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Immunomodulatory Effects of Omega-3 Fatty Acids: Mechanistic Insights and Health Implications

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ABSTRACT

Omega-3 fatty acids play a significant role in immunomodulation, with nutrigenomic approaches highlighting their impact on gene expression related to immune responses. Research indicates that omega-3 fatty acids can modulate inflammatory pathways, potentially reducing chronic inflammation and enhancing immune function. This review discusses the intersection of nutrigenomics and nutriepigenomics, focusing on how omega-3 fatty acids influence gene expression, immune function, and overall health. The immune system is a complex network responsible for defending the body against pathogens and maintaining internal balance. Comprised of innate and adaptive immunity, the system involves various cells, tissues, and organs working together to combat infections and prevent diseases. Omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), play a significant role in modulating the immune system. These fatty acids influence immune cell function, membrane fluidity, and signaling processes, enhancing immune responses and reducing inflammation. Furthermore, EPA and DHA affect several signaling pathways, reducing the expression of proinflammatory cytokines and inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, a critical transcription factor in the inflammatory response. Additionally, they activate PPAR-γ, further diminishing inflammatory gene expression. As precursors to specialized proresolving lipid mediators, EPA and DHA help shift the lipid mediator profile from proinflammatory to antiinflammatory derivatives, thus aiding in the resolution of inflammation.

Abbreviations: AA, arachidonic acid; ALA, alpha-linolenic acid; CD40, cluster of differentiation 40; CD80, cluster of differentiation 80; CD86, cluster of differentiation 86; CTX, cyclophosphamide; cys-LT, cysteinyl leukotrienes; DHA, docosahexaenoic acid; EFOEPA, enriched fish oil; EPA, eicosapentaenoic acid; FcεRI, high affinity IgE receptor; GM1, monosialotetrahexosylganglioside; GPR120, G protein-coupled receptor 120; IFN-γ, interferon gamma; IL-10, interleukin-10; IL-13, interleukin-13; IL-17, interleukin-17; IL-1β, interleukin-1 beta; IL-2, interleukin-2; IL-4, interleukin-4; IL-5, interleukin-5; IL-6, interleukin-6; LAT, linker for activation of T cells; Lyn, Src family tyrosine kinase; MAPK, mitogen-activated protein kinase; MHCII, major histocompatibility complex Class II; MO, menhaden oil; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells ozounce; PD15, dose of mannitol required to cause a 15% reduction in FEV1; PGD2, prostaglandin D2; PGE2, prostaglandin E2; PKCθ, protein kinase C theta; PLCγ-1, phospholipase C gamma 1; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; Syk, spleen tyrosine kinase; Tbsp, tablespoon; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cells.

[Correction added on 17 May 2025 after first online publication: Email address of author Birsen Yilmaz has been corrected.]

1 | Introduction

Food has been investigated from a chemical perspective as well as for the ability of metabolites produced during food oxidation to directly (nutrigenomics) or indirectly (nutriepigenomics) modify gene expression [1]. Nutrigenomics examines how foods affect the genome and transcriptome patterns [2]. In other words, nutrigenomics primarily focuses on the interaction between nutrition and genetics, particularly how individual genetic variations influence responses to nutrients and dietary patterns, which in turn affects an individual's health and disease risk [3]. Conversely, nutriepigenomics focuses on examining the relationship among gene expression, epigenetics, and diet. It investigates the ways in which food might affect epigenetic processes including DNA methylation, histone modifications, and microRNA expression [4]. During prenatal and neonatal periods, nutrition and environmental variables have a significant role in the development. The majority of epigenetic modifications occur during these phases, which later in life result in the development of metabolic illnesses [5].

The unique structure and biological roles of omega-3 long-chain polyunsaturated fatty acids (PUFAs), or n-3 LC-PUFAs, have attracted a lot of attention. Since they are incapable of being produced by humans, fatty acids like linoleic acid (LA) (18:2n-6) and alpha-linolenic acid (ALA) (18:3n-3) are referred to as essential fatty acids [6]. The essential fatty acids LA and ALA can be used to synthesize other PUFAs, including arachidonic acid (AA) (C20:4, n-6), docosahexaenoic acid (DHA) (C22:6, n-3), and eicosapentaenoic acid (EPA) (C20:5, n-3). The PUFAs are divided into omega-3 and omega-6 fatty acids depending on where the double bond is located. A double bond at the n-3 position is a defining characteristic of omega-3 PUFAs whereas omega-6 PUFAs are distinguished by a double bond at the n-6 location. Vegetable oils, flaxseeds, walnuts, veggies, and fatty fish are rich in omega-3 fatty acids [7]. Although EPA and DHA are mostly found in marine sources [8, 9], ALA is found in plant sources [10]. The best source of the health-promoting omega-3 PUFA is fish, including tuna, mackerel, sardines, anchovies, herring, mullet, and pollock [8, 11]. Recommendations state that taking 2–3 meals of fatty fish each week will provide you with 250 mg of EPA and DHA per day [12]. The quantity of omega-3 PUFA fatty acids varies depending on the species, whether the fish is farmed or wild, and a wide range of internal and external variables, including size, age, nutrition, location of catch, and environmental factors, can affect them [8].

In contrast to the increasing intake of omega-6 fatty acids from vegetable oil and animal fats, many countries still eat relatively little omega-3 fatty acids. The ratios of omega-6 to omega-3 fatty acids or omega-6/omega-3 ratio in human diet vary from 15:1 to 40:1. This is a substantial increase over the 4:1 dietary recommendation made by the UK Department of Health to avoid cardiovascular illnesses [13]. It was known that a diet deficient in omega-3 fatty acids may alter the makeup of the cell membrane. For physiological reactions to be facilitated and fluidity to be maintained, every cell requires a healthy, functional lipid bilayer. The well-established health advantages of omega-3 fatty acids, especially EPA and DHA from marine sources, include support for regulating gut immunity [14], the immune system [15, 16], cognitive function [17], and cardiovascular health [18, 19]. Supplementing with omega-3 fatty acids has been linked to a notable decrease in the course of certain autoimmune disorders such as diabetes [7, 20], rheumatoid arthritis [21], systemic lupus erythematosus [22, 23], and multiple sclerosis [24]. Furthermore, increasing the amount of omega-3 FA in the diet or through supplements may help reduce viral entry, improve immunological function, and lessen the severity of COVID-19 since it is known to release less proinflammatory cytokines [25–27].

1.1 | Nutrigenomics and Omega-3: Overview

With the combination of nutritional science and genetic information, nutrigenomics offers opportunities to improve dietary recommendations and promote individualized approaches to disease prevention and health promotion. The concept of gene-diet interactions is becoming more widely recognized, highlighting the importance of understanding how genetic variations influence responses to dietary factors [28–30]. In addition, numerous systematic reviews and meta-analyses have been conducted to assess the impacts of omega-3 fatty acids on various health outcomes and diseases [31–35].

Recent developments in nutrigenomic studies highlight the need to thoroughly investigate the effects of omega-3 fatty acids on gene expression related to immune function [36–38]. The complex interplay between dietary factors such as omega-3 fatty acids and gene expression requires an in-depth investigation of how these lipids and its metabolites modulate immune mechanisms at the genomic level. This line of research is critical to improving our understanding of the impact of diet on immune health and could lead to precise dietary strategies to optimize immune function [37–39]. Given that omega-3 fatty acids can modulate gene expression and impact various biological pathways, this review will incorporate nutrigenomic perspectives and provide a more comprehensive evaluation of the impacts of omega-3 fatty acids on immunomodulation.

2 | An Overview of Omega-3 Fatty Acids

Omega-3 fatty acids, one of the members of PUFAs, which have double bonds within their carbon chains, can be named differently in the literature such as n-3 fatty acids, n-3 PUFA, ω-3 fatty acids (n-3 FAs), omega-3 polyunsaturated, and omega-3 phospholipids. Within PUFAs, the initial double bond can occur either between the third and fourth carbon atoms from the omega carbon, referred to as omega-3 fatty acids, or between the sixth and seventh carbon atoms, known as omega-6 fatty acids [40, 41]. Both omega-3 and omega-6 are essential for all high organisms including humans due to the absence of endogenous enzymes for omega-3 desaturation [13]. The double bonds in PUFAs are spaced apart by a methylene group. The positions of double bonds in fatty acid molecules are indicated by the designations "omega-3," "omega-6," or "omega- 9" fatty acids. The fatty acid double bond, that is, closest to the methyl end of the molecule is referred to as "omega" or "n minus". There are three main omega-3 fatty acids: α-linolenic acid (ALA; 18:3n-3), EPA (C20:5n3), and DHA (C22:6n3) [40–42]. The initial double bond

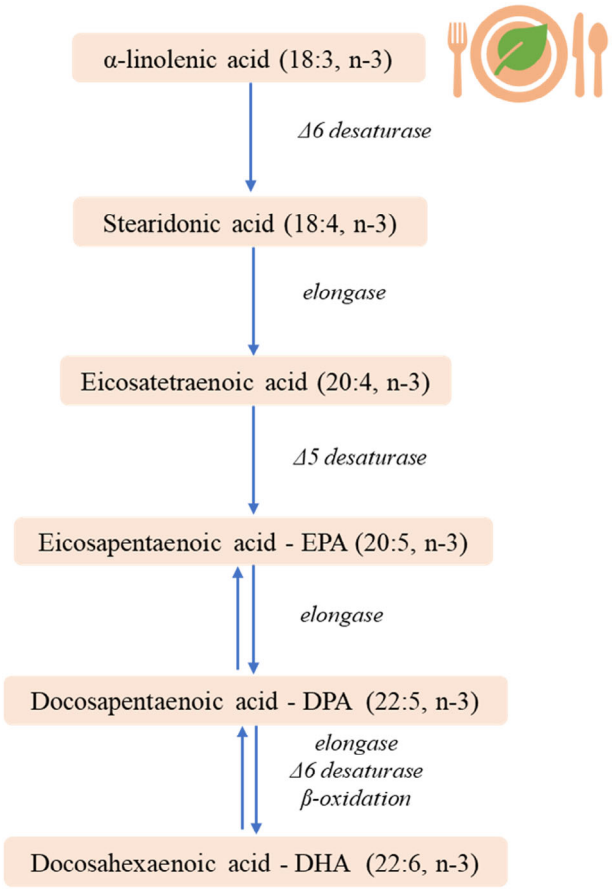

FIGURE 1 | Metabolic pathway of omega-3 polyunsaturated fatty acids.

in ALA is present three carbon atoms from the methyl end, for instance, it is classified as C18:3 n-3. If the precursors of EPA and DHA are taken by diet adequately, they can be biosynthesized in organisms. The amount of EPA and DHA produced is influenced by the relative abundance of ALA and LA rather than the body's metabolic demand. ALA and LA compete for the same enzymes involved in desaturation and elongation processes, impacting their conversion rates [42, 43]. The metabolic pathway for the biosynthesis of omega-3 PUFAs from ALA to DHA involves a series of enzymatic steps essential for producing long-chain omega-3 PUFAs (Figure 1). This metabolic pathway is started by ALA, a significant fatty acid obtained from different dietary sources. Desaturase and elongase enzymes play a pivotal role in the conversion of dietary fatty acids into EPA-DHA. Desaturase enzymes facilitate the addition of double bonds in the metabolic pathway, while elongase enzymes facilitate the addition of carbon atoms. Desaturase enzymes add an additional double bond, facilitating the conversion of ALA to stearidonic acid. Elongase enzymes subsequently insert two carbon atoms into stearidonic acid to form eicosatetraenoic acid (20:4n-3). Docosapentaenoic acid (DPA, 22:5n-3) is created by extending EPA, while DHA (22:6n-3) is generated through the desaturation of DPA. However, the human body has a very limited ability to convert ALA to DHA, and the conversion rate from EPA to DHA is particularly low, less than 1% [44]. The conversion of omega-3 PUFAs is a complex procedure that requires the involvement of many desaturases and elongase enzymes. This emphasizes the multi-faceted control of lipid metabolism and the importance of dietary approaches that provide a sufficient intake of omega-3 PUFA for the function of maintaining health and preventing disease [42, 43, 45].

Omega-3 fatty acids are essential and need to be taken via diet. The main sources of omega-3 fatty acids are summarized in Table 1. Although flaxseed oil (cold pressed), chia seeds, and walnuts are the best sources of the ALA, cold-water fatty fishes such as salmon, menhaden, tuna, and sardines, are the best sources of EPA and DHA (Table 2).

Fortified foods are also considered to be good sources of omega-3 fatty acids [47]. Table 2 highlights the omega-3 content and portion sizes of various foods, such as flaxseed (22.8 g ALA per tablespoon [Tbsp]), salmon (1.12 g DHA per 3 ounce [oz]), and caviar (3.8 g DHA per Tbsp), emphasizing the substantial contributions these foods make to dietary omega-3 intake.

Epidemiological studies and clinical trials have reported that adequate intake of omega-3 fatty acids as well as a proper balance between omega-6 and omega-3 may result in reducing the risk of cardiovascular diseases, blood pressure, inflammation, and a few types of cancer ([48–52]). Consuming more marine n-3 PUFA in the diet was linked to a reduced risk of breast cancer [52]. In individuals without prior cardiovascular disease who consume a high amount of fish, dietary ALA, primarily found in walnuts and olive oil, was associated with lower all-cause mortality (hazard ratio 0.63 [95% confidence interval (CI) 0.45–0.87]). Although omega-3 PUFAs, particularly EPA and DHA derived from fish, have shown potential in lowering triglycerides and exerting antiinflammatory effects, the evidence for their cardioprotective benefits remains mixed. Although protection against cardiac mortality is often attributed to long-chain n-3 PUFAs, as noted by Sala-Vila et al. [50], other studies have yielded inconclusive or conflicting results. For instance, the STRENGTH trial evaluated a high-dose carboxylic acid formulation of EPA and DHA in statin-treated patients with high cardiovascular risk but found no significant reduction in major adverse cardiovascular events compared to a corn oil control. This large trial, which involved 13 078 patients, indicated that this specific omega-3 formulation may not effectively lower cardiovascular risk for individuals with a high baseline risk [53]. Similarly, the ASCEND trial, which focused on diabetic patients without established cardiovascular disease, found that omega-3 supplementation did not significantly reduce the risk of serious vascular events when compared to placebo [54].

Additionally, some studies have failed to identify a consistent relationship between dietary omega-3 intake and a reduction in cardiovascular disease or cancer risk [55, 56]. Despite omega-3 fatty acids' known effects on lipid profiles and inflammation, factors such as formulation, dosage, and patient demographics appear to influence the outcomes. Purified EPA supplements, for instance, may provide more targeted benefits, though further research is needed to confirm these effects in different populations [53].

This mixed evidence highlights the complexity of omega-3 PUFA supplementation for cardiovascular health, suggesting that while benefits exist, they may not apply universally across formulations

TABLE 1 | Structure and dietary sources of omega-3 fatty acids.

Fatty acid	Structure	Dietary sources	References
Alpha-linolenic acid C18:3, n-3			[46, 47]
EPA C20:5, n-3			[46, 47]
DHA C22:6, n-3			[46, 47]

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

TABLE 2 | ALA, EPA, and DHA contents of various foods.[47]

Food	Total lipid (fat) g/100 g	Omega-3 fatty acid g/100 g	Amount per serving size
Alpha-linolenic acid C18:3, n-3			
Flaxseed	42.2	22.8	2.35 g/Tbsp
Chia seeds, dried	30.7	17.8	1.78 g/Tbsp
Walnut, English	65.2	9.08	2.57 g/4.2 Tbsp
Flaxseed oil, cold pressed	100.0	53.4	7.26 g/Tbsp
Kale, raw	1.49	0.378	0.25 g/cup
EPA C20:5, n-3			
Salmon, Atlantic, wild, raw	6.34	0.321	0.273 g/3 oz
Cod, Atlantic, raw	0.67	0.064	0.054 g/3 oz
Sardine, Atlantic, canned	11.4	0.473	0.402 g/3 oz
Crab, blue, canned	0.74	0.101	0.086 g/3 oz
Caviar, black and red, granular	17.9	2.74	0.438 g/Tbsp
DHA C22:6, n-3			
Salmon, Atlantic, wild, raw	6.34	1.12	0.952 g/3 oz
Cod, Atlantic, raw	0.67	0.12	0.102 g/3 oz
Sardine, Atlantic, canned	11.4	0.509	0.432 g/3 oz
Crab, blue, canned	0.74	0.067	0.057 g/3 oz
Caviar, black and red, granular	17.9	3.8	0.608 g/Tbsp

Note: oz: ounce, Tbsp: tablespoon.
Abbreviations: ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

or patient groups. Further research is required to clarify the conditions and populations in which omega-3s are most effective for cardiovascular protection. In addition to the consumption of omega-3 fatty acids, the ratio between omega-6 and omega-3 has significant impacts on health outcomes. Although some diets maintain a balanced omega-6/omega-3 ratio as low as 2:1, Western diets are deficient in n-3 fatty acids, resulting in an elevated ratio as high as 16.7:1 and 40:1. This high dietary omega-6/omega-3 ratio has been linked to numerous human diseases including coronary artery disease, hypertension, diabetes, arthritis, osteoporosis, autoimmune disorders, cancer, and psychiatric disorders [26, 57–59]. Conversely, maintaining a low dietary omega-6/omega-3 ratio has shown beneficial effects [13, 43, 60]. According to ISSFAL, omega-3 fatty acids, particularly EPA and DHA, are recommended at various doses depending on individual health needs and life stages. For the general population, ISSFAL suggests a daily intake of 250–500 mg of combined EPA and DHA to support cardiovascular health. For pregnant and lactating women, a daily intake of 200–300 mg of DHA is recommended to aid fetal and infant brain development. In high-risk populations, such as individuals with a history of cardiovascular disease, approximately 1 g of EPA and DHA per day may be beneficial for heart health. To prevent early preterm birth, pregnant women are advised to consume around 1000 mg of DHA daily, beginning before 20 weeks of gestation. For the management of elevated triglycerides, doses ranging from 2 to 4 g per day are recommended, although these higher doses should be taken under medical supervision to ensure safety and efficacy [61, 62]. It is known that a high intake of omega-3 may cause some health problems such as increasing oxidative stress [63]. Therefore, it is significant to consume a balanced dietary intake of n-6 and n-3 fatty acids to be able to optimize from their beneficial effects.

3 | The Immune System and Omega-3

3.1 | Structure and Function of the Immune System

The immune system, an intricate network of cells, tissues, and organs, defends against pathogens and maintains bodily integrity. Lymphocytes, such as T and B cells, along with macrophages and dendritic cells, form the core of this defense network. Although the bone marrow and thymus generate immune cells, organs like the spleen and lymph nodes are crucial for their differentiation and activation. The immune response is categorized into innate and adaptive immunity, with innate immunity providing immediate defense and adaptive immunity offering targeted and memory-based responses. The coordination between these elements ensures the immune system's dynamic and adaptive nature, crucial for the body's defense against various threats [38, 64].

The immune system's function extends beyond simple defense mechanisms, as it also plays a crucial role in regulatory processes that ensure self-tolerance and prevent autoimmune diseases. The adaptive immune system's ability to remember past pathogens enables more effective responses to subsequent exposures, highlighting its evolutionary advantage in dealing with persistent threats [65, 66]. Understanding the immune system's structure and function is vital for comprehending how it combats infections and coordinates various responses to maintain homeostasis and protect against diseases [64–66].

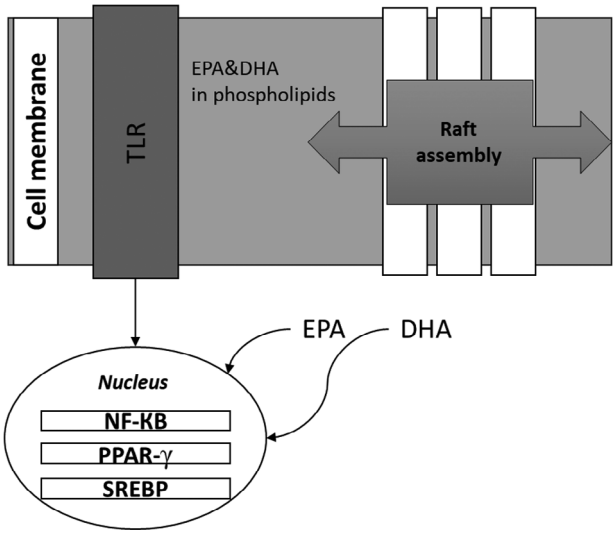

FIGURE 2 | Role of omega-3 fatty acids in cellular membrane structure and function.

A deeper understanding of the immune system's structure and function is essential not only for appreciating its role in disease prevention but also for understanding how nutrients and nutrition influence immune responses [67]. A healthy, well-balanced diet is essential for the proper functioning of all the body's systems, including the immune system. In addition, several dietary factors have been shown to have immunoregulatory properties, including micronutrients such as vitamin D or macronutrients such as omega-6 and omega-3 fatty acids [68, 69]. Although the health benefits of omega-3 fatty acids, such as reduced cardiovascular risk [70], reduced inflammation, which is beneficial for conditions such as rheumatoid arthritis [71], and neuroprotective effects that support cognitive and mental health [72, 73], are widely known, studies investigating their effects on immune system modulation are quite limited.

3.2 | Mechanisms of Omega-3 in Immune Modulation

Omega-3 fatty acids play a crucial role in immune system modulation through various mechanisms that influence cellular functions and responses (Figure 2). As essential components of cell membranes, they impact the fluidity and flexibility of these structures, enhancing communication, signal reception, and response to infections and inflammation in immune cells such as lymphocytes, macrophages, and dendritic cells. This modification of cell properties significantly boosts immune effectiveness [74]. Omega-3 fatty acids exert significant modulatory effects on the immune system through their interaction with cell membrane structures. These effects are primarily mediated by two distinct mechanisms. Firstly, omega-3 fatty acids are incorporated into the cell membranes, thereby altering the membrane's fluidity. This alteration facilitates a reorganization of membrane proteins, which are crucial for the signaling

processes of immune cells. Consequently, increased membrane fluidity enhances the ability of immune cells to communicate and respond swiftly to infections or inflammatory stimuli. Such changes are essential for the rapid activation and initiation of immune responses [74–77]. Secondly, these fatty acids influence the structure and functionality of lipid rafts—cholesterol and sphingolipid-rich microdomains critical for cell signaling and the orchestration of the immune response. The disruption of lipid rafts by omega-3 fatty acids impairs the signaling capabilities of key immune cells, including T cells and macrophages. This disruption may potentially impair the cells' capacity to effectively respond to microbial infections. Although disrupting lipid raft stability may lead to reduced responsiveness to certain microbial stimuli, this effect is highly selective and does not equate to general immune suppression. Instead, it enables immune cells to maintain a balanced response, allowing for inflammatory moderation without completely inhibiting infection response [76, 78, 79]. Although EPA and DHA do not directly bind to DNA to regulate gene expression as transcription factors do, they exert significant indirect effects on gene regulation. These effects occur through mechanisms involving nuclear receptor activation, epigenetic modifications, transcription factor modulation, and microRNA regulation. Through these pathways, omega-3 fatty acids and their metabolites can play critical roles in controlling inflammation, lipid metabolism, and immune responses, all of which are vital for maintaining health and preventing disease.

3.3 | Omega-3 and Immune Cell Functions

Previous research has reported that omega-3 fatty acids inhibit multiple components of immune cell functions, such as neutrophil activity, dendritic cells, monocyte, and lymphocyte activities including the production of proinflammatory mediators [80–82] (Table 3). PUFAs, particularly essential PUFAs omega-3 and omega-6 fatty acids, play a major role in the regulation of a variety of physiological functions as well as gene expression through complex biological mechanisms and thus maintain health, prevent diseases, and regulate mechanisms [76, 83, 84]. The fatty acids can influence the activity of central lipid regulators including sterol regulatory element-binding proteins (SREBPs) and peroxisome proliferator-activated receptors (PPARs), key pathways in lipid metabolism and homeostasis, ultimately modulating inflammation and improving lipid profiles [85–88]. However, n-3 PUFAs were able to be activated by endogenous ligands, that is, EPA and DHA, both function as natural ligands of PPAR-γ. When activated, PPAR-γ physically binds specific DNA sequences cells use to regulate lipogenesis and adipogenesis-known as peroxisome proliferator response elements (PPREs)-to affect gene expression. These reflect the upregulation of lipogenic genes, such as perilipin 2 (PLIN2), elongation of very long chain fatty acid 4 (ELOVL4), and sterol O-acyltransferase 1 (SOAT1) that are associated with lipid droplet formation and utilization for LC-PUFA biosynthesis and metabolism [45, 89, 90]. In macrophages, omega-3 fatty acids result in a reduction in the production of inflammatory molecules and an enhancement of the cells' capacity to consume pathogens. This affects the balance between inflammation-promoting states and inflammation-resolving states. These effects are due to alterations in gene expression and cell signaling [74, 91, 92]. Similarly, in neutrophils, omega-3 fatty acids influence movement, ingestion of pathogens, and production of inflammation-related chemicals. They also lead to the creation of substances such as resolvins, which help control inflammation [93–95]. Regarding T and B lymphocytes, omega-3s limit T cell proliferation and guide their development into regulatory T cells (Treg), which are important for preventing excessive immune responses [74, 96]. In B cells, these fatty acids regulate antibody production and the display of molecules involved in cell activation, which are essential for the immune system's ability to respond to infections effectively [74, 97].

Table 4 provides a summary of the effects of omega-3 fatty acids and their metabolites on various immune cells in humans, highlighting their potential to influence immune cell function and inflammatory responses. One study demonstrated that supplementation with EPA and DHA resulted in a significant reduction in T lymphocyte activation, as evidenced by decreased CD69 expression. Interestingly, this effect was specific to T cells, as monocyte and neutrophil functions, such as phagocytosis, cytokine production, and adhesion molecule expression, were not significantly affected by omega-3 supplementation [154]. This suggests a targeted effect of DHA on adaptive immunity without broadly suppressing innate immune responses. Further, DHA supplementation was found to significantly decrease the number of circulating white blood cells, particularly granulocytes, without altering lymphocyte proliferation. This reduction in granulocytes may reflect a specific antiinflammatory effect of DHA, contributing to its overall immunomodulatory properties [155]. Additionally, fish oil rich in EPA led to a reduced release of interleukin-2 (IL-2) in T and B cells. This reduction in IL-2, alongside decreased serum immunoglobulin levels, indicates a mild immunosuppressive effect of omega-3 fatty acids on both T and B cell functions [156]. DHA-rich fish oil was also shown to significantly enhance the phagocytic activity of neutrophils and monocytes, as well as increase neutrophil chemotaxis and lymphocyte cytokine production. These effects were associated with an increase in reactive oxygen species (ROS) production and the upregulation of specific immune-related genes, highlighting the potential of DHA to enhance innate immune responses [157].

In another study, EPA-rich oil supplementation increased the production of the antiinflammatory cytokine interleukin-4 (IL-4) but had limited effects on T cell proliferation and natural killer (NK) cell activity, particularly in healthy young males [160]. This suggests that while EPA may enhance specific antiinflammatory pathways, its impact on broader immune cell functions might be limited under normal physiological conditions. Furthermore, omega-3 fatty acid supplementation has been associated with a reduction in proinflammatory cytokines, such as IL-6, and a modulation of T-helper cell polarization. Specifically, omega-3 fatty acids were found to shift the Th1/Th2 balance toward a more balanced ratio, which could be particularly beneficial in conditions associated with chronic inflammation or immune dysregulation [188]. These findings underscore the potential of omega-3 fatty acids as modulators of immune function, with implications for their use in managing inflammatory and autoimmune diseases. The evidence suggests that omega-3 fatty acids, particularly DHA and EPA, can selectively influence immune cell activities, enhancing certain antiinflammatory responses while modulating others without broadly suppressing immune function.

TABLE 3 | The effects of omega-3 and its metabolites on different immune cells.

In vitro studies		
Cell type	**Outcomes**	**References**
Mast cells	Alpha-linolenic acid and its metabolites significantly decreased the production of cytokines IL-4, IL-5, and IL-13 in activated mast cells and bone marrow-derived mast cells.	[98]
Mast cells	EPA and DHA inhibit ROS generation and reduce the secretion of IL-4 and IL-13 in mast cells. AA increased PGD2 and TNF-α secretion. EPA and DHA's suppression of IL-4 and IL-13 is mediated through the inhibition of ROS and MAPK pathways.	[99]
Monocytes (human)	EPA and DHA suppressed PAF synthesis, monocyte rolling, and adhesion to endothelial cells. This indicates that ω-3 fatty acids inhibit monocyte–endothelium interaction by reducing endothelial PAF generation.	[100]
Monocytes (human)	Fish oil supplementation reduced the ability of monocytes to induce endothelial cell (EC) recruitment of neutrophils by reducing endothelial activation and neutrophil adhesion.	[101]
Monocytes and macrophages (human THP-1 cells)	Lowering the n-6/n-3 PUFAs ratio inhibits foam cell formation by reducing intracellular cholesterol and inflammatory cytokine levels (IL-6 and TNF-α), and downregulating CD36 and ACAT1 mRNA expression through the PPAR-γ pathway.	[102]
Monocytes and macrophages (human THP-1 cells)	EPA and DHA downregulate proinflammatory miRNAs (miR-155) and upregulate antiinflammatory miRNAs (let-7b), modulating the expression of inflammation-related genes such as IL-6, TNF-α, SERPINE1, and TLR4. Oleic acid shows similar effects but to a lesser extent.	[103]
Monocytes (human)	Polyunsaturated fatty acids (DGLA and AA) enhance phagocytic activity and IL-1β release in human monocytes and U937 cells, while PGE2 inhibits these processes in a concentration-dependent manner.	[104]
Macrophages	In RAW 264.7 cells lines, omega-3 modulated the posttranscriptionally stabilized existing COX-2 and decreased IL-10 production.	[105]
Macrophages	EPA reduced TNF mRNA expression and NFκB activity in LPS-stimulated macrophages, indicating an inhibitory effect on TNF gene transcription by altering NFκB subunit composition (P65/P50 dimers).	[106]
Macrophages	EPA, DHA, and EPA + DHA decreased the expression of genes in the NF-κB pathway (MAPK, AKT1, NFKB), and inflammatory cytokine genes (IL1β, MCP1, TNFA). EPA was more effective than DHA and EPA + DHA in modulating gene expression	[107]
Macrophages (mouse)	Fish oil HFD uncouples obesity from mammary tumor growth by inducing ROS production and apoptosis in pro-tumor macrophages via A-FABP. This indicates that n-3 fatty acids promote macrophage cell death, reducing tumor-supportive macrophages.	[108]
Macrophages (RAW 264.7 cells)	DHA induced M2 polarization and enhanced efferocytosis through PPAR-γ activation. Knockdown of PPAR-γ abolished the effects of DHA on M2 polarization and efferocytosis, while LPS-induced M1 polarization was unaffected.	[109]
Macrophages (mouse model)	DHA antagonizes the boosting effect of palmitic acid on LPS-induced inflammatory signaling by inhibiting NF-κB-dependent gene transcription and ceramide de novo synthesis.	[110]
Macrophages (mouse model)	DHA significantly reduces IL-6 expression more than TNF-α in LPS-stimulated RAW 264.7 cells by reducing NF-κB activity. PGE2 plays a dual role in regulating TNF-α expression.	[111]
Macrophages (mouse and human)	DHA activates cPLA2 via GPR120, leading to the production of PGE2, which inhibits LPS-induced IL-6 secretion by inhibiting NF-κB signaling through the EP4 receptor.	[92]
Macrophages (mouse model)	EPA and DHA reduce TNF-α and IL-6 secretion induced by TLR4 activation without altering the surface expression of TLR4, TLR4-MD2 complex, or CD14. Inhibition occurs downstream of TLR4 activation.	[112]

(Continues)

TABLE 3 | (Continued)

In vitro studies		
Cell type	**Outcomes**	**References**
Macrophages (mouse model)	PUFA, including n-3 (EPA, DHA) and n-6 (LA, AA), downregulate IL-1β, IL-6, TNF-α, and CD86 expression. DHA increases IL-10 production in LPS, P. aeruginosa, and R. equi stimulated cells, suggesting an antiinflammatory effect.	[113]
Macrophages (human and mouse)	DHA suppresses inflammasome activation by inhibiting NF-κB translocation to the nucleus and enhancing autophagy, reducing IL-1β production. This effect requires FFAR4 (GPR120) and β-arrestin2.	[114]
Macrophages (mouse model)	PUFA, including n-3 (EPA, DHA) and n-6 (LA, AA), inhibits TLR4-mediated activation of NF-κB by disrupting membrane microdomain organization and preventing the clustering of TLR4 and CD14 in lipid rafts, leading to reduced proinflammatory cytokine production.	[115]
Macrophages (mouse model)	PUFA supplementation does not alter the mRNA or protein expression of TLR1, TLR2, and TLR6. The membrane localization of TLR1, TLR2, and TLR6 within lipid rafts remains unaffected by PUFA enrichment.	[116]
Dendritic Cells (human)	DHA modulates dendritic cell differentiation and function via PPAR-γ heterodimers, reducing IL-6 expression, and IL-10 and IL-12 secretion, while inhibiting lymphoproliferative stimulation capacity.	[117]
Dendritic cells (human	EPA and DHA reduced the expression of CD80, CD86, and HLA-DR, decreased IL-12 and TNF-α production, and inhibited LPS-induced p38 MAPK phosphorylation, impairing dendritic cell maturation and T cell proliferation.	[96]
Dendritic cells and T cells (mouse model)	Arachidonic acid (AA) and DHA induce dendritic cell maturation with increased CD40, CD83, CD86, and PDL-1 expression but reduce T-cell proliferation and increase the proportion of regulatory T cells (Tregs).	[118]
B cells (human)	DHA inhibits IgE production by interfering with STAT6 and NFκB pathways, reducing CD40-dependent NFκB-p50 nuclear translocation and IL-4-driven STAT6 phosphorylation, leading to decreased IgE secretion.	[119]
B cells (human)	Specialized proresolving mediators (17-HDHA, RvD1) enhance the differentiation of B cells into antibody-secreting cells, increasing IgM and IgG production by upregulating Blimp-1 and Xbp-1 and downregulating Pax-5.	[120]
B cells (human)	DHA and AA reduce surface expression of HLA class I molecules, impairing antigen presentation and reducing susceptibility to lysis by $CD8^+$ T cells.	[121]
B cells (Raji cell line)	EPA (12.5 μM) increased proliferation two-fold, DHA (12.5 μM) increased proliferation 1.5-fold. EPA and DHA (25 μM) decreased IL-10, TNF-α, and IFN-γ production. EPA affected 25.9% of genes investigated, while DHA affected 8.4%. Significant changes in genes involved in signal transduction and transcription.	[122]
Mast cells	n-3 PUFAs (EPA and DHA) inhibit FcεRI-mediated mast cell activation. They reduce degranulation, cytokine/chemokine production (TNF, CCL2), and lipid-derived mediator release (cys-LT). This is associated with reduced phosphorylation of Lyn, Syk, and LAT, and disrupted FcεRI localization to lipid rafts.	[123]
Monocytes (human) and macrophages (mouse)	DHA and EPA preferentially inhibit TLR2 and TLR4-mediated COX-2 expression by suppressing NF-κB activation. This inhibition occurs at the receptor level, not downstream components, demonstrating the antiinflammatory potential of n-3 PUFAs.	[124]
Monocytes (mouse model)	Fish oil reduced JE/MCP-1 production by spleen cells, suggesting a decrease in monocyte chemoattraction and a potential delay in arthritis progression.	[125]
Macrophages and monocytes (human and rat models)	Omega-3-carboxylic acids (OM-3 CA) reduce crystal-mediated IL-1β production, cell migration, exudate volume, and PGE2 levels. They inhibit WBC infiltration and modify inflammation progression in models of crystal arthritis.	[126]
Neutrophils and monocytes (human and mouse)	Oxidized EPA significantly inhibited leukocyte adhesion to endothelial cells, reduced expression of endothelial adhesion receptors (ICAM-1, VCAM-1, E-selectin), and decreased leukocyte rolling and adhesion in vivo via PPAR-γ activation.	[127]

(Continues)

TABLE 3 | (Continued)

In vitro studies		
Cell type	**Outcomes**	**References**
Macrophages (mouse model)	DHA and its precursor resolvin D1 promote resolution of adipose tissue inflammation by shifting macrophage polarization toward an M2-like phenotype, reducing proinflammatory cytokines, and enhancing nonphlogistic phagocytosis.	[128]
Macrophages (mouse model)	Omega-3 fatty acids (EPA and DHA) inhibit NLRP3 inflammasome activation, caspase-1 activation, and IL-1β secretion, preventing inflammation and metabolic disorders through GPR120 and GPR40 pathways.	[129]
Macrophages (mouse model)	15-LOX metabolites of α-linolenic acid (13-(S)-HPOTrE and 13-(S)-HOTrE) inactivate NLRP3 inflammasome via PPAR-γ pathway, reducing proinflammatory cytokines and ROS, and increasing antiinflammatory cytokines and apoptosis.	[130]
Macrophages (mouse model)	Combination of EPA and DHA reduces atherogenesis by inhibiting macrophage activation, reducing TLR4 expression in lipid rafts, and decreasing proinflammatory markers such as MCP-1, TNF-α, and MMP9.	[131]
Macrophages (mouse model)	α-Linolenic acid (ALA) and its gut lactic acid bacteria metabolites (13-OH, 13-oxo) promote M2 macrophage differentiation via GPCR40 and PPAR-γ signaling, enhancing antiinflammatory markers CD206 and Arginase-1 (Arg1) in the presence of IL-4 or IL-13.	[132]
Macrophages (mouse model)	DHA poststroke treatment reduces brain infarct and improves neurological deficits by promoting macrophage polarization toward the M2 phenotype, increasing antiinflammatory markers (CD206, IL-10, Arg1) and reducing proinflammatory cytokines (TNF-α, IL-1α).	[133]
T cells and macrophages (mouse model)	DHA alleviates atopic dermatitis by generating FoxP3+ T regulatory cells and M2 macrophages. M2 macrophages drive TGF-β and IL-10 conversion of CD4 T cells to T regulatory cells, reducing inflammation and atopic symptoms.	[134]
Macrophages	DHA promotes proliferation and phagocytic activity of macrophages, activates the GPR120-MAPKs-NF-κB p65 pathway, enhances spleen and thymus indexes, and increases IL-1β, IL-2, TNF-α, and IFN-γ production. DHA treatment also repairs spleen damage induced by CTX.	[135]
Natural killer (NK) cells and phagocytic cells	Fish oil and olive oil consumption inhibited natural killer cell activity compared to omega-6 fatty acids and saturated fatty acids.	[136]
B cells (splenic, mouse model)	DHA from fish oil increased DHA levels in B cells, reduced GM1 microdomain clustering, enhanced LPS-induced IL-6 and TNF-α secretion, and increased CD40 and MHCII expression. In vivo, it increased B cell populations and Th2-biasing cytokines (IL-5, IL-13, IL-9) in plasma and cecal IgA.	[137]
Dendritic cells	DHA maintains an immature phenotype in dendritic cells by preventing the upregulation of MHCII and costimulatory molecules. It inhibits the production of proinflammatory cytokines, including IL-12p70, IL-23, and IL-27. The effect of DHA on cytokine expression is mediated through PPAR-γ activation and inhibition of NF-κB nuclear translocation. DHA exerted a similar inhibitory effect on cytokine expression in splenic DCs from LPS-inoculated mice maintained on a DHA-enriched diet.	[138]
Dendritic cells	PUFAs (AA and EPA) inhibit LPS-induced maturation and cytokine production in human monocyte-derived dendritic cells. They decrease the expression of surface molecules (CD80, CD86, MHC class II) and reduce TNF-α and IL-12 production without affecting NF-κB activation.	[139]
Neutrophils (mouse model)	Fish oil increased a specific subpopulation of neutrophils in blood and total neutrophils in the peritoneum following endotoxin-induced inflammation. Enhanced neutrophil migration was observed late in the inflammatory phase.	[140]
T cells and macrophages (mouse model)	EPA and its metabolite 5-HEPE enhance macrophage-mediated Treg induction via GPR119 and GPR120, increasing Treg numbers and antiinflammatory markers in adipose tissue, demonstrating the potential for mitigating obesity-related inflammation.	[141]

(Continues)

TABLE 3 | (Continued)

In vitro studies		
Cell type	**Outcomes**	**References**
T cells (rat model)	Diets high in n-3 PUFA (menhaden oil) reduce T cell proliferation and IL-2 receptor expression in the spleen and thymus, suggesting immunosuppressive properties beneficial for treating conditions with inappropriate T cell activation.	[142]
T cells (mouse model)	Endogenous n-3 PUFAs in fat-1 transgenic mice protect against T cell-mediated hepatitis by enhancing autophagy, reducing T cell activation, Th1 differentiation, and proinflammatory cytokine production.	[143]
T cells (mouse model)	Dietary ω-6/ω-3 PUFA ratios of 2:1 and 4:1 modulate Th/Treg balance, reducing Th1/Th17-associated cytokines and enhancing Treg cells, thus alleviating colonic inflammation in DSS-induced colitis.	[144]
T cells (mouse model)	Fish oil diet with a ω-6/ω-3 PUFA ratio of 2:1 reduces Th1 and Th17 cells, decreases IL-6 and TNF-α levels, and attenuates lung injury in polymicrobial sepsis by enhancing PPAR-γ expression and reducing neutrophil infiltration.	[145]
T cells (mouse model)	Diets enriched with EPA, DHA, or a combination significantly reduced Th17-cell polarization by downregulating IL-17A and RORγt expression, indicating omega-3 PUFAs suppress Th17-mediated inflammation.	[146]
T cells and macrophages (mouse model)	High-fat diets supplemented with fish oil reduce obesity-associated Th17 and Th1 cells, decrease inflammatory cytokine levels, and improve colonic inflammation by modulating the inflammatory gene expression profile.	[147]
T cells (human and mouse models)	Resolvin D1, D2, and Maresin 1 reduce TNF-α and IL-17 production in $CD8^+$ and $CD4^+$ T cells, inhibit Th1 and Th17 differentiation, and promote Treg induction via GPR32 and ALX/FPR2 receptors.	[148]
T cells (mouse model)	n-3 PUFAs, particularly DHA, enhance lipid raft formation, disrupt the localization and phosphorylation of signaling proteins at the immunological synapse, and suppress $CD4^+$ T cell proliferation.	[149]
T cells (mouse model)	n-3 PUFAs, specifically DHA, inhibit mitochondrial translocation to the immunological synapse and modulate calcium signaling, reducing $CD4^+$ T cell activation and proliferation.	[150]
T cells (mouse model)	DHA suppresses T cell PKCθ lipid raft recruitment and IL-2 production, reducing T cell activation and proliferation by altering membrane lipid composition and signaling pathways.	[151]
B1 and B2 cells (mouse model)	Fish oil increased the number of peritoneal B1 cells and serum IgM antibodies but did not affect B2 cell response or IgG levels. Enhanced B1 cell response suggests better protection against secondary infection and improved homeostasis following antigenic challenge.	[152]
B cells (mouse model)	EPA-enriched fish oil (EFO) increased microdomain clustering, decreased MHCII expression, and reduced IL-6 production, while DHA-enriched fish oil (DFO) and menhaden oil (MO) decreased clustering, increased CD40 expression, and enhanced cytokine secretion.	[153]

3.4 | Immunoregulatory Effects of Omega-3

In addition, omega-3 fatty acids have antiinflammatory and anticancer properties also by their action into downregulated proinflammatory biomechanisms and carcinogenic genes, for example, cyclooxygenase-2 (COX-2) and upregulated apoptotic factors, that is, caspases in colon carcinoma cells, demonstrating a significant potential for cancer therapeutic use [189, 190]. They also mediate protective effects on cardiovascular health by suppressing the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, leading to decreased transcriptional activation of proinflammatory genes in endothelial cell activation which, respectively, would reduce the risk of atherosclerosis and other cardiometabolic diseases [80, 191, 192]. Furthermore, in regard to neurological contexts, omega-3 fatty acids can also sustain brain health by activating a range of genes responsive for synaptic plasticity and neuroprotection, promoting cognitive functions, and potentially exerting a neuroprotection effect against neurodegenerative diseases [193, 194]. When taken together, the multiple pathways through which omega-3 fatty acids can influence gene transcription emphasize the importance of these nutrients as regulators of gene expression and potentially important dietary intervention agents for health promotion and disease prevention.

TABLE 4 | The effects of omega-3 fatty acids and their metabolites on immune cells in human.

Cell type	Sample size/duration	Intervention	Control	Outcomes	References
Monocytes	27/14 days	4 g/day MAT9001 (EPA + DPA)	EPA ethyl esters (EPA-EE)	MAT9001 and EPA-EE reduced fasting TG levels, decreased lipid accumulation in classical and intermediate monocytes, and reduced CD11c and CD36 levels on monocyte subsets. MAT9001 was more effective than EPA-EE in reducing postprandial TG levels and lipid content in monocytes.	[158]
T lymphocytes, monocytes, neutrophils	42/4 weeks	EPA (4.7 g/day) or DHA (4.9 g/day)	Placebo (olive oil)	DHA decreased T lymphocyte activation (CD69 expression). Neither EPA nor DHA significantly affected monocyte or neutrophil phagocytosis, cytokine production, or adhesion molecule expression.	[154]
Neutrophils and monocytes	8/10 weeks	SuperEPA (9.4 g EPA, 5 g DHA) daily	There was no control	EPA and DHA supplementation significantly decreased neutrophil chemotaxis and IP3 formation, indicating suppression of signal transduction and inflammatory response.	[95]
Peripheral blood mononuclear cells (PBMCs)	11/120 days	6 g DHA per day	Basal diet (no DHA)	DHA supplementation did not alter lymphocyte proliferation but significantly decreased the number of circulating white blood cells, primarily due to a reduction in granulocytes.	[155]
T and B cells	6/6 weeks	2.4 g EPA/day from fish oil	In vivo (human study)	Fish oil supplementation reduced IL-2 release after PHA and PWM stimulation and decreased serum immunoglobulin levels. It had a mild immunosuppressive effect on T and B cell functions.	[156]
Neutrophils (human)	50/6 weeks	1.1 g marine n-3 PUFA (640 mg EPA, 480 mg DHA)	Olive oil (2 g/day)	PUFA supplementation increased neutrophil content of EPA, DHA, and DPA.	[159]
T cells and natural killer cells (human)	93/12 weeks	EPA-rich oil providing 1.35, 2.7, or 4.05 g/day EPA	Placebo (corn oil)	EPA supplementation increased IL-4 production but had limited effects on T cell proliferation and NK cell activity in healthy young males, suggesting minimal impact on overall immune function.	[160]
Peripheral blood mononuclear cells (PBMCs), B cells	23/28–30 days	2 g/day marine oil supplement enriched with 14-HDHA, 17-HDHA, and 18-HEPE	There was no control	The intervention increased plasma levels of specific SPMs (e.g., Resolvin E1) and select HDHAs. However, no significant changes were observed in the abundance of immune cells. Ex vivo B cell IgG production was reduced post-supplementation, suggesting a potential immunomodulatory effect.	[161]

(Continues)

TABLE 4 | (Continued)

Cell type	Sample size/duration	Intervention	Control	Outcomes	References
T-helper cells (Th1/Th2)	120/8 weeks	Omega-3 fatty acids (1200 mg/day)	Placebo (soybean oil)	Omega-3 supplementation was found to modulate the Th1/Th2 polarization index, favoring a shift toward a more balanced Th1/Th2 ratio in individuals with high PM2.5 exposure.	[162]
$CD3^+$ T lymphocytes	31/8 weeks	450 mg/day of EPA + DHA from transgenic Camelina sativa oil (tCSO) or fish oil (FO)	There was no control	Both tCSO and FO resulted in comparable incorporation of EPA and DHA into PBMCs. FO induced more upregulated transcripts in pathways associated with immune function and cell proliferation.	[163]
T helper cells (Th17, Treg)	40/3 weeks	n-3 PUFA-enriched hen eggs (~1053 mg/day)	Regular hen eggs (~249 mg/day n-3 PUFAs)	n-3 PUFA supplementation led to a significant increase in serum levels of antiinflammatory prostanoids and proresolving oxylipins, and decreased IL-6 secretion by T helper cells. Additionally, a significant reduction in peripheral Th17 cell frequency and Treg cells was observed in both groups, but the n-3 PUFA group showed a more pronounced antiinflammatory shift.	[164]
Lymphocytes (T cells, B cells)	101/14 days	Omega-3 supplementation (1000 mg/day, 400 mg EPA + 200 mg DHA)	Control group without omega-3 supplementation	Lymphocyte count increased marginally in the omega-3 group compared to the control group.	[165]
Treg cells ($CD4^+CD45RA^+$ $Foxp3^+$, $CD4^+CD45RA^-$ $Foxp3^{++}$)	88/20 weeks	Omega-3 PUFA supplementation + *L. reuteri*	Placebo	The study found a significant reduction in activated ($CD4^+CD45RA^-Foxp3^{++}$) and resting ($CD4^+CD45RA^+Foxp3^+$) Treg cells in the *L. reuteri* group compared to the placebo group after delivery. No significant effects were observed in the omega-3 group.	[166]
$CD4^+$ T-cells, $CD8^+$ T-cells, IL-6	69/12 weeks	Omega-3 supplementation (3 g/day: 1.8 g EPA, 1.2 g DHA)	Placebo (safflower oil, 44.8 mg/day)	Omega-3 supplementation significantly decreased IL-6 levels (−0.78 pg/mL) compared to an increase in the placebo group (+3.2 pg/mL; $p = 0.04$). There was also an increase in $CD8^+$ T-cell counts in the omega-3 group, particularly in Kaposi's sarcoma patients (+60 cells/mm^3), though not statistically significant ($p = 0.11$).	[167]
Leukocytes (various subtypes)	24/12 weeks	Omega-3 PUFA supplementation (2.7 g/day EPA and DHA)	Corn oil (placebo)	Omega-3 supplementation led to the downregulation of proinflammatory genes (e.g., IL-1, TNF-α) and upregulation of immune response genes.	[168]

(Continues)

TABLE 4 | (Continued)

Cell type	Sample size/duration	Intervention	Control	Outcomes	References
$CD4^+$ T lymphocytes, $CD8^+$ T lymphocytes, hsCRP	37/30 days	EPA and DHA supplementation (2 g/day)	Placebo (mineral oil)	EPA and DHA supplementation maintained the levels of $CD4^+$ T lymphocytes and hsCRP, whereas the placebo group showed a significant decrease in $CD4^+$ T cells and an increase in hsCRP, suggesting a protective effect on immune function and inflammation.	[169]
Neutrophils	64/8 weeks	Fish oil supplementation (2.9 g/day n-3 LCPUFA)	Olive oil (control)	Fish oil supplementation increased oxidative burst in neutrophils. The effect was associated with the DHA content in PBMCs, suggesting a dose–response relationship.	[170]
Lymphocytes, monocytes	8/8 weeks	DHA supplementation (200–1600 mg/day)	Baseline (presupplementation)	DHA intake increased IL-2 mRNA expression in lymphocytes dose-dependently, indicating enhanced lymphocyte activability. It also increased monocyte resistance to oxidized LDL-induced apoptosis, suggesting a protective effect against atherosclerosis.	[171]
Peripheral blood mononuclear cells (PBMCs)	111/26 weeks	High-dose EPA + DHA (1.8 g/day)	High-oleic acid sunflower oil (HOSF)	High-dose EPA + DHA significantly altered the gene expression profile of PBMCs, decreasing the expression of genes involved in inflammation, atherosclerosis, and oxidative stress pathways. These changes suggest an antiinflammatory and antiatherogenic effect.	[172]
White blood cells (WBCs)	12/1 week	Fish oil-enriched high-protein medical food (2.4 g EPA, 1.2 g DHA/day)	None	Rapid incorporation of EPA into WBC phospholipids, increasing from 0.5% to 2.8% within 1 week. The intervention also increased proinflammatory cytokine production (IL-1β, IL-6, IL-8, TNF-α, IFN-γ) in LPS-stimulated whole blood cultures, indicating enhanced immune responsiveness.	[173]
Neutrophils, monocytes, lymphocytes	150/6 months	Flaxseed oil (4.5 or 9.5 g ALA/day) or fish oil (0.77 or 1.7 g EPA + DHA/day)	Placebo (no additional n-3 PUFAs)	The interventions did not alter immune cell functions such as phagocytosis, oxidative burst, lymphocyte proliferation, cytokine production, or delayed-type hypersensitivity response. However, the fatty acid composition of PBMC phospholipids was significantly altered in the groups receiving higher intakes of ALA or EPA + DHA.	[174]

(Continues)

TABLE 4 | (Continued)

Cell type	Sample size/duration	Intervention	Control	Outcomes	References
Neutrophils, monocytes, T lymphocytes	42/4 weeks	EPA-rich oil (4.7 g/day) or DHA-rich oil (4.9 g/day)	Placebo (olive oil)	DHA supplementation decreased T lymphocyte activation (CD69 expression), while EPA had no significant effect. Neither oil significantly affected monocyte or neutrophil phagocytosis, cytokine production, or adhesion molecule expression.	[154]
Neutrophils, monocytes	100 young and 69 older men (12 weeks)	EPA-rich oil (1.35, 2.7, or 4.05 g/day)	Placebo (corn oil)	EPA was incorporated dose-dependently into plasma and mononuclear cell (MNC) phospholipids. In older men, higher doses of EPA led to a significant decrease in neutrophil respiratory burst. No significant changes were observed in neutrophil or monocyte phagocytosis or cytokine production in either age group.	[175]
T-lymphocytes, natural Killer cells	100/12 weeks	EPA-rich oil (1.35, 2.7, or 4.05 g/day)	Placebo (corn oil)	EPA supplementation did not significantly alter T-lymphocyte or NK cell numbers or functions. T-lymphocyte proliferation and cytokine production (IL-2, IFN-γ, IL-10) were unaffected, but there was a dose-dependent increase in IL-4 production. NK cell activity showed a slight increase at low effector-to-target ratios but was otherwise unaffected.	[160]
Neutrophils, monocytes, lymphocytes	10/2 months	DHA-rich fish oil supplementation (3 g/day)	Baseline (presupplementation)	DHA-rich fish oil significantly increased the n-3/n-6 ratio in leukocytes, enhancing phagocytic activity in neutrophils (62%) and monocytes (145%), and increasing neutrophil chemotaxis by 128%. There was also an increase in the production of reactive oxygen species by neutrophils and lymphocyte proliferation. Lymphocyte cytokine production (IL-10, IFN-γ, TNF-α) was elevated. Gene expression analysis showed upregulation of 6 genes and downregulation of 71 genes related to signaling pathways.	[157]
Neutrophils, mononuclear leukocytes (MNL)	50/12 weeks	DHA-rich tuna fish oil (2 g n-3 PUFA/day) + exercise	Sunflower oil (6 g/day) + no exercise	DHA-rich fish oil significantly reduced superoxide production by neutrophils but did not enhance other neutrophil functions.	[176]

(Continues)

TABLE 4 | (Continued)

Cell type	Sample size/duration	Intervention	Control	Outcomes	References
Neutrophils, monocytes, lymphocytes	30/2 weeks	Antiinflammatory PUFA blend (ALA, EPA, STA, GLA)	Proinflammatory PUFA blend (AA)	Antiinflammatory PUFA supplementation increased ALA and EPA in plasma and erythrocytes. It also decreased the production of proinflammatory lipid mediators (PGE1, LTB4) after LPS stimulation, without affecting IL-8 or TNF-α. The proinflammatory blend increased PGE2 and IL-10, showing contrasting effects on the immune response.	[177]
T cells (CD25, CD80), B cells, macrophages (CD54)	37 Children/7 months	LCPUFA supplementation (AA: 20–30 mg/day, DHA: 14–21 mg/day)	Placebo	LCPUFA supplementation led to a reduction in $CD8^+$ T cells expressing CD25 and CD80, and a decrease in $CD14^+$ macrophages after stimulation.	[178]
Plasma and immune cells (LPS-stimulated)	12/12 weeks	DHA supplementation (1076 mg/day, free of EPA)	Baseline (presupplementation)	DHA supplementation significantly increased plasma levels of DHA-derived oxylipins (HDHAs, EpDPEs, DiHDPEs) up to 600% in a time-dependent manner. It reduced the formation of AA-derived eicosanoids (TXB2, PGB2, 12-HETE) in LPS-stimulated immune cells while increasing the production of DHA and EPA-derived 12-LOX metabolites (12-HEPE, 14-HDHA).	[179]
Abstract Plasma, platelets, neutrophils, monocytes, T- and B-lymphocytes	8 Male volunteers/12 weeks	Fish oil supplementation (10–15 g/day, providing 1.4–4.2 g EPA/day)	Baseline (presupplementation)	EPA levels increased significantly in the phospholipids of all measured cells by week 2, with no further increase through week 12. Arachidonic acid levels decreased significantly in plasma, platelets, neutrophils, and T- and B-lymphocytes by week 12. The uptake of EPA occurs by phospholipid exchange into mature cells rather than during cell genesis.	[180]
Monocytes	12 Adults/21 days	Fish oil supplementation (n-3 PUFA-rich)	No supplementation	Fish oil supplementation significantly reduced the intensity of expression of MHC class II molecules (HLA-DR, -DP, -DQ), intercellular adhesion molecule-1 (ICAM-1), and leukocyte-function-associated antigen-1 (LFA-1) on monocytes. After IFN-γ stimulation, monocytes from the fish oil group showed reduced expression of HLA-DR and -DP molecules, and a decrease in the percentage of monocytes expressing these molecules. No significant changes were observed in the control group.	[181]

(Continues)

TABLE 4 | (Continued)

Cell type	Sample size/duration	Intervention	Control	Outcomes	References
Monocytes	58/7 weeks	EPA supplementation (3.8 g/day) or DHA supplementation (3.6 g/day)	Corn oil supplementation (placebo)	Monocytes maintained their phagocytic ability and respiratory burst activity after EPA and DHA supplementation.	[182]
White blood cells, lymphocytes, granulocytes	11 Men/120 days	DHA supplementation (6 g/day)	Baseline diet (no DHA supplementation)	DHA supplementation led to a significant decrease in the total number of circulating white blood cells, primarily due to a reduction in granulocyte numbers. The percentage of lymphocytes in white blood cells increased, but their absolute numbers remained unchanged. There were no significant changes in lymphocyte proliferation, delayed hypersensitivity skin response, or the production of IL-2 by T cells.	[155]
Peripheral blood mononuclear cells (PBMNCs), natural killer cells	11 Men/120 days	DHA supplementation (6 g/day)	Baseline diet (no DHA supplementation)	DHA supplementation significantly increased DHA concentration in PBMNC lipids and decreased arachidonic acid concentration. It also reduced the production of prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) by 60%–75%. Natural killer cell activity and the secretion of IL-1β and TNF-α were significantly reduced. B-cell functions and T-cell functions were not affected.	[183]
Peripheral blood mononuclear cells (PBMCs), plasma phospholipids	8/12 weeks + 8-week washout	Fish oil supplementation (3.2 g EPA + DHA/day, 205 mg α-tocopherol/day)	Placebo oil (coconut/soybean mix), olive oil, safflower oil, evening primrose oil	Fish oil supplementation significantly increased EPA and DHA levels in plasma phospholipids and PBMCs, with a corresponding decrease in arachidonic acid. Plasma α-tocopherol levels were elevated, but there were no changes in PBMC functions, including lymphocyte proliferation, NK cell activity, cytokine production, or expression of adhesion molecules. The lack of functional changes may be attributed to the level of α-tocopherol in the supplements.	[184]
Natural killer cells (NK cells)	8/12 weeks + 4-week washout	EPA + DHA supplementation (1 g/day, 720 mg EPA + 280 mg DHA)	Placebo oil (palm + sunflower oil), ALA, GLA, AA, DHA	EPA + DHA supplementation caused a significant reduction (mean decline: 48%) in NK cell activity, which was fully reversed after a 4-week washout period. No significant changes in NK cell activity were observed with ALA, GLA, AA, or DHA supplementation. The fatty acid composition of plasma phospholipids changed significantly in the GLA, AA, DHA, and fish oil groups.	[185]

(Continues)

TABLE 4 | (Continued)

Cell type	Sample size/duration	Intervention	Control	Outcomes	References
T lymphocytes	8/12 weeks + 4-week washout	GLA supplementation (770 mg/day) or fish oil supplementation (1 g EPA + DHA/day)	Placebo oil (palm + sunflower oil), ALNA, ARA, DHA	GLA and fish oil supplementation caused a significant decrease (up to 65%) in mitogen-stimulated lymphocyte proliferation, which was partially reversed after a 4-week washout. There were no significant changes in IL-2 or IFN-γ production, or in the number or proportion of T or B lymphocytes, helper or cytotoxic T lymphocytes, or memory helper T lymphocytes in the circulation.	[186]
Lymphocytes, cytosolic phosphodiesterase (PDE)	20/6 weeks	Marine oil supplementation (600 mg/day, providing 150 mg DHA + 30 mg EPA)	Placebo group (600 mg sunflower oil/day)	The marine oil group showed a significant decrease in lymphocyte proliferation in response to mitogens, accompanied by a decrease in cytosolic PDE activity, a significant increase in particulate PDE activity, and a slight increase in intracellular cyclic nucleotide levels.	[187]

Abbreviations: ALA, alpha-linolenic acid; CD, cluster of differentiation; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; IFN-γ, interferon gamma; IL, interleukin; PUFA, polyunsaturated fatty acid; SPM, specialized proresolving lipid mediator; TNF-α, tumor necrosis factor-alpha.

Omega-3 PUFAs exert their antiinflammatory effect through a number of mechanisms, including the regulation of expression and activity of various inflammatory mediators and cytokines. EPA and DHA decrease levels of proinflammatory eicosanoids, cytokines, and ROS due to reduced action on inflammatory pathways. These effects occur by changing the composition of cell membranes and by reducing the production of proinflammatory mediators [189, 195]. In addition, the incorporation of these fatty acids into cell membranes within different immune cell lines has been demonstrated to affect the function and response of T cells, B cells, and macrophages. Disruption of this interaction results in an attenuated inflammatory response, with potential implications for the treatment of certain chronic inflammatory and autoimmune conditions [75, 76, 196]. Omega-3 fatty acids, on the other hand, are also precursors for a variety of specialized proresolving lipid mediators such as resolvins and protectins, which play a critical role in the resolution of inflammation and restoration of tissue homeostasis [197, 198].

4 | Inflammation and Omega-3

Inflammation serves as a critical physiological response integral to the body's defense system, facilitating the repair of damaged tissues and the eradication of pathogens. However, chronic inflammation is implicated in the pathogenesis of numerous diseases, highlighting the importance of precise regulatory mechanisms in health maintenance [199, 200]. Omega-3 fatty acids, particularly EPA and DHA, have been gaining considerable scientific interest for their potent antiinflammatory properties. These fatty acids modulate inflammatory processes by altering the phospholipid composition of cell membranes, which in turn influences the production of eicosanoids-key mediators of inflammation. Furthermore, EPA and DHA modulate several signaling pathways, thereby exerting a comprehensive effect on the inflammatory response, and offering potential therapeutic benefits in the prevention and management of chronic inflammatory conditions [189, 195].

4.1 | Pro- and Antiinflammatory Eicosanoids: Modulatory Role of Omega-3 Fatty Acids

Although n-3 fatty acids like EPA and DHA are widely recognized for their antiinflammatory actions, they can also give rise to certain proinflammatory eicosanoids, including prostaglandins (PGs), leukotrienes (LTs), and thromboxanes (TXs). This occurs through enzymatic pathways similar to those of n-6 fatty acids. However, n-3-derived eicosanoids are markedly less potent in promoting inflammation compared to those from n-6 fatty acids, such as AA, which is known to generate highly proinflammatory compounds [195, 201]. For example, EPA-derived eicosanoids include prostaglandin E3 (PGE3) and LT B5 (LTB5), which exhibit a relatively mild proinflammatory effect. Studies indicate that PGE3, though capable of eliciting an inflammatory response, is far less potent than prostaglandin E2 (PGE2, produced from AA), which is a major mediator in acute inflammation, promoting vasodilation, pain, and fever [202, 203]. Similarly, LTB5, another EPA metabolite, competes with LTB4 (an AA metabolite) at LT receptors, but demonstrates significantly reduced efficacy in recruiting neutrophils and activating leukocytes [204]. These differences highlight the unique modulatory role of n-3 fatty acids, whereby their metabolites allow a controlled inflammatory

TABLE 5 | Comparative Effects of EPA and DHA on Inflammation and Immune Function.

Eicosapentaenoic acid (EPA) (C20:5, n-3)	Docosahexaenoic acid (DHA) (C22:6, n-3)
Common effects	
↓ Proinflammatory cytokines (TNF-α, IL-1β)	↑ Membrane fluidity
↑ Antiinflammatory signaling	Supports receptor function in cell signaling
Immune cells: Enhances monocyte and neutrophil response	Gene regulation: Nuclear receptor activation and epigenetic modifications
Specialized mediators	
E-series resolvins (promote inflammation resolution)	D-series resolvins, protectins, and maresins (inflammation resolution and neuroprotection)

Abbreviations: IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha.

response without the high intensity typically associated with n-6-derived eicosanoids.

The mechanisms behind these varying potencies are partly due to the competition between n-3 and n-6 fatty acids for the same enzymatic pathways, such as cyclooxygenase (COX) and lipoxygenase (LOX) enzymes [189]. EPA and DHA can inhibit the formation of highly inflammatory AA metabolites by acting as alternative substrates for these enzymes. When EPA or DHA competes for COX and LOX binding, the resulting eicosanoids—PGE3, LTB5, and other n-3 metabolites—are less effective in initiating and sustaining an inflammatory response than their n-6 counterparts [205, 206]. This reduced inflammatory potential of n-3 fatty acid derivatives supports a balanced immune response, one that enables necessary inflammatory reactions but limits the risk of excessive or chronic inflammation. This balance is crucial in preventing the progression from acute to chronic inflammation, which is often associated with n-6-dominated pathways [202, 207]). Therefore, n-3 fatty acids, through their lower-potency eicosanoids, function as modulators of inflammation, promoting immune homeostasis and facilitating a smoother transition from the inflammatory phase to resolution, a process that is often disrupted by high levels of n-6-derived eicosanoids [195, 208].

4.2 | Antiinflammatory Mechanisms of EPA and DHA

EPA and DHA modulate inflammatory responses via several mechanistic pathways (Table 5). They impact the production of crucial inflammatory cytokines, with EPA specifically lowering levels of tumor necrosis factor-alpha (TNF-α) and the TNF-α/IL-10 ratio, thus influencing monocyte inflammatory responses. DHA amplifies this effect by also reducing interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and interleukin-10 (IL-10) expression, indicating its expansive role in suppressing proinflammatory cytokines [209]. Both EPA and DHA inhibit the activation of NF-κB, a key transcription factor in the inflammatory pathway, by influencing its nuclear translocation and transcriptional activity, which results in decreased expression of proinflammatory genes [210]. Furthermore, they activate PPAR-γ, significantly diminishing NF-κB activity and reducing inflammatory gene expression, thereby enhancing their antiinflammatory effects [83]. As precursors to specialized proresolving lipid mediators (SPMs) like resolvins, EPA and DHA transition the lipid mediator profile from proinflammatory to antiinflammatory and proresolving derivatives, significantly curtailing the inflammatory response [112].

4.3 | Specialized Proresolving Mediators (SPMs) Derived From Omega-3: Resolving Inflammation and Promoting Tissue Repair

Specialized proresolving mediators (SPMs) are a unique class of bioactive lipid molecules derived from omega-3 PUFAs, primarily EPA and DHA. These mediators play a fundamental role in controlling and resolving inflammation without compromising the immune system's ability to defend against infection. Unlike traditional antiinflammatory agents, which often suppress immune functions broadly, SPMs facilitate a "pro-resolving" pathway that naturally brings inflammation to an end and aids in tissue recovery, ultimately helping to restore immune homeostasis [206, 208].

SPMs include resolvins, protectins, and maresins, each with distinct properties and roles in immune modulation. Resolvins, for example, are divided into two series based on their origin: E-series (from EPA) and D-series (from DHA). These mediators actively participate in the resolution of inflammation by limiting the recruitment and activity of neutrophils, essential players in acute inflammation. Resolvins inhibit neutrophil chemotaxis and transmigration, thus reducing tissue infiltration and potential damage. Furthermore, they facilitate efferocytosis, the clearance of apoptotic cells by macrophages, allowing inflammation to subside without reactivating the immune system [211]. Resolvins exert these effects through specific receptors such as GPR32 and ALX/FPR2, modulating intracellular signaling pathways that downregulate proinflammatory cytokines like TNF-α and interleukin-1 beta (IL-1β) and inhibit leukocyte trafficking to the inflamed areas. This ultimately reduces further tissue damage and promotes cellular repair, positioning resolvins as vital agents in maintaining inflammatory balance [212].

Protectins, particularly protectin D1 (PD1) derived from DHA, exhibit both antiinflammatory and neuroprotective properties. PD1 inhibits the production of proinflammatory cytokines, including TNF-α and IL-1β, while also reducing leukocyte recruitment to sites of inflammation [206]. Beyond their role in peripheral antiinflammatory responses, protectins have shown potential in protecting neural tissues in models of neurodegenerative diseases. This neuroprotective function is essential in limiting neuroinflammation and underscores the therapeutic possibilities of protectins for diseases where neural integrity is at risk [213].

Maresins, short for "macrophage mediators in resolving inflammation," represent another family of DHA-derived SPMs. Maresin 1 (MaR1), a prominent member of this family, promotes the resolution phase of inflammation by enhancing macrophage-

mediated phagocytosis of apoptotic cells and debris, a critical step for restoring tissue architecture after an inflammatory response [214]. MaR1 also reduces neutrophil infiltration at sites of inflammation and modulates the expression of proresolving receptors, which are vital for wound healing and maintaining tissue integrity. This multifaceted role not only halts the initial inflammatory response but also fosters a tissue environment conducive to repair, preventing the progression to chronic inflammation [212]. In summary, resolvins, protectins, and maresins collectively facilitate the resolution of inflammation by orchestrating immune cell responses and enabling tissue repair. Their biosynthesis from EPA and DHA underscores the importance of omega-3 fatty acids in maintaining immune equilibrium and preventing the shift from acute to chronic inflammation [208, 211]. Given their dual role in inflammation resolution and tissue regeneration, SPMs hold promise as therapeutic targets for chronic inflammatory diseases where conventional antiinflammatory approaches may be insufficient.

4.4 | Clinical Evidence Supporting Omega-3's Role in Immune Modulation

Clinical studies have demonstrated the benefits of omega-3 fatty acids in various inflammatory and autoimmune conditions [192, 209, 215]. A study by Naeini et al. (2019) investigated the impact of DHA-enriched fish oil on PPAR-γ activity and the gene expression of NF-κB and p53 in patients with Type 2 diabetes mellitus (T2DM) [192]. It was found that DHA supplementation significantly increased PPAR-γ activity in peripheral blook mononuclear cells (PBMCs), although changes in NF-κB and p53 expression were not statistically significant [192]. So et al. (2020) conducted a study to explore the independent effects of EPA and DHA on monocyte inflammatory responses (209). Their findings demonstrated that EPA and DHA differentially modulate cytokine expression, with DHA reducing the expression of TNF-α, IL6, and MCP1 more extensively than EPA. This study evaluates the distinct roles that these fatty acids play in modulating immune responses through specialized proresolving lipid mediators [209]. In the ComparED study, Vors et al. [215] assessed the effects of EPA and DHA on inflammatory gene expression in individuals at risk for cardiometabolic diseases. This study investigates the antiinflammatory effects of EPA and DHA on gene expression in immune cells of individuals at risk for cardiometabolic diseases through a randomized, double-blind crossover trial involving 154 participants. Subjects underwent three 10-week supplementation phases with EPA, DHA, and corn oil, separated by 9-week washouts. No significant differences were found between the effects of EPA and DHA on the genes studied; however, both supplements similarly altered certain antiinflammatory and proinflammatory gene expressions. Overall, EPA and DHA consistently modulated antiinflammatory gene expression more than proinflammatory gene expression in at-risk individuals. Both EPA and DHA were found to modulate the expression of inflammation-related genes, similarly, suggesting their potential utility in the management of chronic inflammation conditions [215]. An umbrella meta-analysis of 32 prior meta-analyses to evaluate the effects of omega-3 PUFAs on inflammatory biomarkers in adults with varying health conditions. The research revealed significant reductions in serum C-reactive protein (CRP), TNF-α, and IL-6 following n-3 PUFA supplementation [216]. Overall, omega-3 fatty acids play a significant role in regulating inflammation and immune responses, offering therapeutic potential in the management of chronic inflammatory and autoimmune diseases.

5 | The Impact of Climate Change on The Omega-3 Content of Food

Recent reports highlight the impact of climate change on the omega-3 content of foods [217–219]. K. Tan, Zhang, and Zheng (2022) suggested three possible ways through which climate change might be lowering the amount of naturally occurring omega-3 fatty acids in grazing food webs: (1) by decreasing the total biomass of phytoplankton (the main producers of omega-3 PUFAs) and altering the composition of plankton communities toward smaller species, thereby decreasing the biomass of higher trophic level animals; (2) by decreasing the quality ratio (omega-3:omega-6) and/or content of all marine organisms; and (3) by decreasing the efficiency with which omega-3 fatty acids are transferred within the grazing food webs [218]. Bivalves are known to be one of the main sources of omega-3 fatty acids. In the fatty acid profiles of various bivalve species from different regions and time periods (until 2020), researchers found that global warming negatively affects the lipid content and quality of temperate bivalves the most (reduction in PUFA/saturated fatty acid, EPA + DHA, and omega-3/omega-6), while its impact is relatively smaller on bivalves in other regions [217]. The impacts of climate change on the omega-3 content of food are reported to have drastic impacts on countries where the diet of the community mostly relies on fish and other seafood. Cheung et al. (2023) have shown that the tropical low-income nations that currently rely heavily on nutrients from seafood are expected to have a disproportionate decline in nutritional availability as a result of climate change. Furthermore, nutrient availability is predicted to drop by around 30% by 2100 at 4°C of warming, and by approximately 10% at 1.5–2.0°C of warming [220]. Golden et al. (2016) have already calculated the decline in fish and reported that this will eventually result in a higher burden of malnutrition in many developing countries where malnutrition is already a pressing issue and most children will be affected. These results show the importance of nutritional security in vulnerable countries [221].

6 | Conclusion and Recommendations

Omega-3 fatty acids, specifically EPA and DHA, have a significant impact on the immune system by influencing cell membrane fluidity, signaling pathways, and gene expression. Research has demonstrated that adding these fatty acids to the diet can improve immune responses and help resolve inflammation while maintaining immunological balance. As the relationship between diet and gene expression gains more recognition, there is a huge opportunity for personalized dietary methods that might optimize immune function. Further study in nutrigenomics is crucial to fully understand the complexities of how omega-3 fatty acids affect immune health and to apply these discoveries to practical dietary recommendations that can have a positive impact on global public health. The current examination of the gene–diet relationship highlights the importance of personalized

nutritional approaches, which could result in more effective prevention of diseases and promotion of health.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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