reducing Nox2.	[57]
• Human studies			
1 L daily supplementation of almond and olive oil and α-tocopherol based beverage enriched with a DHA functional beverage five days a week; 5 weeks.	Young/senior male athletes.	Increased PUFAs and reduced SFAs in plasma; increased DHA in erythrocyte; increased blood cell polyphenol concentration in senior athletes; protects against oxidative damage but enhances nitrative damage in young athletes; gene expression of antioxidant enzymes in peripheral blood mononuclear cells after exercise in young athletes (GPx, CAT, and Cu–Zn SOD).	[58]
1 L daily supplementation of almond and olive oil and α-tocopherol based beverage enriched with a DHA functional beverage five days a week; 5 weeks.	Young/senior male athletes.	Increased TNFα levels depending on age and exercise; attenuated the increase in plasma NEFAs, sICAM3 and sL-Selectin induced by exercise; exercise increased PGE2 plasma levels in supplemented young athletes; exercise increased NFkβ-	[59]

		activated levels in PBMCs mainly in supplemented young athletes.	
Polyphenols (741 mg), vitamin E (138 mg), selenium (80 µg), and omega-3 (2.1 g); 60 days of hypoactivity.	Healthy, active male subjects.	Ineffectiveness regarding oxidative muscle damage, mitochondrial content, and protein balance and a disturbance of essential signaling pathways (protein balance and mitochondriogenesis) during the remobilization period.	[60]

Age-related eye disease

- **In vitro studies**

288 ng of Resvega (30 mg of trans resveratrol and 665 mg of omega-3 EPA and DHA, among other nutrients);48 h.	ARPE-19 cells.	Induced autophagy by increased autolysosome formation and autophagy flux; change p62 and LC3 protein levels Cytoprotection under proteasome inhibition	[61]

- **In vivo studies**

Resvega (100 µL/day); 38 days.	C57BL6/J mice.	Less vascular endothelial growth factor (VEGF) protein expression levels and less MMP-9 activity; mitigate choroidal neovascularization and retinal disease.	[62]

Others			
Dermatologic food (EPA+DHA+polyphenols); 8 weeks.	Adult atopic dog.	Reductions in clinical scores of atopic dermatitis.	[63]
Olive oil polyphenols and fish oil (Prospective birth cohort Assessment of Lifestyle and Allergic Disease During INfancy (ALADDIN); September 2004–November 2007, Stockholm area, Sweden).	Placentas.	Altered histone acetylation in placentas.	[64]
Omega-3 fatty acids, polyphenols, and fiber (mother–neonate pairs from the prospective and observational MAMI birth cohort; 18 months, 2015–2017,Spanish–Mediterranean area).	Gut microbiota from mother–neonate pairs.	Higher abundance of the *Ruminococcus* species in maternal gut microbiota; higher relative abundance of *Faecalibacterium prausnitzii* considered as a biomarker of colonic health, associated with anti-inflammatory properties; modulation of neonatal microbiota.	[65]

2. Combined Polyphenols and Fish Oils Intake for Improving Metabolic Syndrome Features. Preclinical and Clinical Evidence.

Several studies in both cell and animal models addressed the effects of the combination between fish oil and polyphenols in restoring the redox homeostasis that is broken in MetS. Additive effects on the activation of the nuclear factor Nrf2 p45-related factor 2/Kelch-like ECH-associated protein 1 (Keap1) pathway were found after the treatment with a mix of the epigallocatechin-3-gallate (EGCG) and DHA in hepatic cells [16], and in the myocardium and aorta of obese male Wistar rats [19], after the supplementation with resveratrol and fish oil. Moreover, the

combined intake of proanthocyanidins from grape seed extract and fish oils showed relevant additive and even synergistic effects on liver redox homeostasis, especially on the modulation of carbonylation of specific liver proteins, lowering lipid peroxidation levels and improving oxygen radical absorbance capacity (ORAC) and the glutathione peroxidase (GPx) activity in plasma, while lowering cholesterol, tumor necrosis factor-alpha (TNFα) and plasma insulin levels in female Wistar–Kyoto rats fed an obesogenic diet [20]. The coadministration of grape seed proanthocyanidins and an oil-rich in DHA improve muscle status as well, because activated muscle β-oxidation, increased the mitochondrial functionality and oxidative capacity, and up-regulated fatty acid uptake gene expressions in obese male Wistar rats [21]. Also, the combination of apple polyphenols with fish oil in male Sprague–Dawley rats fed a high cholesterol diet improved serum and liver lipid profiles and oxidative stress markers [22].

Regarding inflammation, synergistic and additive anti-inflammatory effects between resveratrol and EPA were detected in macrophages in macrophages [17], human peripheral blood leukocytes (PBLs), and articular chondrocytes from knee (NHAC-kn) [18]. In female Wistar–Kyoto rats fed an obesogenic, the combination of grape proanthocyanidins and fish oil [23] caused an enrichment in omega-3 PUFAs while decreasing omega-6 in membranes and tissues, resulting in more favorable inflammatory and redox status, which was defined by a shift in the 12/15-lipoxygenases activities towards omega-3 PUFAs, enhanced GPx activities, and significant modulation of the cyclooxygenase (COX)-dependent synthesis of proinflammatory lipid mediators and the down-regulation of de novo synthesis of arachidonic acid (ARA) leaded by Δ5 desaturase. Moreover, the double supplemention increased monounsaturated fatty acid and polyunsaturated fatty acid-containing diacylglycerols (DAG) and long-chain fatty acid-containing ceramides abundances compared to the control [24]. These lipidomic profiles were correlated with the up-regulation of proteins involved in improving insulin signaling, and lipid and glucose metabolism [25]. Biochemical and biometric parameters confirmed that only the nutraceutical combination could restore insulin, leptin, and triglyceride levels to normal values [26].

Polyphenols and marine omega-3 PUFAs in combination with other biologically active substances were also evaluated in some preclinical studies. Fish oil supplemented with plant oil extracts from *Schisandra chinensis* and *Matricaria chamomilla* [27] demonstrated synergistic effects as free radical scavengers compared to controls in mice. Brown seaweed lipids extracts resulting in less lipid peroxidation in the liver of female KK-Ay mice, even if the hepatic percentage of PUFAs increased [28]. The long-term intake of the BASE diet modulated the expression of relevant genes associated with chronic disorders in the liver of male Sprague–Dawley rats, suggesting a link between diet, reproductive system function, and aging [29]. Moreover, the anti-inflammatory AIDM mixture [30] was effective in improving lipid and inflammatory CVD risk factors in rodents, and a fish oil combined with motherwort oil demonstrated superior cardioprotective properties in rats [31].

The effects of diets rich in fish-derived omega-3 and polyphenols in subjects at high CV risk have been studied in several human trials, which reported a reduction in the postprandial lipid content of large very low-density lipoprotein (VLDL) and increases intermediate-density lipoprotein (IDL) cholesterol; LDL particles richer in triglycerides, and HDL poorer [32][33] while decreasing oxidative stress [33], and blood glucose, insulin secretion and postprandial glucagon-like peptide 1 levels [34]. Other lipid rearrangements in HDL were also reported [35]. Diets

enriched in proanthocyanidins from cranberry juice and fish oil also improved both insulin and lipoprotein metabolisms in patients suffering from diabetes and periodontal disease [36]. Nevertheless, it has been reported that the postprandial chylomicron response to these nutraceuticals depends on supplementation time [37], and should also be considered in this kind of nutrition strategies. The omega-6/omega-3 ratio [38] and the modulation of the microbiota composition [39] seem also critical in the study of their cardioprotective properties. Interestingly, the statin therapy of patients suffering from CVD could be efficiently complemented with a combination of fish oils and polyphenols [40].

Several mixtures of bioactive substances and nutraceutical cocktails, all of them especially rich in polyphenols and fish oils, were also tested in human trials [41][42][43], demonstrating effectiveness in ameliorating lipid profiles, inflammation and atherosclerotic events, but less action on insulin sensitivity.

3. Combined Polyphenols and Fish Oils Intake for Improving Neurodegenerative Diseases. Preclinical and Clinical Evidence.

The benefitial effects of combining polyphenols and fish oils on cognition alteration and neurodegenerative processes have been also investigated. Thus, resveratrol and DHA significantly altered hippocampal expression of gene associated with inflammatory responses [46]. This anti-inflammatory action was further investigated and it was reported that low concentrations of a combination of EPA-rich oil and phytonutrients prevented the transformation of microglia to proinflammatory M1 phenotype and the redox-sensitive NF-κB activation, while the anti-inflammatory IL-10 secretion [44]. In N2a neural cell, the main Mediterranean diet nutrients demonstrated to be potent cytoprotective agents against neurotoxicity [45] and other diets like the LMN, also rich in polyphenols and PUFAs, decreased the behavioral deterioration and delayed the amyloid plaques formation [47], and caused an enhanced modulatory effect on both cholinergic and catecholaminergic transmissions [48] in animal models of aging and Alzheimer's disease. Similar conclusions on the improvement of memory and cognitive performance were also reached in animal models feeding diets rich in those compounds and other bioactive nutrients [49]. However, results were more inconsistent in clinical trials. For instance, the supplementation with Smartfish® increased amyloid-β phagocytosis and resolvin D1 in patients with minor cognitive impairments [51], but it had only a limited beneficial impact in older adults without any other pathology [52].

Mixtures between polyphenols and omega-3 were tested in young subjects to find beneficial effects over the post-mild traumatic brain injury function in adolescent rats [50], and seemed to improve executive function, brain health, and nutritional status in vulnerable young children at risk of undernutrition living in low-income countries [53].

4. Combined Polyphenols and Fish Oils Intake for Improving Cancer. Preclinical and Clinical Evidence.

The bioactivity of the combination between polyphenols and PUFAs was also tested against some types of cancers. In colonic leucine-rich repeat-containing G-protein-coupled receptor 5-positive (Lgr5+) stem cells in mice, which are the cells of origin of colon cancer, the combination between fish oil and curcumin synergistically increased targeted apoptosis in DNA damaged Lgr5+ stem cells, maximally reduced their damaged, drop to the level measured in saline-treated mice. Moreover, p53 signaling in Lgr5+ stem cells from mice exposed to a genotoxic carcinogen (azoxymethane) was uniquely up-regulated only following fish oil plus curcumin cotreatment [54]. Interestingly, some esterified phenols with omega-3 PUFAs (so-called lipophenols), particularly quercetin bound to ALA, EPA and DHA reported antioxidant, anti-inflammatory, and anticarcinogenic properties in lung cells exposure to H_2O_2 insult [66] or cigarette smoke toxicants [67].

A recent study reported that hydroxytyrosol combined with omega-3 and curcumin reduced inflammation and pain in patients with aromatase-induced musculoskeletal symptoms, as one of the side effects of the hormonal therapies for breast cancer [55]. Remarkably, several DHA and phenols conjugated increase the bioactivity of the individual compounds against breast cancer [68], and also might prevent or inhibit the progression of triple-negative breast cancer (TNBC) [69] and inhibit the gelatinolytic matrix metalloproteinase MMP-9 [70]. Morever, the high adherence to diets rich in polyphenols and fish oils, such as the Mediterranean diet, was found inversely associated with the likelihood of suffering from prostate cancer [56].

5. Combined Polyphenols and Fish Oils Intake for Improving Other Pathologies and Physiological Processes. Preclinical and Clinical Evidence.

Physiological processes concomitant with oxidative stress and/or inflammation were also addressed to test the effects of polyphenols and fish oils. As a consequence, it has been found that fish oil and curcumin mayprevent skeletal muscle atrophy [57]. Functional beverages containing these nutraceuticals seemed to protect against oxidative damage [58] and enhance the gene expression of antioxidant enzymes in peripheral blood mononuclear cells [59] in young athletes, but increasing nitrative damage [58] and the proinflammatory circulating environment in response to the exercise [59]. Furthermore, an antioxidant/anti-inflammatory cocktail did not cause any significant effect in the prevention of muscle deconditioning induced by long-term inactivity in healthy men [60]. These heterogeneous results reflect the extremely complexyty of the redox homeostasis in skeletal muscle and the need for more investigation.

Likewise, it has been reported that omega-3 and resveratrol could prevent aged retinal pigment epithelial (RPE) cells damage and age-related macular degeneration [61], choroidal neovascularization [62] and they can be used for designed dermatologic diets to improve skin barrier function for the treatment of dermatitis [63]. Interestingly, several esterified phenols with DHA have shown powerful antioxidant properties and high protection activities against reactive aldehyde all-trans-retinal toxicity and photo-oxidative toxicity and constitute highly promising strategies for the prevention of retinal degeneration [71][72][73][74][75][76].

Finally, some studies revealed that immune priming [64] and microbiota [65] in the newborn are tightly regulated by maternal diet composition, particularly polyphenols and omega-3, affecting the infant health.

6. Conclusions

The health benefits of the combination of the bioactive properties of polyphenols and fish oil have been largely supported by a growing amount of scientific evidence. Several synergistic, additive, or complementary antioxidant and anti-inflammatory effects have been consistently reported, as well as modulation of lipid and lipoprotein metabolism. Modulation of insulin signaling and gut microbiota were also found. Nevertheless, some bioactive cocktails failed in reproducing the beneficial effects in clinical trials. This fact might be explained by the complexity of the interaction of nutraceuticals-metabolism and mechanisms of action, as well as the strongly influence that multiple factors exert on their bioactivity (chemical structure of polyphenols, diet EPA/DHA ratio, dietary framework, presence of other bioactive substances pathophysiological condition, physical activity of patients, age, etc). The adoption of multiomic and system biology strategies, and increasing the number of clinical trials would help fully understanding how those nutraceuticals interact to each other in vivo and with the metabolism of a certain organism. This knowledge is neccessary for the correct use of polyphenols and fish oil as part of personalized nutrition.

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