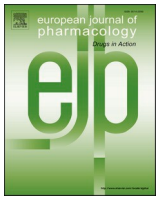
European Journal of Pharmacology 985 (2024) 177107

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar



# The role for ω-3 polyunsaturated and short chain fatty acids in hypertension: An updated view on the interaction with gut microbiota

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ARTICLE INFO

*Keywords:*
Arterial hypertension
Omega-3 polyunsaturated fatty acids
Oxylipins
Vascular reactivity
Intestinal microbiota
Short chain fatty acids

ABSTRACT

As of 2024, arterial hypertension is still considered the leading modifiable cardiovascular risk factor and, due to high rates of undertreatment and poor blood pressure control, the major contributor to human morbidity and mortality. Development of new treatment options and better interventions in lifestyle correction have become a priority of experimental and clinical research. In the last decades, dietary supplementation of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) and generation of gut microbiota-derived short chain fatty acids (SCFAs) have surged as potential and promising interventions for hypertension and cardiovascular prevention. ω-3 PUFAs are considered "essential" fatty acids that can be obtained only from dietary sources. Although previous intervention trials were not consistent in reporting a significant benefit of ω-3 PUFAs, the recent REDUCE-IT trial has provided robust evidence in support of their role in cardiovascular prevention. Recent studies have also identified the intestinal microbiota as a potential player in the pathophysiology and progression of hypertension. Although this might occur through many pathways, generation of SCFAs that is highly dependent on dietary fiber intake is primarily involved, providing an additional target for the development of novel therapeutic strategies. For these reasons, some scientific societies currently recommend dietary supplementation of ω-3 PUFAs and fiber-containing foods in patients with hypertension. In this narrative review, we summarize the results of studies that examined the effects of ω-3 PUFAs and SCFAs on blood pressure, highlighting the mechanisms of action on the vascular system and their possible impact on hypertension, hypertension-related organ damage and, ultimately, cardiovascular outcomes.

## 1. Introduction

Hypertension is the most frequent modifiable cardiovascular risk factor with an estimated prevalence of 35–40% in some populations, and is the leading condition associated with general mortality worldwide (Mancia et al., 2023). The pathophysiology of primary hypertension is complex and multifaceted, with a prominent role played by an imbalance between vasoconstrictive and vasodilatory vascular responses, arising from an interaction between genetic and environmental factors. Due to their proven ability to reduce blood pressure (BP), current guidelines strongly recommend lifestyle changes and dietary interventions in all patients as the first step of hypertension treatment (Mancia et al., 2023).

Pioneering studies conducted in populations traditionally eating high amounts of omega-3 polyunsaturated fatty acids (ω-3 PUFAs)-rich fish reported a surprisingly low incidence of cardiovascular events (Newman et al., 1993). These findings raised quickly the interest of the scientific community over the potential benefits of these molecules in

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https://doi.org/10.1016/j.ejphar.2024.177107
Received 1 June 2024; Received in revised form 24 October 2024; Accepted 5 November 2024
Available online 6 November 2024

cardiovascular prevention. On the one hand, antioxidant, antiinflammatory, antithrombotic, and endothelium-protective effects of ω-3 PUFAs were demonstrated in elegant experimental studies. On the other hand, many epidemiological and interventional studies, together with comprehensive reviews and meta-analyses were published to ascertain the benefits of ω-3 PUFAs in cardiovascular prevention (Brosolo et al., 2023). Dietary supplementation with ω-3 PUFAs was proven to decrease serum triglyceride and increase HDL-cholesterol levels (Colussi et al., 2004; Marston et al., 2019), an effect that could be particularly relevant because current evidence points to triglyceride-rich lipoproteins as major contributors to the "residual lipoprotein attributable risk" (Nordestgaard, 2016). Although results of early randomized controlled trials with triglyceride-lowering drugs were inconsistent in reporting cardiovascular benefits, subgroup analyses of recent studies (Mosca et al., 2017) and the results of the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial) (Bhatt et al., 2019) and JELIS (Japan EPA Lipid Intervention Study)trial (Yokoyama et al., 2007) demonstrated a significant reduction of cardiovascular events with use of ω-3 PUFAs, supporting a potential role of these fatty acids in clinical practice. Based upon these observations, international guidelines for cardiovascular prevention recommend regular consumption of ω-3 PUFAs-rich foods as part of a healthy diet (Lichtenstein et al., 2021). However, we must point out that even if a few meta-analyses could report a statistically significant cardiovascular risk reduction, more results showed insufficient evidence of a possible protective effect. Neither linear assumption-driven meta-regressions nor stratified dose analyses have conclusively estimated the dose-response relationship between ω3 PUFA intake and relative risk reduction, raising the possibility of a nonlinear dose-response curve (Musazadeh et al., 2022). Moreover, JELIS was often challenged for its selection of patients with a relatively high background of fish consumption and REDUCE-IT was revisited for the use of mineral oil as a comparator, respectively.

In the past decade, the gut microbiota has emerged as a factor potentially involved in BP regulation. This might occur through multiple mechanisms including immune-dependent and independent pathways, and reciprocal interactions with the nervous ("gut-brain axis") endocrine, and renal systems ("gut-kidney axis"). Short chain fatty acids (SCFAs) are the best characterized products of intestinal bacterial fermentation that mainly come from plant-derived undigestible fibers and are now considered the leading mediators of microbe-host interactions in BP regulation. Importantly, current hypertension guidelines recommend a regular consumption of fiber-containing foods for prevention and treatment of hypertension and improvement of cardiovascular outcomes (Charchar et al., 2024).

The aim of this narrative review is to provide an updated view of the relevance that ω-3 PUFAs and gut microbiota-derived SCFAs may have in hypertension. We systematically searched the medical literature using the PubMed MeSH and the terms « omega-3», «polyunsaturated fatty acids», «fish fat», «gut microbiota», «short chain fatty acids», «blood pressure», and «arterial hypertension » for extraction. We considered full-text articles with original data for the effect of ω-3 PUFAs and SCFAs on BP, and meta-analyses and comprehensive reviews on this same subject. Articles were retrieved by G.B. and were reviewed and discussed with C.C. and L.A.S. for subsequent selection. Studies were selected according to the quality of evidence based on the study protocol, size, consistency, and magnitude and dose-dependency of effect that was estimated according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria (Gordon Hguyatt et al., 2008).

## 2. Polyunsaturated fatty acids in hypertension

### 2.1. Biochemistry and sources of ω-3 PUFAs

ω-3 PUFAs are currently named according to the number of carbon units in the molecule and the position of the first double-bond relative to the terminal methyl carbon. Omega (ω) indicates the last methyl carbon as opposed to the carboxyl group of the acyl chain, and −6 or −3 indicates the position of the first double-bond from the last methyl group (Colussi et al., 2007). PUFAs are further classified into essential and nonessential according to the ability of the human body to synthesize them *de novo*. Among essential PUFAs, the ω-3 and ω-6 families that cannot be synthesized ex novo must necessarily be obtained from food. Alpha-linolenic acid is the precursor of long-chain ω-3 PUFAs through elongation and desaturation of its acyl chains (Fig. 1), and is predominantly found in flaxseed, soybean, canola oils, pumpkin seeds, perilla seed, tofu, walnuts, and some algae. The two most relevant ω-3 PUFAs, eicosapentaenoic acid (C20:5, EPA) and docosahexaenoic acid (C22:6, DHA), however mainly derive from food, including seafood and fatty fish (oysters, shrimp, sardines, mackerel, salmon, trout, seabass) (Colussi et al., 2010). Western diets that are rich in meats and poultry alongside deep-fried food, are abundant in ω-6 PUFAs and relatively poor in ω-3 PUFAs, with ratios of ω-6 PUFAs to ω-3 PUFAs as high as 16:1 (Simopoulos, 2008). Moreover, even subjects who eat fish regularly have a low ω-3 index (O3i), a biomarker of overall ω-3 PUFA status defined as the ratio of both EPA and DHA to total fatty acids in erythrocyte membranes, with values that are below those (8%) that were previously validated as a risk factor for cardiovascular events (Dempsey et al., 2023).

### 2.2. Physiological effects of ω-3 PUFAs

Multiple mechanisms could explain the physiological effects ω-3 PUFAs, including structural and functional interactions with cellular membranes, modulation of intracellular signalling, and production of metabolites (e.g. oxylipins) that are directly involved in regulation of vascular function (Fig. 2). ω-3 PUFAs are incorporated in phospholipids of plasma membranes of different cell types including erythrocytes, neutrophils, and platelets. Experimental studies suggest that EPA and DHA interact differently with cell membranes, with EPA seemingly more efficient in the mitigation of the atherosclerotic process (Mason et al., 2016). This might be due to a more stable interaction of EPA with the surrounding saturated fatty acids, leading to improved membrane stability and inhibition of lipid oxidation and cholesterol domain formation (Sherratt and Mason, 2018). ω-3 PUFAs are incorporated into membrane phospholipids, mainly in the cerebral cortex, retina, testes, muscle, and liver, where they usually account for less than 10% of the total amount of fatty acids, but the daily intake of ω-3 PUFAs could substantially modify the composition of cell membranes in a relatively short time (from days to weeks) (Faber et al., 2011). Plasma membranes are composed by an agglomerate of functional microdomains (lipid rafts and

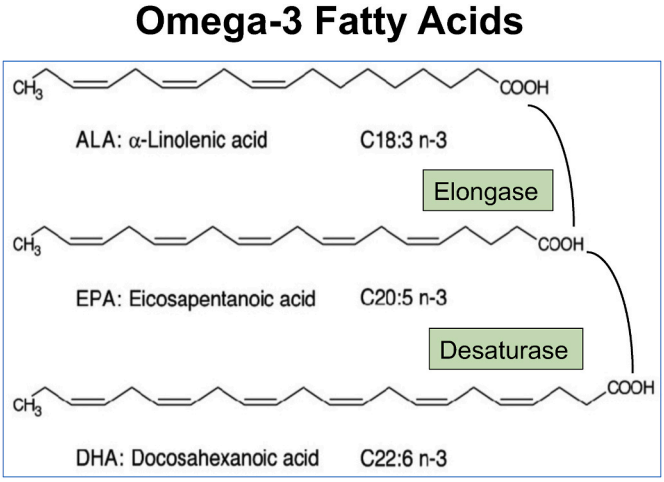


**Fig. 1.** Structure of ω-3 polyunsaturated fatty acids and their formation from alpha-linolenic acid through elongation and desaturation.

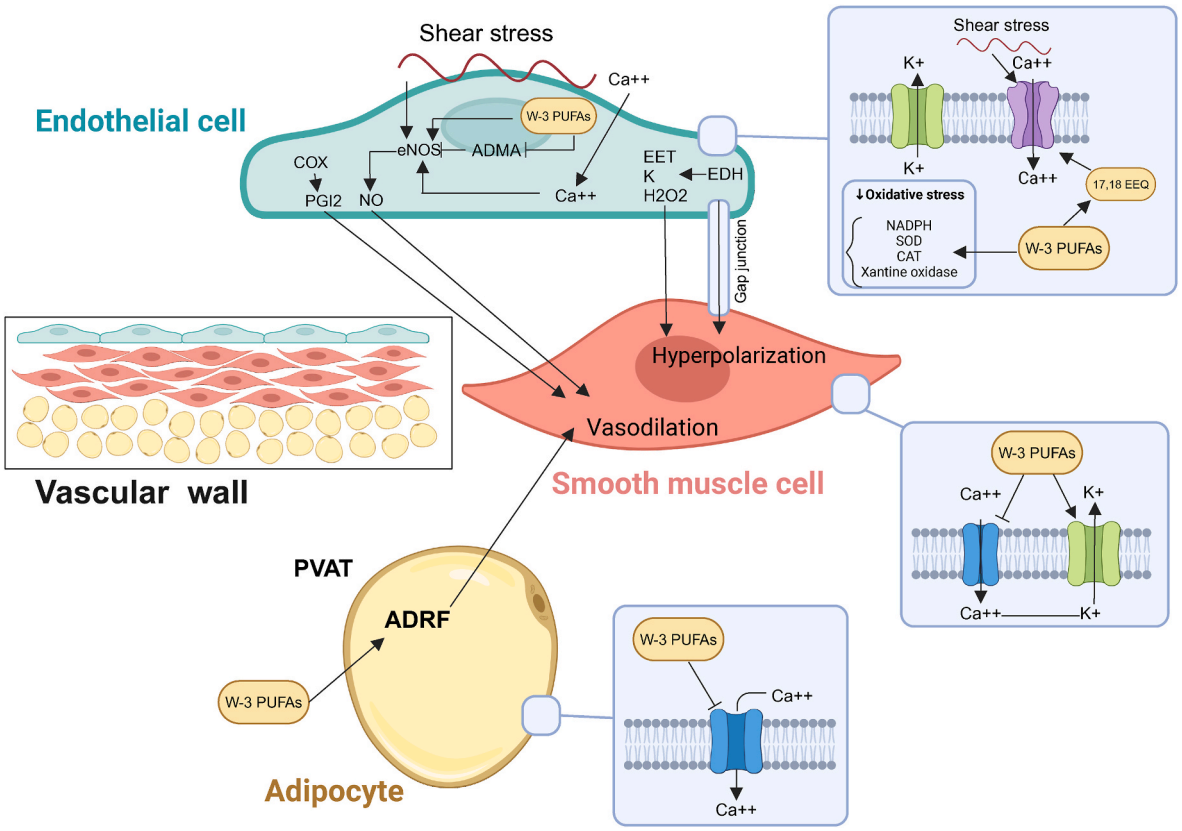


**Fig. 2.** Effects of ω-3 polyunsaturated fatty acids (ω-3 PUFAs) on cell membranes and intracellular signalling and relevance for endothelial and vascular smooth muscle cells and perivascular adipocytes. EEQ, epoxyeicosatetraenoic acid; NADPH, nicotinamide adenine dinucleotide; SOD, superoxide dismutase; CAT, catalese; ADRF, adventitium-derived relaxing factor; COX, cyclooxygenase; PGI2, prostacyclin; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; ADMA, asymmetric dimethylarginine; EET, epoxyeicosatrienoic acid.

caveolae) that facilitate interactions between resident proteins and lipids, thereby influencing the function of cells and intracellular organelles (Laude and Prior, 2004; Hancock, 2006). Incorporation of ω-3 PUFAs in membrane phospholipids changes lipid rafts and caveolae characteristics, improving membrane fluidity and biophysical properties. These effects of ω-3 PUFAs cause downstream modulation of protein function and protein–protein interactions, triggering intracellular signals (G-proteins), modulating membrane ion channels, activating enzymes (nitric oxide synthase), and increasing production of tumor necrosis factor alpha, adhesion molecules, and Toll-like receptors (Jump, 2002; Dart, 2010, Layne et al., 2011). In addition to structural effects on cell membranes, ω-3 PUFAs specifically and directly bind to membrane proteins such as the G-protein-coupled receptor 120 that was renamed "*free fatty acid receptor 4*" (Oh et al., 2010). This receptor is highly expressed in macrophages and adipocytes (Im, 2016) and triggers a downstream signalling cascade, ultimately leading to decreased production of some cytokines and acute-phase reactants (interleukin-1, interleukin-6, and C-reactive protein) with potent anti-inflammatory effects (Oh et al., 2010; Yan et al., 2013). ω-3 PUFAs were also shown to directly regulate gene expression via nuclear receptors, including peroxisome proliferator-activated receptors, hepatic nuclear factors, retinoid X receptors, and liver X receptors (Wolfrum et al., 2001), thereby providing further evidence in support of their possible effects on metabolic and inflammatory pathways (Adkins and Kelley, 2010). Last, anti-inflammatory and anti-atherosclerotic actions of ω-3 PUFAs might result from production of a variety of bioactive metabolites, named "*ω-3 oxylipins*". Oxylipins are derived from oxygenation of ω-6 and ω-3 PUFAs of cell membranes and include eicosanoids (prostaglandins, thromboxanes, and leukotrienes), epoxy-metabolites, and specialized "pro--resolvin mediators" (resolvins, protectins, and maresins) that have potent antioxidant and vasoprotective properties (Serhan et al., 2008; Schunk, 2015; Westphal et al., 2015).

### 2.3. *ω-3 PUFAs and blood pressure*

The effects of ω-3 PUFAs on BP have been characterized in the last decades in randomized clinical trials, systematic reviews, and meta-analyses, most of which included both normotensive and hypertensive subjects (Brosolo et al., 2023). Cumulative meta-analyses demonstrated that high-doses of ω-3 PUFAs (more than 3 g/day) administered for several weeks, lead to a small but significant BP fall, particularly in patients with untreated hypertension. In these early meta-analyses, a median dose (5g/day) of ω-3 PUFAs reduced systolic BP from 2.1 to 5.5 mm Hg and diastolic BP from 1.6 to 3.5 mm Hg (Appel et al., 1993; Morris et al., 1993; Geleijnse et al., 2002). Effects of ω-3 PUFAs on BP were further analysed in subsequent meta-analyses, all confirming a small albeit meaningful reduction (Dickinson et al., 2006; Campbell et al., 2013; Miller et al., 2014; Abumweis et al., 2018; Guo et al., 2019). Recently, this evidence has received further support by the results of an *umbrella meta-analysis* that included 10 meta-analyses of 131 trials conducted between 1989 and 2021, with ω-3 PUFAs doses from 2.2 to 6 g/day, and duration of intervention from 4 to 29 weeks (Musazadeh et al., 2022). Results showed that ω-3 PUFAs decreases systolic (−1.19 mm Hg; 95% CI: 1.76,-0.62; $p < 0.001$) and diastolic (−0.91 mm Hg; 95% CI: 1.35, −0.47; $p < 0.001$) BP levels, with effects that were more evident in elderly hypertensive patients who were supplemented with amounts greater than 2 g/day for more than 10 weeks. Despite consistency of results obtained in all meta-analyses, important variability of findings in each single study reflecting heterogeneity in the source (fish, fish oil, capsules, powders), relative content of EPA and DHA, duration

of interventions, and differences in terms of comorbidities and additional treatments should not be overlooked (Minihane et al., 2016). For example, comorbidities associated with hypertension might influence the effects of ω-3 PUFAs supplementation on blood pressure, as pointed out by subgroup analyses indicating a stronger effect in patients with dyslipidaemia and in kidney transplant recipients (Musazadeh et al., 2022). Moreover, like other dietary intervention studies, assessment of adherence to dietary prescription is difficult and only a minority of trials had measurement of ω-3 PUFAs in cell membranes done. In a prospective study, we tested the effects on BP of a diet containing meals (three times/week for 6 months) of farmed fish fed with ω-3 PUFAs-enriched chow, in uncomplicated hypertensive patients who were maintained on usual antihypertensive treatment (Colussi et al., 2014a,b). Ambulatory BP levels were assessed at baseline and at the end of the study together with measurements of ω-3 PUFAs content in plasma membranes of erythrocytes. We found that 24-h and nighttime BP fell significantly only in those patients who had increased membrane content of ω-3 PUFAs (systolic BP: 24-h −5 mm Hg, nighttime −5 mm Hg; diastolic BP: 24-h −3 mm Hg, nighttime −4 mm Hg, all $p < 0.05$), and this effects was more pronounced in those patients who had lower baseline membrane content of ω-3 PUFAs. Thus, the BP-lowering effect of dietary ω-3 PUFAs in patients with verified changes in cell membrane ω-3 PUFAs content is well established. The same cannot be claimed for a possible dose-dependent effect of these molecules on BP, with some cumulative analyses suggesting a linear relationship (Appel et al., 1993) and others reporting either a J-shaped (Yang et al., 2016) or L-shaped (Chen et al., 2019) relationship. In summary, although modest, the BP-lowering effect of ω-3 PUFAs could be relevant on a population level, as epidemiologic studies have estimated that a 2 mm Hg decrease in systolic BP decreases stroke-related and coronary heart disease-related deaths by 10% and 7%, respectively (Lewington et al., 2002). Therefore, ω-3 PUFAs supplementation might have a place in treatment of low-risk patients with mild hypertension in addition to other measures that are adopted for lifestyle correction.

The mechanisms potentially involved in the hypotensive effects of ω-3 PUFAs are mainly related to their effects on peripheral vasculature with reduction of total peripheral resistance, whereas effects on cardiac hemodynamics seem unremarkable. In fact, cardiac output is not affected by ω-3 PUFAs because a modest increase in stroke volume obtained through improvement of ventricular diastolic filling (Grimsgaard et al., 1998) is counterbalanced by a decreased heart rate (Mozaffarian et al., 2005). Conversely, a large body of evidence obtained from experimental animal and human studies supports the view that ω-3 PUFAs have a role in the regulation of functional responses of peripheral arteries (Khan et al., 2003), affecting both endothelium-dependent and endothelium-independent mechanisms.

It is well-known that endothelial cells play a crucial role in the regulation of many vascular functions including, through release of vasodilator and vasoconstrictor agents, vasomotility. Under physiological conditions, production of vasoconstrictive and vasodilatory mediators is balanced, whereas, under pathological conditions this balance shifts towards vasoconstriction. Multiple studies have shown that ω-3 PUFAs improve the endothelial response of both normal and damaged endothelium (Skulas-Ray et al., 2011; Colussi et al., 2017). Incubation of endothelial cells with EPA leads to increased production of nitric oxide (NO) through activation of NO synthase (Omura et al., 2001) and endothelial NO production is stimulated by ω-3 PUFAs-induced decrease of circulating dimethylarginine, an endogenous inhibitor of NO synthase (Raimondi et al., 2005). ω-3 PUFAs reduce also oxidative stress in endothelial cells by reducing the activity of intracellular enzymes (e.g. nicotinamide adenine dinucleotide phosphate, xanthine oxidase) involved in generation of reactive oxygen species (ROS) (Suzuki et al., 1998; Niazi et al., 2017). Further contribution to endothelium-dependent regulation of vascular tone is linked to the action of ω-3 oxylipins that decrease production of ROS by increasing expression of antioxidant enzymes such as catalase and superoxide dismutase (Wang et al., 2019). Additional ω-3 PUFAs-related mechanisms that are independent of endothelial NO production might contribute to regulation of vascular tone. In isolated blood vessels obtained from experimental animals, ω-3 PUFAs cause vasodilation even after endothelial NO synthase blockade (Singh et al., 2010; Limbu et al., 2018). This suggest a direct effect of ω-3 PUFAs on smooth muscle vascular cells that is corroborated by evidence that ω-3 PUFAs interact with ion channels located in the plasma membrane of these cells (e.g. L-type calcium channels, potassium ATP-channels, transient receptor potential cation channel) whose modulation can contribute to the vasodilatory properties (Mies et al., 2004; Riedel and Light, 2005, Wang et al., 2011).

### 2.4. ω-3 PUFAs hypertension and vascular damage

As already stated, solid data support the evidence of a modest but significant beneficial effect of ω-3 PUFAs on BP. In this context, epidemiological studies examined the possibility that long-term ω-3 PUFAs consumption, either as fishmeal or supplementation, might decrease the risk to develop hypertension. Although initial data of the National Health and Nutrition Examination Survey-I (NHANES-I) indicated that black women who regularly consumed fishmeal had lower risk to develop hypertension (Gillum et al., 2001), the Coronary Artery Risk Development in Young Adults (CARDIA) study (Steffen et al., 2005), the Korean Genome Epidemiology Study (Baik et al., 2010), and the Physicians Health Study (PHS) (Christen et al., 2000) failed to demonstrate a significant interaction between regular fish consumption and the development of hypertension. The possible association of fish consumption with the development of hypertension was the subject of a meta-analysis that included 8 observational prospective studies including more than 50,000 subjects who were normotensive and free of cardiovascular complications at enrolment and were followed up to 20 years (Lewington et al., 2002). In this study, risk of incident hypertension was not associated with fish consumption, although higher plasma levels of EPA and DHA were associated with lower incidence of hypertension.

Another relevant issue is related to the possible contribution of ω-3 PUFAs to the metabolic syndrome. The Korean Genome Epidemiologic Study reported an odds ratio of 0.43 for development of the metabolic syndrome in men who ate fish daily in comparison with men who ate fish less than once a week (Baik et al., 2010). The association of ω-3 PUFAs with the metabolic syndrome was also investigated by measuring fatty acids composition of red cell membranes in 55 uncomplicated hypertensive patients, reporting significantly lower membrane content of ω-3 PUFAs in patients who had the metabolic syndrome (Colussi et al., 2015a,b,c). Thus, while lower levels of ω-3 PUFAs are seemingly associated with higher prevalence of the metabolic syndrome, the current evidence in support of benefits of ω-3 PUFAs in preventing hypertension is still inconsistent and deserves further investigation.

In addition to the effects of ω-3 PUFAs on BP levels, these fatty acids might also contribute to the development of hypertension-related vascular damage. Arterial stiffening is a progressive process generally associated with aging that is accelerated by high BP and increased levels of plasma lipoproteins. Stiffening results from both structural and functional changes of the vascular wall, including depletion of elastin fibers, expansion of the extracellular matrix, and enhanced tone of the smooth muscle layer, this latter possibly induced by impaired release of NO from endothelial cells. In clinical practice, arterial stiffening can be readily assessed noninvasively with measurement of the pulse wave velocity (PWV) and is an independent predictor of major cardiovascular events. In a randomized clinical trial on healthy subjects, administration of 6 g/day of fish oil had better effects on arterial stiffness than a dose of 3 g/day (Pase et al., 2015). Effects of ω-3 PUFAs supplementation on carotid-femoral PWV were examined in a systematic review of 10 trials that enrolled both healthy and hypertensive subjects who were randomized to ω-3 PUFAs (doses ranging from 0.64 to 3.00 g/day) or

placebo, showing a significant and BP-independent improvement in arterial stiffness (Pase et al., 2011). Other markers of hypertension-related vascular involvement can be obtained with assessment of endothelium-dependent and independent vascular responses that, like PWV, are significant predictors of worse cardiovascular outcome (Yeboah et al., 2009). In uncomplicated hypertensive patients, we measured the content of free fatty acids in erythrocytes membranes and assessed the vasodilatory response of the brachial artery to a nitrate donor compound (endothelium-independent vasodilation) and post-ischemic reactive hyperemia (endothelium-dependent flow-mediated vasodilation, FMD) (Colussi et al., 2015a,b,c). Baseline diameter of the brachial artery was significantly smaller and vasodilatory response to nitrate was significantly greater in patients with higher polyunsaturated-to-saturated fatty acid ratio (PUFA/SFA), while no difference was observed in FMD. Moreover, the PUFA/SFA ratio was inversely and independently correlated to brachial artery diameter and directly with vasodilatory response to nitrate strongly suggesting a contribution of ω-3 PUFAs to endothelium-independent vascular response.

Thickening of the inner arterial layer anticipates formation of atherosclerotic plaques and can be easily detected by measurement of the so-called carotid intima-media thickness (IMT). In a prospective intervention study, uncomplicated hypertensive patients received nutritional counselling and 3 weekly meals of farmed trout fed with high amounts of ω-3 PUFAs, and the carotid IMT was measured together with the erythrocyte membrane fatty acid composition at baseline and after 1 year (Colussi et al., 2014a,b). In this study, baseline PUFA/SFA ratio was inversely related with carotid IMT. At the end of study, PUFA/SFA ratio increased in almost half of patients and, only in these patients the carotid IMT decreased with a change that was independent of body mass index, BP, and plasma lipids. Similar observations on the beneficial effects of ω-3 PUFAs on carotid atherosclerosis were reported in additional groups patients (He et al., 2008; Dai et al., 2014). Moreover, stabilization of atherosclerotic plaques causing carotid stenosis was demonstrated with use of ω-3 PUFAs (Cawood et al., 2010, Yamano et al., 2015), an effect that could be related to thickening of the fibrous cap and decrease of intraplaque inflammation that are coupled with increased HDL-cholesterol and decreased lipoprotein(a) in plasma (Shinozaki et al., 1996; Colussi et al., 2004).

Although a large body of evidence supports existence of beneficial vascular effects of ω-3 PUFAs, findings of cardiovascular prevention studies that tested the effects of these fatty acids have been controversial. This could be due to many limitations in most of these studies, including differences in subjects enrolled, types of ω-3 PUFAs supplements, doses, and duration of exposure. To our knowledge, no clinical outcome study selectively included hypertensive patients, and data of supplementation in hypertension are necessarily extrapolated from cardiovascular prevention trials that enrolled sizeable proportions of hypertensive patients (Colussi et al., 2015a,b,c). Although some evidence suggests possible benefits of ω-3 PUFAs in preventing atrial fibrillation (Colussi et al., 2018), early studies dating back to the '90s and early 2000s, reported somehow inconsistent results. Among the 11,324 study patients who had a recent history of acute coronary syndrome and were included in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) Prevenzione study, 36% had hypertension (GISSI study, 1999). In this study, 1 g/day of ω-3 PUFAs lowered by 10% the risk of the primary combined cardiovascular endpoint of death, nonfatal myocardial infarction, and stroke, over a 3.5-year follow-up. In the open-label, placebo-controlled JELIS trial, 35% of the 18,645 primary and secondary prevention subjects had hypertension (Yokoyama et al., 2007) and received 1800 mg/day of EPA for 5 years. Only patients in the EPA group had a significant reduction in triglyceride levels with a significant 19% reduction in the primary composite cardiovascular endpoint. In the randomized, double-blind, placebo-controlled GISSI-Heart Failure study, patients with class II–IV heart failure were enrolled and randomly assigned to receive either ω-3 PUFAs 1g/day or placebo for a median of 3.9 years (Tavazzi et al., 2008). Hypertensive patients accounted for 55% of the entire study population. Treatment with ω-3 PUFAs decreased mortality and hospital admissions by 2%, indicating a small but significant benefit. Conversely, no cardiovascular benefits of ω-3 PUFAs supplementation were observed in studies that included more substantial proportions of hypertensive patients, such as the Outcome Reduction with an Initial Glargine Intervention (ORIGIN; 12,536 high-risk patients, 79% with hypertension) trial (Bosch et al., 2012) and the GISSI Risk and Prevention studies (12,513 high-risk patients, 85% with hypertension) (Roncaglioni et al., 2013).

More recently, large-scale intervention trials have been performed using greater daily doses of ω-3 PUFAs, and selecting patients with elevated plasma triglyceride levels, thus overcoming some of the limitations of most of the previous studies. The REDUCE-IT was a randomized, double-blind, placebo-controlled trial enrolling 8179 hypertriglyceridemic (from 133 to 499 mg/dL) patients with either established cardiovascular disease or diabetes, and at least one additional cardiovascular risk factor (Bhatt et al., 2019). Patients were randomized to either 4 g/day of icosapent ethyl (a purified EPA preparation) or placebo. After a median follow-up of 4.9 years, patients treated with icosapent ethyl had a 25% reduction in the primary composite cardiovascular endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, unstable angina) and, prompted by these results, the European Medicines Agency (EMA) now recommends high dose icosapent ethyl for secondary cardiovascular prevention in patients with elevated plasma triglycerides. High dose ω-3 PUFAs (4 g/day) were tested also in a double-blind, placebo-controlled, primary prevention trial of 13,078 patients with hypertension, high plasma triglyceride and low HDL-cholesterol (Nicholls et al., 2020), but no difference in the primary composite cardiovascular endpoint was observed between treatment groups. Thus, current evidence suggests that the benefits of ω-3 PUFAs on prevention of cardiovascular events are restricted to secondary prevention.

## 3. Short chain fatty acids in hypertension

### 3.1. Gut microbiota definition and composition

The gut microbiota identifies a complex symbiotic microbial system, composed of more than 100 trillion mutualistic microorganisms (predominantly bacteria and viruses, but also fungi and protozoans) that colonize the human gut (Agus et al., 2012). The gut microbiota acts as an "internal ecosystem" directly involved in the digestion of macronutrients that harvests energy from food and produces vitamins that are essential for metabolic homeostasis and modulation of the immune system (Zhang and Davies, 2016). Microorganisms of the gut microbiota are organized in functional communities, with *Bacteroides* and *Firmicutes* representing the most abundant populations (>90%), followed by *Actinobacteria* and *Proteobacteria* (Mohajeri et al., 2018). The gut microbiota is now considered like an endocrine system that generates a broad spectrum of metabolites that reach the bloodstream and play a crucial role as mediators of host-microbial interactions, triggering responses both in the local intestinal microenvironment and at distant organ sites (Zhang and Davies, 2016). Imbalances and changes in the composition of microbiota, referred to as "dysbiosis", lead to deterioration of the gut barrier function and have been observed in multiple diseases, including hypertension (Yang et al., 2018). SCFAs are among the main metabolites produced by the intestinal microbiota, together with secondary bile acids, trimethylamine, lipopolysaccharides, imidazopropionic acid, branched-chain amino acids, and indole (Fan and Pedersen, 2021).

### 3.2. Structure and function of SCFAs

SCFAs include the three straight-chain compounds acetate, propionate, and butyrate that are produced in the large intestine by specific gut microbes during the process of fermentation of otherwise undigestible dietary fibers (Van der Hee and Wells, 2021) (Fig. 3). Acetate is by far the most abundant of the three SCFAs in the colonic lumen, where acetate, propionate, and butyrate are present in an approximate molar ratio of 60:20:20 (Den Besten et al., 2013). Acetate and propionate are produced by *Bifidobacterium* spp. and *Akkermansia muciniphila* (Venegas et al., 2019) and are rapidly absorbed into the bloodstream of the host by diffusion and activity of a monocarboxylate transporter. Once absorbed, acetate and propionate are taken up by the liver (Cummings et al., 1987) where acetate serves as a substrate for cholesterol synthesis and propionate acts as an essential precursor of protein synthesis, lipogenesis, and gluconeogenesis (Wolever et al., 1991). Butyrate is mainly produced by bacteria from the families *Ruminococcaceae*, *Lachnospiraceae*, *Anaerobutyricum hallii*, and *Anaerostipes* spp. and serves as fuel for colonocytes, being absorbed only in very small amounts. Therefore, in physiologic conditions, circulating concentrations of acetate and propionate are significantly higher than those of butyrate.

### 3.3. Gut microbiota and hypertension

Metabolites produced by the gut microbiota are key mediators of the host-microbiota relationship that can affect BP levels via immune-dependent and immune-independent mechanisms (O'Donnell et al., 2023). Gut microbiota-derived metabolites can be beneficial (e.g. SCFAs, indole-3-lactic acid, arachidonic acid) or detrimental (e.g. trimethylamine *N*-oxide) to BP levels. In the last decade, the growth and widespread use of next generation sequencing techniques, bioinformatics, and metagenomics, have provided increasing evidence on the role of gut microbiome and dysbiosis in the development and progression of hypertension (Li et al., 2017). This association between gut microbiota and hypertension has received support from both experimental data obtained in rodent models of hypertension and human studies. Animal studies involving Dahl salt-sensitive, spontaneously hypertensive, stress-hypertensive, and angiotensin II-induced hypertensive rats, and deoxycorticosterone acetate-salt mice showed that gut microbiota is dysbiotic and significantly different from the microbiota of normotensive wild-type control animals (Mell et al., 2015; Yang et al., 2015; Adnan et al., 2017; Marques et al., 2017). These differences include a reduction in the richness, diversity, and uniformity of microorganisms, an increased *Firmicutes/Bacteroides ratio* (F/B ratio: a recognized marker of imbalanced microbiota) due to lower abundance of SCFAs-producing bacteria, and higher abundance of lactate-producing bacteria. Moreover, experimental hypertension is associated with disruption of the gut epithelial barrier that might lead to greater permeation of some molecules that contribute to BP raise (O'Donnell et al., 2023).

In humans, many cross-sectional studies suggested an association between gut microbiome composition and BP levels or hypertension (Li et al., 2017; Kim et al., 2018; Dan et al., 2019; Huart et al., 2019; Sun et al., 2019). Although limited by some discrepancies in results, largely due to the heterogeneity of intestinal microbiota and confounders such as age, body mass, and dietary factors, interesting conclusions can be drawn from these studies. Some studies identified a reduced alpha diversity (an indicator of microbial variance) in hypertensive patients, while others showed lower abundance of SCFAs-producing microbiota and higher concentration of Gram-negative microbiota (*Klebsiella*, *Parabacteroides*, *Desulfovibrio*, *Prevotella*), a known source of pro-inflammatory lipopolysaccharides. These differences point to a role of SCFAs and lipopolysaccharides in hypertension, although this association might differ among different ethnic groups, as recently suggested by the HEalthy LIfe in an Urban Setting (HELIUS) study (Verhaar et al., 2020a,b). Although the association between microbiota and hypertension could be bidirectional (Yan et al., 2017; Kim et al., 2018), evidence obtained in the last few years strongly suggests that alterations of gut microbiota are causally related with hypertension development and progression. For instance, fecal transplantation from hypertensive donors to normotensive recipients resulted in hypertension development (Durgan et al., 2016; Adnan et al., 2017), and cohousing studies of hypotensive germ-free rats that acquired microbiota from conventional normotensive rats, progressively normalized their vascular tone (Bina et al., 2020). Thus, clinical and experimental evidence suggest that changes in the gut microbiota are associated with and might lead to development of hypertension (Verhaar et al., 2020a,b). Gut microbiome modulation might therefore represent a fully innovative therapeutic approach to lowering BP, perhaps through the oral delivery of gut microbial metabolites such as SCFAs.

### 3.4. SCFAs as mediators of blood pressure regulation

Among gut microbiota-derived metabolites, SCFAs are by far the most studied and first reported to regulate BP both in animal models (Pluznick et al., 2013; Pluznick, 2016; Wang et al., 2017) and humans (de la Cuesta-Zuluaga et al., 2018; Huart et al., 2019). Early *ex vivo* experiments conducted both in rat caudal (Nutting et al., 1991) and human colonic (Mortensen et al., 1990) arteries demonstrated that SCFAs cause vasodilation. Later on, experimental studies have revealed that SCAFs act through several G protein-coupled receptors, including free fatty acid receptors (*FFAR-2* and *FFAR-3*), other G-protein coupled receptors (*GPR109A*), and olfactory receptors 78 (*Olfr78*) (Felizardo et al., 2019; Kaye et al., 2020). These receptors can be found in a variety of tissues and organs, including the kidney, brain, sympathetic nervous system, blood vessels, and heart. The effects of SCFAs on vascular tone differ according to the receptors involved. Binding of SCFAs with *FFAR-2* and *FFAR-3*, highly expressed both in renal arteries and endothelial cells, causes vasodilation, whereas activation of *Olfr78*, by inducing renin release from the juxtaglomerular cells, is associated with

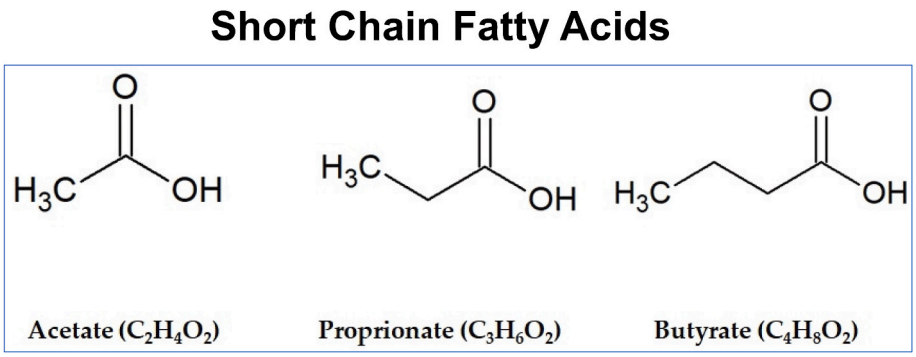


**Fig. 3.** Structure of the short chain fatty acids that are produced in the large intestine by microbiota during the process of fermentation of dietary fibers.

vasoconstriction and BP elevation (Pluznick, 2016; Wang et al., 2017) (Fig. 4).

SCFAs affect BP not only through activation of vascular and renal receptors, but also by modulation of the host immune system and inhibition of inflammatory responses. Both these mechanisms have been implicated in the development of hypertension and progression of hypertensive organ damage (Dixon et al., 2020; Zhang et al., 2021). SCFAs decrease the rate of pro-inflammatory *Th1* and *Th17* cell differentiation (Duscha et al., 2020), while increasing the differentiation and suppressive capacity of anti-inflammatory *Treg* cells (Arpaia et al., 2013). SCFAs are also involved in the inhibition of histone deacetylase, a key regulator of cell growth and differentiation, further enhancing the anti-inflammatory effects through inhibition of expression of the angiotensin II-type1 receptor and reduction of ROS generation (Cardinale et al., 2010) (Fig. 5).

An additional mechanism through which SCFAs might contribute to BP regulation is linked to modulation of the "gut-brain axis". This is a complex system consistent of multiple interactions between the gastrointestinal tract and the central nervous system, involving multiple neural, hormonal, and immunologic pathways (Cryan and Mazmanian, 2022). In this context, SCFAs have the potential to greatly influence the host's production of neuroactive metabolites dampening the elevated sympathetic drive often associated with hypertension (Kimura et al., 2011). Because vagal afferents have been found to express SCFAs-specific G protein-coupled receptors, SCAFs could also be involved in parasympathetic activation, thus providing another possible pathway for BP regulation (Lal et al., 2001).

### 3.5. Dietary fibers, SCFAs, and hypertension

As stated above, SCFAs are produced by the gut microbiota during fermentation of undigestible dietary fibers (Van der Hee and Wells, 2021). This prompted investigations of the possible benefits of regular consumption of fiber-rich foods on BP. One seminal study, conducted more than 40 years ago in 42 healthy subjects, showed that doubling the daily fiber intake over 4 weeks decreased by 3.2% systolic BP (Wright et al., 1979). Small-sized randomized clinical trials that were subsequently performed with relatively short duration and marked heterogeneity in terms of type and doses of fiber containing foods provided inconsistent results. For this reason, data of these studies were recently analysed in cumulative reviews and meta-analyses (Reynolds et al., 2019). In a recent meta-analysis of 12 trials including 878 patients with hypertension, high fiber intake reduced significantly systolic (−4.3 mm Hg, 95% C.I. 2.2–5.8) and diastolic (−3.1 mm Hg, 95% C.I. 1.7–4.4) BP (Reynolds et al., 2022). In agreement, another meta-analysis that included 83 studies of 5985 participants reported significant dose-dependent decrease of systolic (−1.36 mm Hg, 95% C.I. 0.60–2.13) and diastolic (−0.72 mm Hg, 95% C.I. 0.18–1.26) BP with soluble fiber supplementation (Ghavami et al., 2023). The magnitude of the effect of fiber intake on BP was greater in hypertensive patients, and specifically in those patients free of cardiovascular complications, highlighting the potential relevance of fiber consumption in primary cardiovascular prevention. To note, cardiovascular benefits of fiber supplementation might go beyond those on BP, and these cumulative analyses showed that high fiber intake was associated with a significant decrease of cardiovascular events and overall mortality.

Increased consumption of fiber-rich foods was included among dietary recommendations provided by most international hypertension guidelines for all patients with high BP. However, because of the partial gap in knowledge of fiber-related BP lowering mechanisms and uncertainty of the magnitude of the effect, specific indications on daily amounts to be consumed were not provided. Findings of recent meta-analyses prompted the International Society of Hypertension to recommend a fiber intake of 25–29 g/day to reduce the risk of new-onset hypertension in predisposed subjects (Charchar et al., 2024). Moreover, as highlighted by a random effects model analysis (Reynolds et al., 2019), a fiber intake of 35–39 g/day may provide further reduction of cardiovascular risk, suggesting that the optimal dietary target for patients with established hypertension should be higher than in primary prevention, with recommendations of >28 g/day for women and >38 g/day for men (Charchar et al., 2024). Unfortunately, estimates of overall fiber intake across low-, middle-, and high-income countries are still far from being optimal, with an average daily amount of approximately 11 g. Worrisome barriers to optimal fiber consumption include misconceptions about fiber content in different types of food and specific types of dietary fibers (each with different effects on BP), financial barriers due to the rising cost of healthy food over time and, most important, widespread unawareness of their potential cardiovascular benefits.

### 3.6. ω-3 PUFAs and gut microbiota

Initial investigations suggested that a complex reciprocal interplay might exists between dietary ω-3 PUFAs and the gut microbiota (Costantini et al., 2017). Studies of diets enriched of ω-3 PUFAs demonstrated that these fatty acids preserve a healthy microbiota and

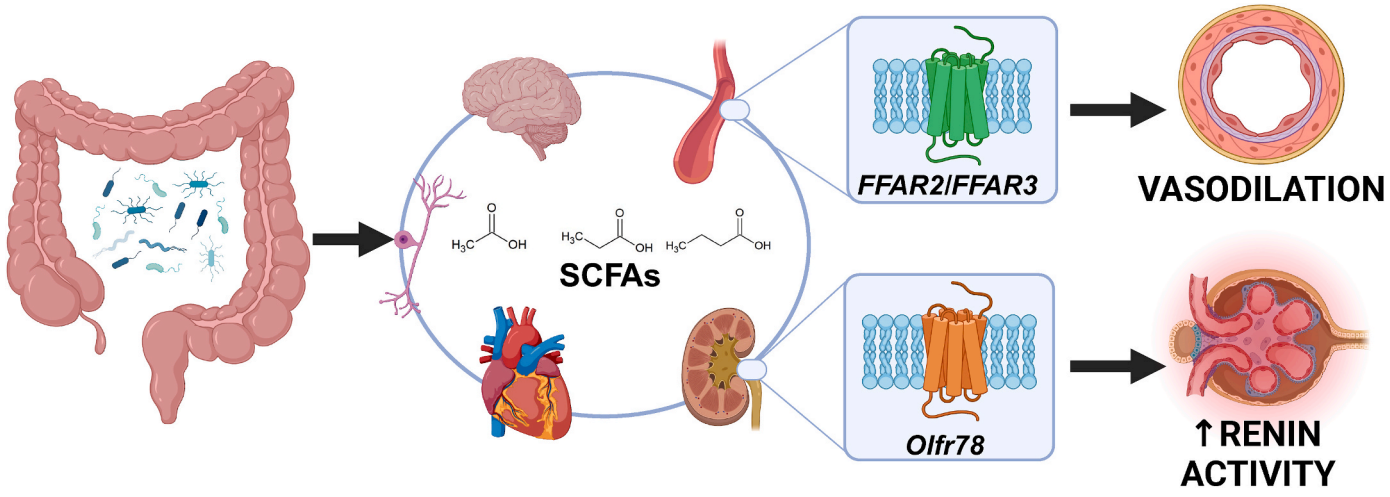


**Fig. 4.** Short chain fatty acids (SCFAs) can directly regulate blood pressure by binding to specific receptors. Activation several G protein-coupled receptors, including free fatty acid receptors (*FFAR-2* and *FFAR-3*) and olfactory receptors 78 (*Olfr78*) cause decreased and increased intracellular cAMP production, respectively, leading to arterial vasodilation and activation of renin release in the kidney.

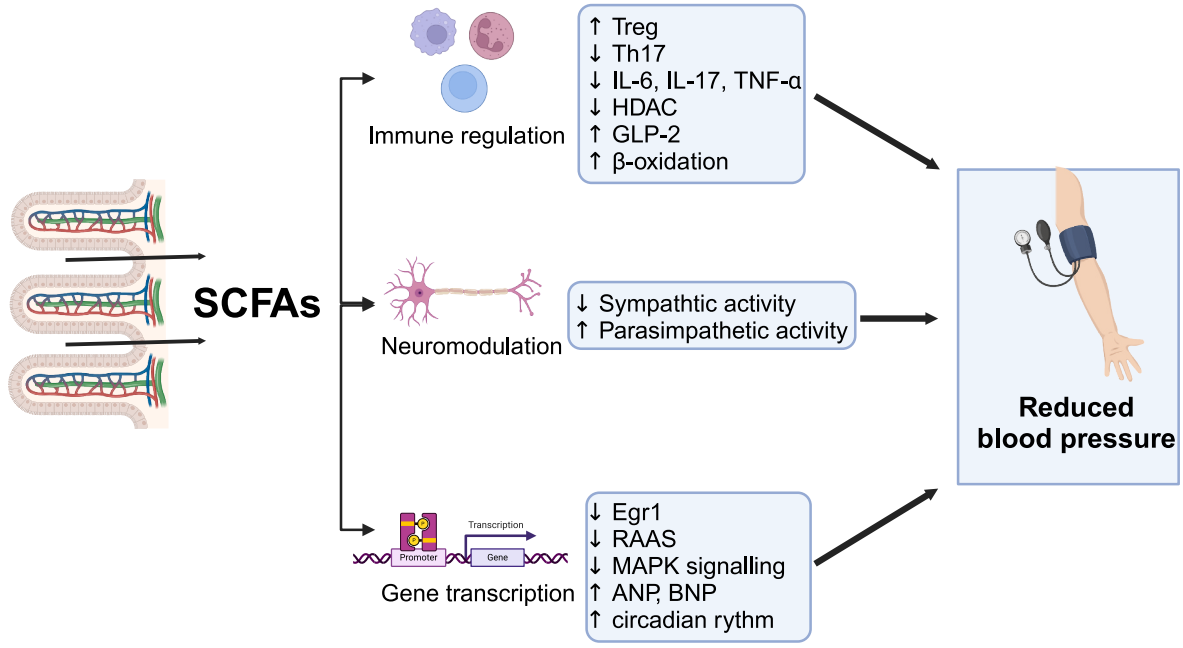


**Fig. 5.** Short chain fatty acids (SCFAs) can regulate the intestinal barrier and immune response, modulate activity of the autonomic nervous system, and transcription of genes, all effects that can contribute to blood pressure regulation. Treg, regulatory T cell; Th17, T helper cell; IL, interleukin; TNF, tumor necrosis factor; HDAC, histone deacetylase; GLP-2, glucagon-like peptide-2; Egr1, early growth response-1; RAAS, renin-angiotensin-aldosterone system; MAPK, mitogen-activated protein kinase; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

the integrity of the intestinal barrier (Rousseau, 2021). Moreover, ω-3 PUFAs alleviate the dysbiosis seen in patients with cardiovascular disease and hypertension by affecting the composition of the intestinal bacterial flora and preventing the induction of low-grade inflammation (Jayapala et al., 2023; Zhang et al., 2023). Animal studies suggest that ω-3 PUFAs slow the growth of *Enterobacteria* and facilitate proliferation of *Bifidobacteria* causing substantial changes in the microbiota composition (Onishi et al., 2017; Zhu et al., 2020). In a randomized trial on healthy volunteers, ω-3 PUFAs supplementation for 8 weeks induced an increase in many fatty acid-producing bacteria (Watson et al., 2018). These changes could lead to decreased generation of molecules that act as cardiovascular disease promoters such as trimethylamine (Tang et al., 2017) and increased production of antiinflammatory molecules such as butyrate (Noriega et al., 2016; Fu et al., 2021). Changes ω-3 PUFAs also contribute to maintain the integrity of the intestinal barrier, thus preventing the translocation of intestinal contents into circulation (Seethaler et al., 2023).

On the other hand, animal studies suggest that gut microbiota might be involved in biotransformation, absorption, and bioavailability of ω-3 PUFAs (Shama and Liu, 2020) and it was shown that gut microflora can produce PUFA-derived biologically active metabolites. Some bacterial species (e.g. *Clostridium proteoclasticum* and *Lactobacillus plantarum*) can convert the ω-3 PUFA precursor alpha-linolenic to conjugated alpha-linolenic acid and to saturated fatty acids, thus reducing the PUFA components (Jenkins et al., 2008). Moreover, the conjugated alpha-linolenic acid could have a role in lipid metabolism via activation of peroxisome proliferator-activated receptor-alpha (Kim et al., 2012). Finally, many additional microbiota components including lactic acid bacteria express the enzymes that catalyze transformation of ω-3 PUFA to saturated molecules (Kishino et al., 2013). Thus, there is early evidence of an interaction of dietary ω-3 PUFA with gut microbiota that will have to be further investigated to better understand what its impact on human health could be.

## 4. Conclusion

Findings of recent large-scale, randomized clinical trials have highlighted the possible benefits of high-dose EPA formulations in cardiovascular prevention. These effects have been attributed to targeting of the "residual" cardiovascular risk linked to triglyceride-rich lipoproteins, but also to a broad spectrum of additional pleiotropic actions. These actions include protection from vascular inflammation and thrombotic events, improvement of endothelial function, and BP reduction. The latter effect is obtained through reduction of peripheral vascular resistance, mediated by both endothelium-dependent and endothelium-independent mechanisms. Also, additional benefits of ω-3 PUFAs could be related to protection from hypertension-induced vascular complications that include decreased vascular stiffening, slowing of atherosclerosis, and increased arterial plaque stability. According to current evidence, we suggest that ω-3 PUFAs supplementation could provide specific benefits in hypertension and therefore might be recommended together with other measures of dietary and lifestyle correction in hypertensive patients with elevated serum triglyceride levels.

In the last decade, our views of the mechanisms related to essential hypertension have evolved, with a sort of paradigm shift in which new concepts have made inroads, suggesting that hypertension might be, at least in part, a disorder of the *holobiont* (host plus microbiota). This has prompted an expansion of Page's mosaic theory of hypertension in 2021 to include the gut microbiota as an emerging key modulator of BP (Harrison et al., 2021), thus paving the way to an innovative "holobiont-focused" approach, based on the use specific dietary formulations to modify gut microbiome and its metabolites to possibly prevent and even treat hypertension with its organ complications.

## CRediT authorship contribution statement

**Gabriele Brosolo:** Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andrea Da Porto:** Writing – review & editing, Validation, Supervision, Methodology, Data curation. **Stefano Marcante:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Filippo Capilupi:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Nicole Bertin:** Writing – review & editing,

Validation, Supervision, Investigation, Data curation. **Cinzia Vivarelli:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Luca Bulfone:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Antonio Vacca:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Cristiana Catena:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Leonardo A. Sechi:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

## Ethics approval and consent to participate

None.

## Funding

This research was funded by a generous contribution from the PierSilverio Nassimbeni Foundation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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