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Narrative Review

Integrating downstream mediators of Omega-3 fatty acids into enteral nutrition for improved patient care: An expert panel consensus☆

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SUMMARY

Acute inflammation is a crucial biological response necessary for host defense and tissue repair, but unresolved inflammation can contribute to adverse outcomes across critical illness, cardiovascular disease, neurodegeneration, and cancer. Emerging evidence emphasizes that the resolution of inflammation is an active biosynthetic process mediated in part by specialized pro-resolving mediators (SPMs), lipid-derived molecules generated from omega-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (C20:5n-3, EPA) and docosahexaenoic acid (C22:6n-3, DHA). These mediators—including resolvins, protectins, and maresins—exert potent immunomodulatory actions that restore tissue homeostasis and attenuate inflammation without immunosuppression. Despite the established role of SPMs, clinical and preclinical studies demonstrate that SPM biosynthesis is often impaired in disease states, limiting the efficacy of omega-3 PUFA-based nutritional interventions. To explore the potential of standardized SPM enrichment in enteral nutrition (EN), a multidisciplinary panel of experts conducted a Delphi-based consensus process. Consensus statements were developed supporting the rationale for enriching EN with preformed SPMs or their stable precursors to overcome compromised endogenous biosynthesis and enhance clinical benefits. Preliminary human studies suggest that such enrichment may reduce inflammation, improve immune function, and contribute to better outcomes in conditions such as obesity, atherosclerosis, infections, and chronic pain. The panel emphasized the need for rigorously designed clinical trials to determine whether enteral SPMs have measurable clinical effects and, if so, to define effective dosing strategies. Overall, SPM-enriched EN represents a potential advancement in the nutritional modulation of inflammation, warranting further investigation to guide evidence-based clinical application.

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1. Introduction

Acute inflammation is a fundamental biological response that is central to host defense, wound healing, tissue repair, and return to homeostasis following insult or injury. The resolution of inflammation, which is now known to be a biosynthetically active response, is key to preventing pathological consequences of the inflammatory response, as unresolved inflammation can have adverse health impacts and is associated with a number of chronic conditions ranging from persistent inflammation, immunosuppression, and catabolic syndrome (PICS) after critical illness, to metabolic disorders, cardiovascular diseases and cancer [1–3]. Indicators of inflammation are not only a marker of disease severity but also a key determinant of clinical outcomes in critically ill patients, including those receiving nutritional interventions [1]. Furthermore, previous reports demonstrated a significant association between elevated inflammatory markers at baseline and diminished clinical benefits from nutritional support in intensive care unit (ICU) patients [4]. Systemic inflammation may interfere with nutrient metabolism, impair cellular uptake of nutrients, and contribute to adverse metabolic responses, ultimately reducing the efficacy of nutritional interventions [5,6]. Thus, promoting inflammation resolution should be one of the therapeutic goals of nutritional interventions for critically ill patients.

Several anti-inflammatory nutrients have been investigated for their potential therapeutic effects, predominantly omega-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (C20:5n-3, EPA) and docosahexaenoic acid (C22:6n-3, DHA) [7]. Long-chain omega-3 PUFAs are abundant in marine sources (e.g., fish and fish oil) and microalgal oils, and have been shown to modulate inflammatory processes through various mechanisms that actively facilitate the resolution of inflammation [7]. Clinical studies have explored the effects of EN enriched with omega-3 PUFAs on patient outcomes. Some evidence suggests that omega-3 PUFA-enriched EN can positively influence inflammatory and immune markers, improve nutritional indicators, and reduce the risk of infections and sepsis [8]. However, the overall evidence remains equivocal, with other studies showing no significant clinical benefits of omega-3 PUFA-enriched EN in critically ill patients [9,10].

The resolution of inflammation is now recognized as an active biosynthetic process that involves a complex interplay of molecular and cellular mechanisms to restore tissue integrity and function [11]. A pivotal discovery in this field is the identification of specialized pro-resolving mediators (SPMs), a superfamily of endogenous bioactive lipid compounds derived from the PUFA precursors: arachidonic acid (C20:4n-6), EPA, n-3 docosapentaenoic acid (C22:5n-3, n-3 DPA) and DHA [12,13]. SPMs, which include lipoxins, resolvins, protectins, and maresins, actively orchestrate the resolution phase of inflammation by modulating immune responses, promoting macrophage phagocytosis and efferocytosis, and facilitating tissue repair across various organs and tissues [14]. The therapeutic potential of SPMs has gained significant interest, particularly concerning their role in mediating the beneficial effects of omega-3 PUFAs. However, studies indicate that in disease states, the conversion of EPA, n-3 DPA and DHA to SPMs may be compromised, leading to insufficient endogenous production of these mediators [15,16]. To counter this, several strategies have been proposed to actively promote SPM-mediated inflammation resolution, including developing SPM receptor agonists, synthesizing stable SPM analogs and mimetics, and administering standardized levels of SPMs [17]. In EN settings, there may be merit in incorporating standardized levels of SPMs directly into EN formulas to enhance their anti-inflammatory and inflammation-resolving efficacy. However, current research is predominantly at the preclinical stage.

To bridge the gap between experimental research and the potential applications of bioactive lipid mediators in EN settings, this narrative review and consensus aims to assess the current evidence on SPMs in critical illness, with a focus on the feasibility, potential, and challenges of enriching EN formulas with standardized levels of SPMs or their precursors.

2. Methods

2.1. Study design and panel recruitment

This expert consensus was developed using a structured, modified, three-step Delphi approach, combining systematic evidence review, iterative feedback from a multidisciplinary panel of experts, and voting on statements. Panel members were recruited through purposive sampling to ensure diverse and comprehensive input. The panel members were selected based on the member's contributions to EN, omega-3 fatty acid or lipid mediator research, and active involvement in clinical practice or translational research. Formal invitations outlining the study objectives and methodology were sent via email. A total of 10 experts agreed to participate in this multidisciplinary expert panel, including academic scientists and clinical nutrition experts from academic and non-academic institutions. All panel members signed a conflict-of-interest declaration before the first voting round to maintain objectivity.

2.2. Delphi process

The consensus development process consisted of three key phases (Fig. 1). First, a comprehensive literature review was conducted to summarize the current evidence and develop consensus statements on omega-3 PUFAs, SPMs, and their precursors in EN.

The online bibliographic search targeted studies indexed in major biomedical databases, including PubMed, Scopus, Embase, the Cochrane Library, and Web of Science. Search terms included combinations of "omega-3 fatty acids", "eicosapentaenoic acid", "docosahexaenoic acid", "specialized pro-resolving mediators", "lipid mediators", "nutritional therapy", "enteral nutrition", "enteral feeding", "clinical nutrition", "inflammatory diseases", "critical care", "chronic illness", and "malnutrition". Boolean operators (AND/OR) were employed to refine the search, and filters were applied to limit results to studies published in English within the past 20 years. Additional references were identified through manual searches of key article bibliographies. Based on the findings from the literature review, draft consensus statements were developed, covering key aspects of lipid mediators in disease states, with a particular focus on EN.

The draft consensus statements were shared with panel members as preparatory reading material before the panel meeting. The panel members were gathered during the Lipid Forum held on 12th December 2024 in Switzerland. The meeting was divided into two parts; the first part discussed the current evidence regarding the role of SPMs in inflammation resolution and their potential benefits across various disease states. During these discussions, the panel explored the potential benefits of standardizing SPM levels in EN and identified knowledge gaps in the field. The second part of the meeting discussed the draft consensus statements, which were refined during the meeting through an iterative discussion process.

The updated statements were circulated among the panel members after the meeting for anonymous voting to evaluate the level of agreement with each statement. Voting was conducted electronically using Microsoft Forms, with panelists asked to select "agree," "disagree," or "decline to vote" for each statement. An

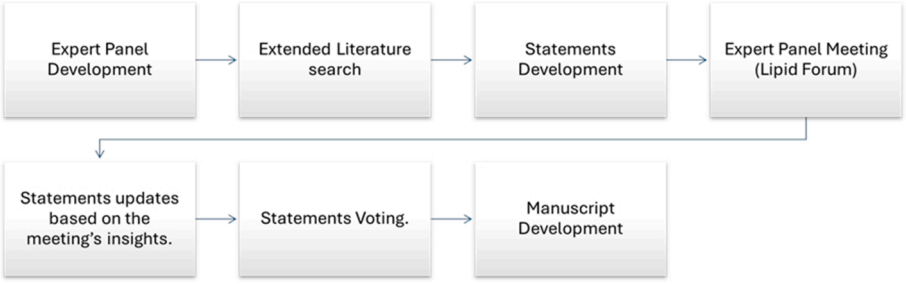

Fig. 1. The modified Delphi-based Process.

agreement level of ≥80 % was needed for each statement to achieve consensus. Statements not meeting this threshold were removed from the final set of statements. All authors approved the final version of the consensus statements (Table 1).

3. Inflammation resolution as a goal in patients receiving EN

3.1. The interplay between inflammation and nutrition

Inflammation, a core biological response to stress, injury, or infection, is typically classified as either acute or chronic, with each type involving distinct immune pathways and durations. Acute inflammation, which predominates in critically ill patients, is mediated by innate immunity and acute-phase proteins, such as C-reactive protein (CRP) [5]. During this phase, immune cells, including leukocytes, mast cells, and macrophages, generate a "respiratory burst" marked by increased oxygen uptake and reactive oxygen species (ROS) release. In parallel, inducible nitric oxide synthase (iNOS) is upregulated, producing nitric oxide (NO) and contributing to vasodilation. These immune cells also release a broad array of chemokines and cytokines, such as interleukin (IL)-8, tumor necrosis factor-alpha (TNF-α), and IL-1β, which orchestrate the recruitment and activation of additional immune cells. Lipid mediators like prostaglandins and leukotrienes are produced, further amplifying the inflammatory response. Collectively, these mediators induce changes in vascular permeability and blood flow, facilitating immune cell infiltration into the affected tissue [18]. While ROS are essential for host defense, excess production without sufficient antioxidant capacity can result in oxidative stress, damaging DNA, proteins, and cellular membranes and contributing to cell death [19,20].

The interplay between inflammation and nutrition is complex and bidirectional. Inflammation is a key driver of disease-related malnutrition since it can cause anorexia, reduce food intake, and initiate muscle catabolism, anabolic resistance, and insulin resistance, collectively stimulating a catabolic state [5]. Conversely, nutritional status and dietary patterns significantly influence inflammatory responses [4]. In the context of nutritional interventions, elevated systemic inflammation has been associated with diminished benefits from nutritional support in ICU and non-ICU patients [4]. Notably, patients with high CRP levels (>100 mg/L) derive limited survival benefits from standard nutrition interventions, and patients with low CRP also showed limited benefit, as shown in subgroup analyses from the EFFORT trial [4,21]. Inflammatory cytokines can suppress appetite, slow gastric motility, and induce insulin resistance, impairing nutrient intake, absorption, and metabolism. This results in a catabolic and anabolic-resistant environment characterized by lipolysis, muscle proteolysis, and hepatic gluconeogenesis, exacerbating malnutrition despite the provision of nutritional therapy [22,23]. Inflammation may also disrupt intracellular nutrient signaling and cellular repair mechanisms, such as autophagy, which plays a key role in clearing damaged organelles and regulating immune responses [24]. SPMs may engage distinct resolution pathways beyond inflammation suppression, though, for example, the transcriptional reprogramming of target cells [25].

Such findings highlight the complexity of malnutrition in the context of inflammation and suggest that nutritional interventions cannot be universally applied without considering the underlying inflammatory state. Consequently, a paradigm shift is warranted: the resolution of inflammation should be established as a central objective of nutritional interventions in order to improve clinical outcomes across a range of acute and chronic conditions.

3.2. Inflammation resolution as a biosynthetically active process

The initiation of an inflammatory response is accompanied not only by the rapid activation of immune mechanisms aimed at clearing pathogens or damaged tissue but also by the near-immediate activation of the resolution phase. Contrary to the traditional notion of resolution as a passive tapering of inflammation, it is now well established that inflammation resolution is a biosynthetically active, highly orchestrated process governed by endogenous mechanisms that restore immune homeostasis and support tissue repair [26,27]. Key features of this pro-resolving phase include the downregulation of pro-inflammatory signaling pathways—particularly those involving nuclear factor kappa B (NF-κB) and the NLRP3 inflammasome—and the induction of specialized mediators that counterbalance the inflammatory cascade (Fig. 2) [28].

Among these mediators, a prominent group is the SPMs, which are discussed in the following sections. Efferocytosis, the process by which dead or dying cells (especially apoptotic cells) are cleared by phagocytic cells like macrophages, also contributes to the phenotypic shift of these cells from a pro-inflammatory to a pro-resolving, tissue-reparative state [29,30]. Regulatory T cells (Tregs) have emerged as active participants in this process. Beyond their classical anti-inflammatory functions, Tregs facilitate the resolution of inflammation by promoting SPM biosynthesis and enhancing macrophage efferocytosis [31]. The failure of these resolution mechanisms has been implicated in the persistence of inflammation and progression of chronic disease states, including atherosclerosis, hypertension, and non-alcoholic steatohepatitis [28].

Overall, these findings position inflammation resolution as an active, targetable biological process with therapeutic implications (Table 1; *Statement 1*).

4. Omega-3 PUFA-derived SPMs: biological functions and recent evidence

The discovery of SPMs marked a paradigm shift in our understanding of how inflammation is resolved. Pioneering work from

Table 1
Consensus statements regarding the potential role of SPMs in inflammation resolution.

Consensus Statements	Voting
Statement 1: The resolution of inflammation is a biosynthetically active process.	100 %
Statement 2: The resolution of inflammation is partially driven by the endogenous production of SPMs, such as resolvins, protectins, and maresins, endogenously synthesized from EPA and DHA. These mediators play an important role in resolving inflammation, restoring homeostasis, modulating immune response, and facilitating tissue repair.	100 %
Statement 3: Preclinical evidence demonstrates that circulating levels of SPMs in the plasma are compromised in animal models of some disease states. Emerging human data aligns with these observations, showing that altered SPM levels are associated with worse clinical outcomes, supporting the need for clinical research.	100 %
Statement 4: Patients who rely solely on enteral nutrition therapy often lack a source of DHA and EPA. Enteral formulations enriched with fish oils may provide significant benefits.	90 %
Statement 5: Fish oil-enriched enteral formulas may be considered in select clinical conditions and scenarios as a primary source of EPA and DHA, which provide well-documented anti-inflammatory and immunomodulatory effects.	90 %
Statement 6: In certain clinical scenarios, the conversion of EPA and DHA substrates to SPMs may be compromised.	90 %
Statement 7: The unique relevance of the oxidized derivatives of DHA and EPA 17 S-hydroxydocosahexaenoic acid and 18 R-hydroxyeicosapentaenoic acid, which serve as direct precursors of SPMs, is that they increase the efficacy of SPM production, bypassing early biosynthetic steps in the conversion of EPA and DHA to SPM.	100 %
Statement 8: Currently, available fish oil supplements provide EPA, DHA and non-standardized levels of SPM precursors.	90 %
Statement 9: While several studies have shown a dose-dependent effect of fish oil supplementation on the resolution of inflammation, the dose relationship between fish oil consumption and the level of endogenous SPM production remains unclear.	100 %
Statement 10: Preclinical evidence has demonstrated that administration of SPMs and SPM precursors enriched supplements can increase SPM plasma levels in a time and dose-dependent manner.	100 %
Statement 11: Supplementation enriched with SPMs and their precursors may promote the resolution of inflammation in relevant clinical conditions and scenarios, such as obesity, cancer, critical illness, surgery, cardiovascular disease, chronic inflammatory diseases, and wound healing.	90 %
Statement 12: Multiple studies have demonstrated that fish oil does not significantly increase the risk, even in patients on anti-platelet or antithrombotic medications.	100 %
Statement 13: Studies indicate a potential for a statistically significant increase in AF in certain high-risk populations. The clinical significance of this risk, balanced with the multiple benefits, needs to be determined.	100 %
Statement 14: Although multiple mammalian models have reported significant benefits, limited clinical evidence supports the efficacy of SPM precursors, and the appropriate concentrations of SPM precursors in enteral formulas remain unknown, highlighting the need for further investigation.	90 %
Statement 15: Enteral formulas containing standardized levels of SPMs and SPM precursors should be developed and investigated in clinical trials in relevant short- and long-term treatment settings.	100 %
Statement 16: When investigating the influence of SPMs and designing studies, it is essential to recognize common pitfalls in nutrition research and focus on selecting appropriate patient populations, identifying relevant biological signatures, and optimizing trial design. This approach enhances clinically meaningful outcomes related to inflammation resolution, homeostasis restoration, immune modulation, and tissue repair.	100 %

SPM: Specialized Pro-resolving Mediator, EPA: Eicosapentaenoic Acid, DHA: Docosahexaenoic Acid, AF: Atrial Fibrillation.

the Serhan laboratory in the early 2000s led to the identification of novel lipid-derived molecules that emerged during the natural resolution phase of acute inflammation. These compounds were first isolated from self-limiting inflammatory exudates in animal models and demonstrated potent, stereoselective bioactivity in cellular systems involved in inflammation control. These mediators are derived from omega-3 PUFAs, notably EPA, DHA, and n-3 DPA [32]. In-depth reviews of the biosynthesis and biological functions of omega-3 PUFA-derived SPMs are available [33–35]; these aspects are considered beyond this manuscript's scope. This section briefly reviews the biological functions of EPA- and DHA-derived SPMs, as well as evidence supporting their roles in different disease states.

4.1. SPM biosynthesis and biological functions

Most SPMs are biosynthesized from omega-3 PUFAs through regulated enzymatic processes initiated during the resolution phase of inflammation. Initially isolated from self-limiting inflammatory exudates, omega-3 PUFA-derived SPMs comprise four distinct families: resolvins, protectins (or neuroprotectins in neural contexts), maresins, and the aspirin-triggered epimers of the resolvins and protectins. These mediators are endogenously generated and exhibit potent stereoselective actions [34]. SPMs exert highly cell-specific effects that orchestrate the resolution of inflammation through distinct immunomodulatory mechanisms (Table 2).

E-series resolvins (RvE), derived from EPA via lipoxygenation to form 18-hydroperoxy-eicosapentaenoic acid (18-HpEPE), include RvE1 to RvE4. RvE1, the first SPM identified, is generated through interactions between polymorphonuclear leukocytes and endothelial cells. RvE1 targets neutrophils by inhibiting their trans-epithelial and trans-endothelial migration and reducing superoxide production [33]. In macrophages, RvE1 enhances non-phlogistic phagocytosis of apoptotic neutrophils, while in dendritic cells, it suppresses IL-12 production and inhibits migratory activity [36]. Additionally, RvE1 upregulates CMKLR1 receptors in natural killer (NK) cells, suggesting a role in modulating innate immunity [37]. RvE2 and RvE3 exhibit similar pro-resolving actions, with RvE3 synthesized by eosinophils via the 12/15-lipoxygenase (LOX) pathway [38]. RvE4, identified under hypoxic conditions during leukocyte interactions, stimulates efferocytosis and has been detected in human cerebrospinal fluid (CSF) [39].

D-series resolvins (RvD), produced via 17-lipoxygenation of DHA to form 17 S-HpDHA, comprise RvD1 to RvD6. RvD1 attenuates neutrophil transmigration and suppresses lipopolysaccharide (LPS)-induced TNF release in macrophages while promoting phagocytosis of allergens and apoptotic cells [40]. Other series members, such as RvD3 through RvD6, contribute to inflammation resolution, tissue regeneration, and host defense against infections. For instance, RvD5 enhances bacterial clearance, while RvD6 plays a role in corneal repair and nerve regeneration [41].

Protectins, including protectin D1 (PD1), are biosynthesized from DHA and exhibit regulatory activities within the peripheral and central nervous systems. When generated in the brain, PD1 is referred to as neuroprotectin D1 (NPD1), reflecting its role in neuronal differentiation and protection. PD1 reduces neutrophil infiltration and glial cytokine production and promotes stem cell differentiation [33,42]. Its biosynthesis proceeds through an epoxide intermediate, 16 S,17 S-epoxy-PD (ePD), which also displays independent bioactivity by inhibiting leukotriene (LT) B4 synthesis [43].

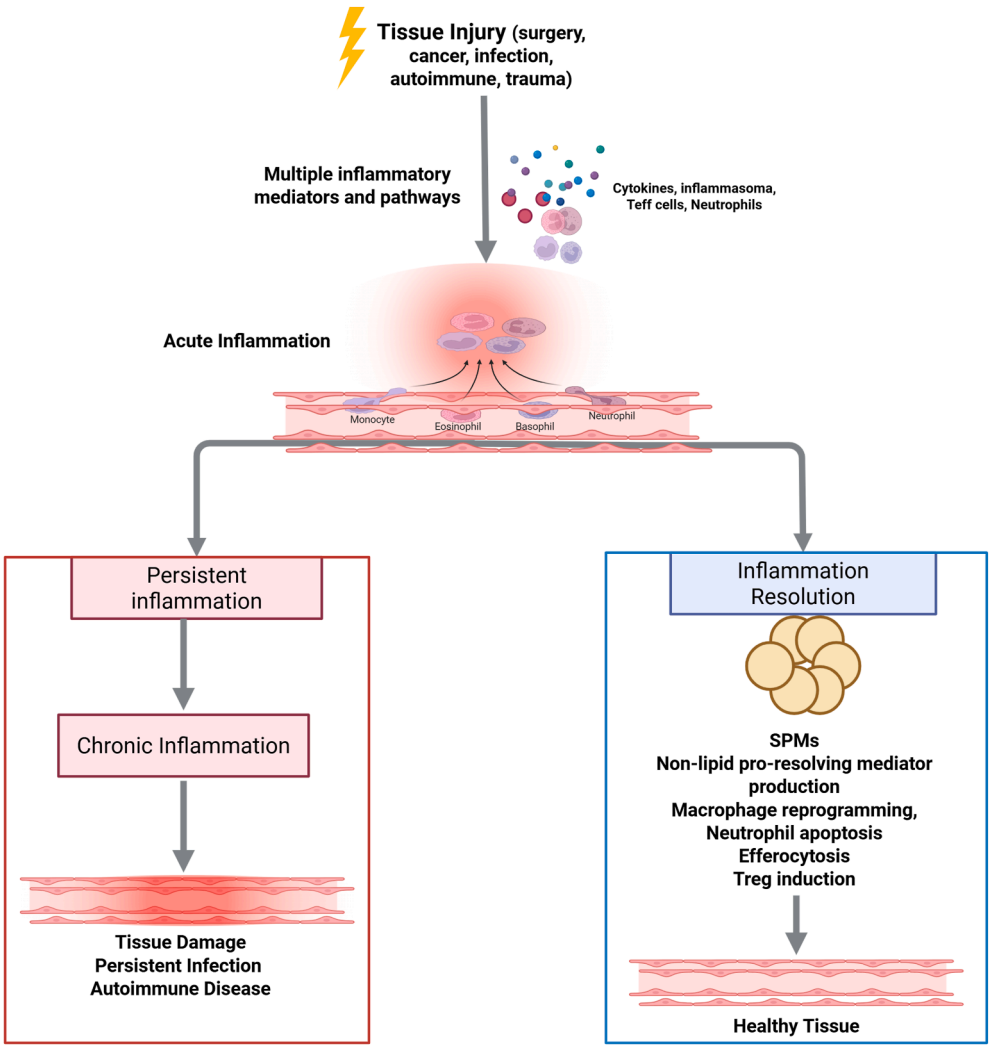

Fig. 2. Schematic representation of the acute inflammatory response and the role of specialized pro-resolving mediators in promoting inflammation resolution. SPM: Specialized Pro-resolving Mediator. Created in https://BioRender.com.

Maresins were initially identified as macrophage-derived mediators produced during the resolution phase of inflammation. Maresin 1 (MaR1) affects innate lymphoid cells (ILC2) by decreasing IL-13 and increasing amphiregulin production. MaR1 supports their expansion in regulatory T cells and promotes amphiregulin release, a cytokine linked to tissue repair [44]. Furthermore, MaR1 suppresses the release of pro-inflammatory cytokines induced by organic dust exposure in bronchial epithelial cells, suggesting a protective role in airway inflammation [33]. Maresin 2 (MaR2), produced via the interaction of 12-LOX and soluble epoxide hydrolase 2, shares similar bioactive functions and has been implicated in modulating hepatic inflammation in obesity [45]. Additionally, the maresin biosynthetic intermediate, eMaR, exhibits activity in promoting M2 macrophage polarization and inhibiting leukotriene synthesis [42].

SPMs act via high-affinity binding to specific G protein-coupled receptors (GPCRs) expressed on phagocytes and other immune or stromal cell types. These interactions occur at low nanomolar to picomolar concentrations, consistent with physiological receptor binding kinetics [14,46]. Key receptors include ChemR23 (RvE1), BLT1 (RvE1), ALX/FPR2 (RvD1), GPR32 (RvD1, RvD3), GPR18 (RvD2), GPR101 (RvD5$_{n\text{-}3\ DPA}$), GPR37 (PD1) and LGR6 (MaR1). Functional studies in transgenic animals, receptor knockout models, and receptor antagonism experiments have confirmed the central role of these GPCRs in mediating SPM bioactivity [14,46–49]. Their activation leads to downstream signaling cascades that culminate in reduced leukocyte recruitment, enhanced clearance of apoptotic cells, cytokine release modulation, and inflammation resolution [14].

4.2. Evidence of SPM-mediated inflammation resolution in disease states (Table 3)

Cardiovascular diseases (CVDs) are linked to chronic vascular inflammation and impaired resolution mechanisms. Hypertension is among the most well-established contributors to CVD pathology, a condition often driven by systemic inflammation and endothelial dysfunction [28]. Preclinical studies have primarily supported the antihypertensive potential of SPMs. In murine models of angiotensin II (Ang II)-induced hypertension, administration of RvD1 and RvD2 reduced systolic and diastolic blood pressure, improved vasomotor function, and attenuated cardiac hypertrophy and fibrosis. These benefits were associated with decreased pro-inflammatory cytokine expression and increased vasoprotective factors such as nitric oxide and prostacyclin [50,51]. Other studies have shown that SPMs like RvE1 and MaR1 exert vascular protective effects through modulation of vascular smooth muscle cell (VSMC) phenotype, suppression of immune cell

Table 2
Cell-specific actions of SPMs. Adapted with modifications from Basil and Levy [33] and Serhan and Chiang [14].

Mediator	Target Cell	Action(s)	Receptor(s)
Resolvin E1	Neutrophil	↓ trans-epithelial and trans-endothelial migration ↓ superoxide generation	ChemR23 (↑ RvE1 action limiting PMN) BLT1 (↓ RvE1 regulation of PMN and epithelial wound healing)
	Macrophage	↑ non-phlogistic phagocytosis of apoptotic neutrophils	ChemR23 (↓ phagocytosis, ↑ proatherogenic signaling, ↑ plaque size)
	Dendritic cell	↓ IL-12 production ↓ migration	–
	NK cell	↑ CMKLR1 receptors	ChemR23
Resolvin E3	Neutrophil	↓ infiltration	–
Resolvin D1	Neutrophil	↓ transmigration	ALX (↑ RvD1 action on PMN, cytokines) GPR32 (↓ RvD1 actions in macrophages)
	Macrophage	↓ LPS-induced TNF release ↑ phagocytosis of allergen and apoptotic cells ↓ pro-revascularization transcriptional program	ALX, GPR32
Protectin D1	Neutrophil	↓ TNF and IFNγ release ↓ PMN transmigration ↑ CCR5 expression	GPR37 (↓ PD1 protective actions)
	Macrophage	↑ non-phlogistic phagocytosis of apoptotic PMNs ↓ phagocytic activity↓ PD1 protective actions in LPS/Listeria sepsis	GPR37
Maresin 1	ILC2	↓ IL-13 production ↑ amphiregulin production	LGR6 (↓ MaR1 functions: ↑ cAMP, phagocytosis, efferocytosis)
	Regulatory T cell	↑ regulatory T cell formation ↑ amphiregulin production	LGR6
	Bronchial epithelial cell	↓ organic dust-induced cytokine production	LGR6 (↓ MaR1-inhibited smooth muscle proliferation, ↓ osteoblast activity)

AAA: Abdominal Aortic Aneurysm, ALX: Lipoxin A4 Receptor, BLT1: Leukotriene B4 Receptor 1, cAMP: Cyclic Adenosine Monophosphate, CCR5: C–C Chemokine Receptor Type 5, CLP: Cecal Ligation and Puncture, CMKLR1: Chemokine-Like Receptor 1, CREB: cAMP Response Element-Binding Protein, IFNγ: Interferon Gamma, IL-12: Interleukin-12, IL-13: Interleukin-13, ILC2: Type 2 Innate Lymphoid Cell, LGR6: Leucine-rich Repeat-containing G-protein Coupled Receptor 6, LPS: Lipopolysaccharide, MCAO/R: Middle Cerebral Artery Occlusion/Reperfusion, NK cell: Natural Killer Cell, PMN: Polymorphonuclear Neutrophil, RvD1: Resolvin D1, RvD2: Resolvin D2, RvE1: Resolvin E1, SMC: Smooth Muscle Cell, TNF: Tumor Necrosis Factor, ↑: Increased/Upregulated, ↓: Decreased/Downregulated.

infiltration, and activation of pro-resolving signaling cascades such as AMPKα/Nrf2 and CaMKII/HO-1 [52,53]..

Experimental models have also demonstrated that RvE1 can attenuate aortic wall thickening and reduce vascular inflammation by acting on its receptor ChemR23, while MaR1 promotes arterial remodeling reversal via LGR6-mediated signaling pathways [28]. Notably, serum levels of several DHA- and EPA-derived mediators, including RvE1, are significantly lower in individuals with essential hypertension, suggesting a pathophysiological role for deficient resolution signaling [52].

Beyond their role in hypertension, SPMs have demonstrated atheroprotective effects. Studies have reported a disrupted balance between pro-resolving and pro-inflammatory lipid mediators, such as a decreased RvD1 to LTB4 ratio, in advanced human atherosclerotic lesions [26]. Supplementation with RvD1 in animal models has been shown to restore this ratio, reduce plaque necrosis, and promote fibrous cap integrity, thereby enhancing plaque stability [26].

In aortic valve disease, specifically aortic stenosis, decreased tissue levels of DHA and EPA-derived SPMs have been associated with increased valve calcification and fibrosis. Experimental data have shown that RvE1 mitigates valvular inflammation and calcification, with its receptor ChemR23 representing a novel therapeutic axis in slowing disease progression [17,54]. These findings are further supported by genetic studies linking fatty-acid desaturase (FADS) polymorphisms with altered omega-3 PUFA levels, arterial stiffness, and risk of aortic stenosis [54].

Beyond their established role in resolving sterile inflammation, SPMs have demonstrated host-protective properties across various infections, including bacterial, viral, and parasitic pathogens [11]. These mediators not only dampen excessive inflammation but also enhance microbial clearance and promote tissue integrity, positioning them as potential therapeutic agents in infectious disease contexts [34]. Preclinical studies have shown that RvE1 can modulate viral inflammation, exemplified by its ability to control herpes simplex virus (HSV)-induced ocular inflammation in murine models [55]. Similarly, PD1 and protectin DX (PDX) have been found to directly inhibit influenza virus replication, highlighting their dual anti-inflammatory and antiviral capacities [56]. SPMs also show efficacy in complex infection scenarios. In a murine model of bacterial-viral co-infection pneumonia, the aspirin-triggered epimer of RvD1 (AT-RvD1) was shown to facilitate pulmonary clearance of *Streptococcus pneumoniae*, suggesting that SPMs may aid in resolving secondary bacterial infections that often complicate viral respiratory illnesses [57].

Uncontrolled or unresolved neuroinflammation—a hallmark of several neurodegenerative diseases, including multiple sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD)—can result in persistent immune activation, neuronal damage and progressive cognitive and motor decline [58]. As in peripheral tissues, endogenous mechanisms govern the resolution of neuroinflammation, notably the action of SPMs, which counterbalance pro-inflammatory signaling and support tissue recovery [59]. In MS, chronic neuroinflammation contributes significantly to disease pathology across various stages. Metabololipidomic profiling of blood samples from MS patients has revealed altered lipid mediator signatures characterized by reduced levels of SPMs—such as LXA4, LXB4, RvD1, and PD1—and increased pro-inflammatory eicosanoids. These imbalances correlate with disease severity and progression [59]. Experimental studies in human blood–brain barrier models demonstrated that restoring SPM levels could suppress monocyte activation and inhibit their migration across the endothelium, potentially attenuating central inflammation [60]. In AD, animal and human studies consistently demonstrated dysregulated SPM signaling. Post-mortem brain analyses and CSF lipidomic profiling have revealed significantly lower levels of several resolvins (RvD1, RvD4, RvE4), PD1, and MaR1 in patients with cognitive impairment or AD compared to controls [61–63].

Animal models of neurodegeneration indicated a possible beneficial role for SPMs. For instance, in the LPS-induced rat model

Table 3
Evidence of SPMs-mediated inflammation resolution in disease states.

Disease Area	SPMs Involved	Mechanisms/Benefits	Preclinical/Clinical Evidence	References
Hypertension	RvD1, RvD2, RvE1, MaR1	Lower blood pressure, improved vasomotor function, reduced cardiac hypertrophy, decreased cytokine expression, increased NO and prostacyclin.	Preclinical (murine models of Ang II-induced hypertension)	[50–53]
Atherosclerosis	RvD1	Restored RvD1/LTB4 ratio, reduced plaque necrosis, and improved fibrous cap integrity.	Animal models and human lesion studies	[26]
Aortic valve disease	RvE1	Reduced valve calcification and inflammation, reversed arterial remodeling, associated with FADS polymorphisms.	Tissue and genetic studies	[17,28,54]
Infectious diseases	RvE1, PD1, PDX, AT-RvD1	Enhanced microbial clearance, reduced inflammation, inhibited viral replication, effective in bacterial-viral co-infections.	Murine models (HSV, influenza, pneumonia)	[55–57]
Neurodegenerative diseases	LXA4, LXB4, RvD1, PD1, MaR1	Suppressed monocyte activation, reduced migration across BBB, restored lipid mediator balance, correlated with disease severity.	Human samples and experimental BBB models	[58,59,61–63]
Pain modulation	RvD1, RvD2, MaR1	Reduced inflammatory and neuropathic pain, preserved normal nociception, and restored balance in pain pathways.	Animal models (incisional, fracture, thoracotomy pain)	[67]
Cancer	RvD1, RvD2, MaR1	Reduced pro-inflammatory signaling, modulated macrophage polarization (M2 to M1), decreased VEGF production, and limited angiogenesis.	Preclinical studies on tumor progression and TAMs	[69,70]
Obesity and metabolic syndrome	RvD1, RvD2	Improved insulin sensitivity, reduced inflammatory cytokines, improved autophagy, and ER stress response.	Preclinical and clinical studies in obese subjects and mice	[14,77]

of PD, intrathecal administration of RvD2 significantly ameliorated neuronal damage by suppressing pro-inflammatory mediator expression and TLR4/NF-κB signaling pathway. RvD2 treatment attenuated behavioral impairments as well [64]. In early PD pathology models, sustained intraperitoneal administration of RvD1 mitigated central and peripheral inflammation, prevented neuronal dysfunction, and improved motor performance [65]. In addition to AD, RvD1 has been demonstrated to suppress macrophage-derived IL-6 and TNF-α in amyotrophic lateral sclerosis (ALS) [66].

The role of SPMs in pain modulation has gained increasing interest due to their unique ability to alleviate inflammatory and neuropathic pain without disrupting normal nociceptive function. Preclinical studies using various animal models have consistently demonstrated that SPMs such as RvD1, RvD2, and MaR1 effectively reduce pain associated with tissue injury and inflammation [67]. In models of incisional and bone fracture pain, administration of RvD1 and RvD2 led to significant reductions in pain sensitivity. Similarly, these mediators showed efficacy in reducing pain associated with thoracotomy and amputation—models commonly used to replicate clinical neuropathic pain conditions [67]. Significantly, SPMs do not inhibit normal pain perception—a crucial distinction from traditional analgesics. Instead, they restore homeostatic balance within pain pathways, resolving excessive inflammatory signaling without impairing physiological nociception [68].

Emerging evidence suggests that SPMs may play a crucial role in cancer biology through their immunomodulatory and anti-inflammatory properties. Tumor progression is intricately linked to chronic inflammation, angiogenesis, and immune evasion, which SPMs can influence at multiple levels [69]. In preclinical studies, SPMs have demonstrated the ability to control neoplastic progression by suppressing pro-inflammatory signaling pathways, modulating cell proliferation, and limiting aberrant angiogenesis [69,70]. SPMs can influence macrophage polarization, shifting them from the pro-tumorigenic M2-like phenotype to the pro-resolving M1-like phenotype [71]. This phenotypic shift reduces vascular endothelial growth factor (VEGF) production and promotes clearance of tumor-associated inflammation [72]. Additionally, SPMs have shown the ability to modulate tumor-associated macrophages (TAMs), which are often implicated in immune suppression, angiogenesis, and tumor growth [70].

Chronic low-grade inflammation is a hallmark of obesity and a major contributor to its associated metabolic complications, including insulin resistance, hepatic steatosis, and cardiovascular disease [73]. SPMs have emerged as important regulators of this inflammatory state. In both clinical and preclinical settings, obese individuals have been found to exhibit reduced levels of SPMs in serum and neutrophils and in adipose tissue [74,75]. In mice, this trend appears to be exacerbated by high-fat diets and reversed with weight loss [76]. Animal models have further demonstrated the therapeutic promise of SPMs, particularly RvD1 and RvD2, in mitigating obesity-related metabolic dysfunction. These mediators have been shown to attenuate systemic inflammation and enhance insulin sensitivity through multiple mechanisms. These include modulation of adipokines and cytokines (e.g., increased adiponectin and decreased TNF-α, IL-6, and IL-1β), improvement in insulin signaling pathways (e.g., upregulation of IRS-1/PI3K/Akt and GLUT-4), and enhancement of cellular stress responses such as autophagy and endoplasmic reticulum (ER) stress resilience [14,77].

Overall, inflammation resolution appears to be partially driven by the endogenous production of SPMs, such as resolvins, protectins, and maresins, endogenously synthesized from EPA and DHA. These mediators play an important role in resolving inflammation, restoring homeostasis, modulating immune response, and facilitating tissue repair (Table 1; *Statement 2*). However, it should be noted that SPMs and their immediate precursors (e.g., 17-HDHA, 18-HEPE) are biochemically labile and susceptible to oxidative degradation, with concentrations influenced by storage conditions (temperature, light, oxygen), handling, and formulation excipients [78–80]. These factors potentially contribute to variability across preclinical studies, highlighting the need for stabilization strategies and harmonized pre-analytical procedures (timed sampling, rapid quenching, internal standards) alongside validated methods with appropriate reference materials. Until such controls are standardized, interpretation of measured SPM levels and cross-study comparability should be made with caution.

Additionally, since this evidence was derived from studies utilising non-enteral routes (e.g., intravenous, intraperitoneal, intrathecal), caution is needed when extrapolating these findings to enteral administration.

5. Can EN formulas enriched with Omega-3 PUFAs provide standardized levels of SPMs?

5.1. SPM levels are reduced in disease states

As detailed in the previous section, SPMs are pivotal in orchestrating the resolution phase of inflammation and restoring tissue homeostasis. However, emerging evidence indicates diminished levels of SPMs in various inflammatory states. For instance, aged mice with heightened inflammation showed reduced RvD1 levels and SPMs:LT ratio, while RvD1 treatment reduced inflammatory markers [81]. Similarly, in rheumatoid arthritis (RA), synovial fluid analyses revealed altered lipid mediator profiles, including decreased levels of SPMs such as lipoxins, resolvins, and protectins [82].

Neurological disorders also demonstrate associations with compromised SPM pathways. An alteration in lipid mediator profiles from anti-inflammatory (pro-resolving) to pro-inflammatory patterns has been documented in the CSF during AD progression. A recent study demonstrated lower CSF RvD4, RvD1, NPD1, MaR1, and RvE4 concentrations in patients with AD and mild cognitive impairment (MCI). Conversely, levels of pro-inflammatory mediators were elevated in those with AD or MCI [39]. Complementary findings were observed in post-mortem studies of the entorhinal cortex, where patients with AD demonstrated decreased levels of MaR1, NPD1, and RvD5 compared to age-matched healthy controls, alongside elevated levels of the pro-inflammatory prostaglandin (PG) D2 [83]. Mouse models of AD also exhibited significantly reduced brain cortical levels of SPMs compared to controls [84]. Patients with MS exhibit altered SPM profiles in peripheral blood, which are linked to monocyte and blood–brain barrier dysfunction [59]. Likewise, in mice with early AD pathology, there were reduced levels of RvD1 and increased interferon-gamma (IFN-γ), which were correlated with dopaminergic neuronal abnormalities and motor deficits [65].

The reduced levels of SPMs in inflammatory disease states were also noted in the context of infectious diseases. A study on tuberculous meningitis demonstrated that CSF profiles with reduced SPMs were associated with disease severity and worse patient outcomes [85]. Similarly, in severe SARS-CoV-2 infections, a notable shift in the serum lipidome has been observed, leading to dysregulation of eicosanoid mediators. This dysregulation is characterized by altered levels of pro-inflammatory and pro-resolving lipid mediators, suggesting an imbalance that may contribute to the hyperinflammatory state seen in severe COVID-19 cases [86]. Additional studies support this shift in peripheral blood lipid mediator levels, indicating that altered SPM production is also linked with disease trajectory, as seen with dexamethasone treatment in COVID-19 patients [87].

Collectively, preclinical and human data demonstrate that circulating levels of SPMs in plasma are compromised in disease states with heightened inflammation and are associated with worse clinical outcomes, supporting the need for clinical research (Table 1; *Statement 3*). Clinical studies showed a positive impact of EN enriched with omega-3 PUFAs on inflammatory and immune markers, which can be attributed to SPMs [8,88]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guideline for nutrition in adult ICU patients suggested that enriching EN with omega-3 PUFAs can be considered [89]. Similar recommendations were published for patients with traumatic brain injury and perioperative patients [90]. Despite this guidance, patients who rely solely on EN therapy often lack a source of DHA and EPA. Enteral formulations enriched with fish oils may provide significant benefits and be considered in select clinical conditions and scenarios as a primary source of EPA and DHA (Table 1; *Statements 4 and 5*). Omega-3 PUFA fortification of EN can also be achieved using microalgal oils [91]. Because most microalgal products are DHA-rich, they may preferentially support biosynthesis of D-series resolvins, protectins, and maresins [92]. While this biochemical rationale is compelling, direct comparative data on microalgal versus fish-oil sources for SPM pathway activation and clinical outcomes in EN populations are lacking.

It remains also uncertain whether fish or microalgal oil-enriched EN formulas deliver standardized SPM levels sufficient to counteract the reduced endogenous production observed in certain disease states. For instance, metabolic conditions, such as obesity and non-alcoholic fatty liver disease, were found to be associated with impaired activity of delta-5 and delta-6 desaturases. This may reduce endogenous conversion of α-linolenic acid (C18:3n-3, ALA) to EPA/DHA and contribute to low circulating omega-3 PUFA levels in critically ill patients [93,94].

In the next sections, we discuss recent evidence suggesting the compromised conversion of EPA and DHA to SPMs in disease states and the potential benefits of enriching EN with preformed SPM precursors.

5.2. Compromised conversion of EPA and DHA substrates to SPMs in disease states

Clinical investigations have demonstrated that supplementation with omega-3 PUFAs, EPA and DHA, or marine oils that provide these fatty acids can increase in vivo levels of SPMs. A randomized controlled trial (RCT) in healthy volunteers demonstrated that supplementation with marine oil enriched in SPM precursors significantly increased peripheral blood SPM concentrations. This elevation was accompanied by the reprogramming of peripheral blood cells towards a more pro-resolving phenotype [95]. A study found that short-term, high-dose fish oil supplementation increased plasma concentrations of SPMs, including lipoxin A5 (LXA5) and RvE3, in patients with peripheral artery disease. This was associated with improved endothelial function and reduced markers of inflammation [96,97]. Among statin-treated coronary artery disease (CAD) patients, daily supplementation with EPA and DHA significantly increased circulating concentrations of the SPMs RvE1 and MaR1, as well as their precursor 18-hydroxy-EPA (18-HEPE), which correlated with regression of coronary plaque [98]. Similarly, in patients with chronic kidney disease (CKD), supplementation with omega-3 PUFAs significantly enhanced neutrophil production of multiple SPMs, including RvE1, RvE2, RvE3, and RvD5 [99].

However, recent evidence suggests that in certain conditions, the enzymatic conversion of omega-3 PUFAs to SPMs may be compromised (Table 1; *Statement 6*). In obesity, individuals with persistent low-grade systemic inflammation exhibit impaired leukocyte-derived SPM synthesis. This impairment was characterized by reduced production of DHA-derived monohydroxy fatty acid 17 S-hydroxy-DHA (17-HDHA), alongside decreased formation of D-series resolvins, despite normal DHA cellular uptake. The authors attributed these observations to the impairment in the 15-LOX activity and 5-LOX expression. Notably, incubation of leukocytes from obese subjects with the intermediate precursor 17-HDHA restored the production of D-series resolvins [15], suggesting that supplementation enriched with oxidized derivatives of 17-HDHA and 18 R-HEPE, which serve as direct precursors of

SPMs, may bypass early biosynthetic steps in the conversion of EPA and DHA to SPMs (Table 1; *Statement 7*).

Similar compromised SPM biosynthesis was demonstrated in patients with metabolic syndrome (MetS), whose plasma concentrations of SPM precursors—including 18-HEPE, 17-HDHA, and 14-HDHA—were significantly attenuated following omega-3 PUFAs supplementation compared to healthy matched controls. Despite this impairment in precursor formation, E-series resolvin production increased similarly in both MetS and control groups, whereas the addition of aspirin had no further effect [100]. Similarly, patients with osteoarthritis (OA) displayed lower activity of key enzymes (5-LOX and 15-LOX). While synovial fluid from patients with OA contained detectable levels of SPM precursors, such as 17-HDHA and 18-HEPE, active pro-resolving mediators like RvD2 were only identified in the insoluble cellular fraction, suggesting incomplete or inefficient SPM production in OA-affected joints [101]. Patients with chronic heart failure (CHF) also demonstrated significantly decreased plasma levels of RvD1, attributed to reduced biosynthetic enzyme (15-LOX) activity in leukocytes [102].

Given the current evidence [15,100–102], the available fish oil supplements appear to provide non-standardized SPM precursors (Table 1; *Statement 8*). While several studies have shown a dose-dependent effect of fish oil supplementation on the resolution of inflammation [86–88], the dose relationship between fish oil consumption and the level of endogenous SPM production remains unclear (Table 1; *Statement 9*).

6. Potential benefits of enriching EN formulas with either SPMs or preformed SPM precursors

As demonstrated earlier, preclinical evidence and emerging human data suggest a compromised conversion of PUFAs to endogenous SPMs in various disease states, which provides a mechanistic rationale for providing preformed SPM precursors. Preclinical evidence suggests that preformed SPM precursors, such as 17-HDHA and 18-HEPE, can increase plasma SPM levels in a time and dose-dependent manner (Table 1; *Statement 10*). Isolated human vascular tissues and primary vascular cell cultures efficiently convert 17-HDHA into biologically active resolvins and protectins. This process was accompanied by the translocation of the 5-LOX enzyme from the nucleus to the cytoplasm, facilitating local SPM production. Notably, vascular cells exposed to 17-HDHA demonstrated attenuation of inflammatory responses, as evident by decreased monocyte adhesion to activated endothelial cells [103]. Similarly, preformed SPM precursors have been shown to ameliorate pulmonary inflammation triggered by ozone exposure. The administration of exogenous 14-HDHA, 17-HDHA, and PDX prior to ozone exposure restored pulmonary SPM levels, decreased pro-inflammatory cytokine and chemokine expression, and reduced inflammatory cell infiltration [104]. In inflammatory bowel disease (IBD) and retinal degeneration models, 17-HDHA, along with other SPM precursors, significantly promotes the resolution of inflammation via enhanced macrophage phagocytic activity, shifted macrophage polarization towards the inflammation resolution type M2 phenotype and reduced pro-inflammatory gene expression [105,106]. However, it is worth noting that these findings are mechanistic and preclinical; translation to clinical efficacy remains to be established.

Emerging clinical evidence also supports the benefits of SPM precursor supplementation to enhance endogenous SPM levels, primarily in healthy volunteers or selected outpatient populations, rather than in critically ill patients. A previous double-blinded, placebo-controlled crossover study demonstrated that healthy volunteers receiving SPM precursor-enriched marine oil supplements exhibited dose-dependent increases in circulating SPM levels. This elevation in plasma SPM concentrations corresponded with enhanced neutrophil and monocyte phagocytic function and decreased activation of peripheral leukocytes and platelets. Additionally, transcriptomic analyses revealed significant shifts toward immune and metabolic gene expression patterns consistent with reduced inflammatory potential [95]. While supportive of biological activity, these are surrogate and functional surrogate markers rather than patient-centred outcomes.

Furthermore, in a single-arm, open-label pilot study involving healthy adults with mild-to-moderate inflammatory pain, a combination supplement enriched with SPM precursors significantly improved pain scores, pain severity, and physical function within 30 days of use. Notably, improvements in QoL indices persisted throughout the 60-day intervention period [107]. Another clinical trial evaluating supplementation with a marine lipid enriched with 17-HDHA and 18-HEPE demonstrated significant improvements in health-related QoL, pain intensity, pain interference, and mood in patients with chronic pain [108]. However, these trials were short-term, had limited sample sizes, and were not designed to distinguish specific SPM-mediated effects from broader PUFAs actions; therefore, effect estimates should be regarded as preliminary.

Clinical evidence from patients with symptomatic peripheral artery disease (PAD) revealed that short-term administration of SPM precursor-enriched marine oil supplements significantly elevated circulating SPM levels. This biochemical shift was accompanied by enhanced phagocytic activity in neutrophils and monocytes, reduced expression of leukocyte pro-inflammatory markers, and a marked shift in monocyte-derived macrophage gene expression towards reparative, pro-resolution phenotypes [109]. Recent clinical data from adults with obesity further support these observations. Supplementation with a marine oil product enriched with 18-HEPE, 14-HDHA, and 17-HDHA significantly increased plasma concentrations of RvE1 and MaR1. Although the supplement did not alter the concentrations of D-series resolvins nor affect immune cell abundance, a notable reduction in ex vivo B-cell IgG production was observed, suggesting immunomodulatory potential without yet demonstrating clinical outcome benefits [110].

Based on the currently available preclinical and clinical evidence, supplements enriched with SPMs and their precursors may promote the resolution of inflammation in relevant clinical conditions and scenarios, such as obesity, cancer, critical illness, surgery, cardiovascular disease, chronic inflammatory diseases, and wound healing (Table 1; *Statement 11*). However, direct evidence that enteral administration of preformed produces reproducible increases in bioactive SPMs at target sites, and that these increases translate into improved clinical outcomes, remains limited. Variability in absorption, enzymatic conversion, illness-related metabolism, and tissue distribution may all constrain bioavailability in these settings. Accordingly, current recommendations are hypothesis-generating and should be tested in adequately powered RCTs using harmonised SPM analytics and patient-centred endpoints.

Additionally, emerging data indicate that genetic variabilities may modulate SPM pathway biology and therapeutic responsiveness. In a model that captures human-like diversity, diversity outbred mice displayed heterogeneous metabolic and glycaemic responses to RvE1, suggesting that background genetics influences SPM efficacy windows [77]. This aligns with the concept that variants across the LOX axis (ALOX5/ALOX12/ALOX15) and PUFA desaturases (FADS1/2) can alter precursor availability and endogenous SPM biosynthesis [111], while polymorphisms in SPM receptors, notably ERV1/ChemR23 (CMKLR1), FPR2/ALX [112], and

LGR6 [113] may affect ligand signalling and downstream resolution programs. Taken together, these observations support the need for genotype-aware trial designs (pre-specified subgrouping or stratified randomisation by key loci/ancestry), baseline SPM-metabolome phenotyping, and PK/PD frameworks to parse inter-individual variability in clinical endpoints when testing omega-3–derived SPM strategies in humans.

Research indicates that standard clinical doses of fish oil, rich in omega-3 PUFAs, do not significantly elevate bleeding risk, even among patients concurrently using anti-platelet or anticoagulant therapies (Table 1; *Statement 12*). A comprehensive analysis found that high-dose EPA supplementation resulted in only a modest absolute increase in overall bleeding risk (0.6 %) without a corresponding rise in serious bleeding events such as intracranial hemorrhage or hemorrhagic stroke. Furthermore, this study observed no correlation between bleeding events and the concurrent use of anti-platelet treatments in patients receiving omega-3 PUFAs [114]. A large meta-analysis of 11 RCTs, which included 120,643 patients, reported no increase in bleeding risk. They also reported that fish oils taken simultaneously with anti-platelet medications showed no increase in bleeding. These data provide robust evidence supporting the safety of fish oil in surgical settings [115].

Recent studies have identified an association between omega-3 fatty acid supplementation and increased atrial fibrillation (AF) incidence in certain populations. A 2021 meta-analysis encompassing six RCTs revealed that omega-3 fatty acids were linked to a higher risk of incident AF than placebo, particularly among individuals at high risk of or with established CVD and elevated plasma triglyceride levels [116]. Similarly, a study suggested that regular use of fish oil supplements might be a risk factor for AF and stroke in the general population, although it could be beneficial for the progression of CVD from AF to major adverse cardiovascular events and from AF to death [117]. Conversely, observational studies and analyses of omega-3 fatty acid biomarkers have generally reported an inverse relationship between dietary intake of omega-3 fatty acids and AF risk. For example, the Million Veteran Program study found that higher dietary intake of EPA, DHA, and DPA was associated with a lower risk of incident AF in a nonlinear manner [118]. Similarly, a global consortium study reported that higher in vivo DPA, DHA, and EPA + DHA levels were associated with a reduced risk of incident AF [119].

The clinical implications of these findings remain controversial and under investigation. While fish oil supplements offer various cardiovascular benefits, including triglyceride reduction and anti-inflammatory effects, the potential increased risk of AF necessitates a careful evaluation of the risk-benefit ratio for individual patients (Table 1; *Statement 13*).

7. Future directions in research and practice

Although preclinical studies in mammalian models have consistently demonstrated benefits from supplementation with SPM precursors, clinical evidence to support their efficacy remains limited. While systemic administration of precursors has been shown to elevate SPM levels in healthy individuals, whether enteral delivery can replicate these effects in critically ill or chronically ill patients remains unclear. This must be established before optimal dosing strategies can be developed for different disease states. Future research should prioritize developing and evaluating EN formulations that deliver standardized levels of SPMs and their precursors. Such standardized formulations should be rigorously tested in clinical trials conducted across relevant patient populations, encompassing both acute and chronic inflammatory conditions. Robustly designed studies will facilitate clear conclusions regarding the therapeutic potential and clinical utility of these enriched formulas.

Moreover, when designing these clinical studies, investigators should account for common pitfalls associated with nutritional research. Key considerations include carefully selecting appropriate patient cohorts, identifying relevant biological markers and clinical endpoints, and optimizing trial design parameters. Focusing on these aspects will enhance the likelihood of generating clinically meaningful outcomes, particularly those related to inflammation resolution, restoration of tissue homeostasis, immune modulation, and tissue repair processes. Such a structured and targeted approach will ensure that future trials provide definitive insights, ultimately guiding clinical practice toward evidence-based nutritional strategies leveraging SPM biology.

The erythrocyte omega-3 index (EPA + DHA) is a validated, time-integrated marker of long-chain omega-3 PUFA status [120] and thus a plausible upstream indicator of precursor availability for lipid mediators. In a randomised trial, increasing EPA/DHA intake led to linear, dose-dependent increases in plasma oxylipins and correlations between the omega-3 index and EPA/DHA-derived hydroxy-metabolites (e.g., 18-HEPE, 17-HDHA), supporting biological plausibility for a link between tissue omega-3 status and downstream mediator formation [121]. However, whether the omega-3 index correlates with bioactive SPMs and with patient-centred outcomes in enterally fed populations remains unknown. We therefore recommend that EN studies incorporate (i) baseline and on-treatment omega-3 index measurements aligned with erythrocyte turnover, (ii) harmonised pre-analytical protocols and targeted profiling of SPMs/oxylipins, and (iii) pre-specified correlation and mediation analyses to determine whether erythrocyte EPA + DHA tracks SPM biosynthesis and clinical effects.

8. Conclusion

In conclusion, inflammation involves dynamic and actively regulated processes, including resolution pathways mediated by SPMs. Cumulative evidence has demonstrated multiple mechanisms by which SPMs promote resolution, clarifying how omega-3 fatty acids exert immunomodulatory effects. SPM-enriched EN formulations hold tremendous promise as a nutritional strategy to modulate immune responses and enhance inflammation resolution across diverse acute and chronic clinical scenarios. Additional rigorous clinical studies are needed to evaluate the efficacy of SPM-enriched EN formulas and to inform evidence-based clinical guidelines.

Author contributions

All authors contributed to writing the original draft and critical review/editing. All authors meet the International Committee of Medical Journal Editors (ICMJE) authorship criteria and approve the final version of the manuscript. We confirm that the list of authors does not exclude any name that is eligible for authorship.

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