Chapter

Modulatory Potentials of n-3 Polyunsaturated Fatty Acids in Inflammatory Diseases

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Abstract

Inflammatory diseases (bronchitis, irritable bowel diseases, psoriasis, chronic obstructive pulmonary disease, rheumatoid arthritis, conjunctivitis, hepatitis, rhinitis, etc.) are increasingly becoming the cause of health concern across the world. For both developed and developing countries, the public health cost attached to the management of these complications is increasing each year. Control of diet is one of the critical strategies to improve the therapeutic potentials of clinically proven drugs. Among the dietary factors, bioactive lipids, particularly polyunsaturated fatty acids, elicit essential effects of modulating signaling pathways that could provide a beneficial effect in individuals suffering from various inflammatory complications. Among the polyunsaturated fatty acids, both n-3 and n-6 fatty acids exhibit differential effects, and their dietary ratio plays a significant role in the overall impact in an individual. This is most evident with the fact that the decrease in the n-3 intake in recent times has significantly contributed to the severity of chronic inflammation. The mechanism by which these fatty acids and bioactive unsaponifiable embedded in the dietary oils modulate the critical genes, thereby alter the pathology of inflammatory complications is under study for many decades. In this chapter, the role of polyunsaturated fatty acids and their modulatory effects on some of the significant inflammatory complications are discussed.

Keywords: arthritis, chronic obstructive pulmonary disease, inflammation, irritable bowel diseases, polyunsaturated fatty acids, psoriasis

1. Introduction

Inflammation is a natural phenomenon for healing that occurs through the body's immune response. The cellular reactions remove the threat that may be in the form of a pathogen, damaged cell, irritant, and other foreign particles. Often, they are self-limiting; however, under certain circumstances, they can cause permanent damages to healthy tissues and eventually to the entire organ system. The phenomenon of inflammation is caused by specific lipid-derived and small molecular weight proteins referred to as eicosanoids and cytokines, respectively. The cellular and systemic level of eicosanoids and cytokines, and the relative presence of pro- vs. anti-inflammatory mediators determines overall inflammatory milieu in an individual. Uncontrolled and chronic inflammation triggers

many common conditions and diseases. Bronchitis, conjunctivitis, chronic obstructive pulmonary disease (COPD), hepatitis, irritable bowel disease (IBD), psoriasis, rheumatoid arthritis (RA), and rhinitis are known to have a critical link with eicosanoids productions that eventually leads inflammation [1–8]. Even though effective pharmaceutical interventions are available to treat as well as manage these complications, adjunct therapies involving dietary management is mostly recommended [9, 10]. Nutraceutical intervention in the management of these inflammatory complications is gaining importance due to convenience, safety, and the low-cost attached in it Investigations have pointed out that n-3 polyunsaturated fatty acids (n-3 PUFA) positively alter inflammatory pathways. Their actions aid in reduced levels of eicosanoids (20 carbon lipid-derived molecules) and other inflammatory biomarkers, such as interleukin-1b (IL-1b), IL-6, and tumor necrosis factor-α (TNF- α) in plasma and urine, by serving as secondary messengers or modifying the transcriptional regulation of particular genes involved in inflammation [11]. In contrast, a high intake of dietary n-6 polyunsaturated fatty acids (n-6 PUFA) is associated with increased synthesis of proinflammatory eicosanoids synthesized from arachidonic acid metabolism, which include leukotrienes, lipoxins, thromboxanes, prostaglandins, and hydroxy fatty acids, and suppresses the synthesis of anti-inflammatory eicosanoids derived from EPA and DHA [12].

The modern (mostly western) diet is a poor source of n-3 PUFA, with an abysmal n-3:n-6 fatty acid ratio of 1:15–20, which is in sharp contrast to that found in the diet followed by our ancestors-1:1 [13, 14]. Both n-3 and n-6 PUFA consumed in the diet compete for the same enzymes and also regulate many transcription factors which impact cellular and tissue metabolism, and, a skewed ratio of n-3:n-6 PUFA result in the altered equilibrium in composition and fluidity of cell membrane as well as the functionality of organs [15, 16]. Evidence is accumulating that these physiological changes have led to interactions between constituents of the diet and genes, culminating in the rise of local and systemic inflammation. It is coupled with the disruption of immune/defense mechanism leading to rheumatoid arthritis, chronic obstructive pulmonary disease, irritable bowel diseases, psoriasis, bronchitis, rhinitis, hepatitis, conjunctivitis, etc.

2. Therapeutic potential of polyunsaturated fatty acids in inflammatory diseases

The intervention of cellular functions by bioactive lipids from the diet offers an attractive tool to modify or to prevent many pathophysiological processes of inflammatory diseases including bronchitis, conjunctivitis, COPD, hepatitis, IBD, psoriasis, RA and rhinitis. Dietary n-3 PUFA act via several mechanisms, which they primarily conduct by substituting phospholipid pools containing arachidonic acid (AA) with EPA and DHA. The enhanced physiological levels of EPA and DHA, suppress cyclooxygenase and lipoxygenase and lower synthesis of the inflammatory eicosanoids, thromboxane (TXA2) and leukotriene B4 (LTB4) from 20:4 in platelets and macrophages. Anti-inflammatory effects of n-3 PUFA can also be apart from eicosanoid pathway by affecting the expression pattern of cell surface adhesion molecules which participate in interactions between leukocytes and endothelial cells, thereby facilitating the infiltration of leukocytes into sites of inflammation [17]. Understanding the influence of dietary n-3 PUFA on the modulation of inflammatory complication is hence crucial if they need to be exploited as an adjunct therapy in treating many of these diseases.

2.1 Bronchitis

Chronic bronchitis is associated with high morbidity and mortality worldwide and has a diverse range of associated factors, including occupational, economic, and educational status [18]. The inflammation observed in chronic bronchitis is marked by airway eosinophilia, activated T-lymphocytes, rise in the amount of TNF-α-positive cells and neutrophils in the bronchial mucosa [1]. The advanced stage of the disease also shows similar signs, accompanied by hypertrophy of goblet cells, purulent bronchitis, and dilatation (diffuse or localized). The rise in eosinophils in bronchitis (caused by allergens, chemicals or drugs, etc.) is characterized by asthma and chronic cough and currently treated with anti-inflammatory drugs like inhaled corticosteroids. Although a shortcoming of this treatment is that it is most helpful only in those respiratory illnesses where eosinophils are elevated, and not in other types of bronchitis [19].

Moreover, acute bronchitis which is generally treated with antibiotics has several reported undesired side-effects associated with their use- nausea, vomiting or diarrhea, headaches, skin rash, and vaginitis, apart from population-level harm from antibiotic resistance [20]. Concerning the chronic form of the disease as seen in smokers, etc., rampant use of prophylactic antibiotics does not seem to have a considerable effect [21]. In such a scenario, having an effective treatment option for bronchitis, that eliminates any adverse effects and can always be effective despite widespread and prolonged use, is welcome. Some essential nutrients have proven benefits in this regard. A randomized self-controlled study was done using n-3 PUFA, vitamin C, and Zn supplementation in asthmatic children showed that nutritional intervention could lower the severity of inflammatory diseases. This was confirmed by testing the pulmonary function and inflammatory markers present in the sputum, where a remarkable improvement was seen in results of those on a diet supplemented with n-3 PUFA, vitamin C, and Zn [22]. When n-3 PUFA are considered individually, it was established from a study that daily ingestion of 3 g of n-3 PUFA for a month by atopic patients, showed reduced bronchial hyperactivity and improved responsiveness towards the ultrasonically nebulized distilled water [23]. To validate the connection between dietary fats and bronchitis, the pathophysiology of this condition needs to be addressed. The inflammation is related to altered level in membrane fatty acid composition of erythrocytes and an imbalance in the precursor of a pro to anti-inflammatory eicosanoid ratio [24]. A comparative assessment of the impact of n-3 and n-6 PUFA on respiratory function was done, by supplementation of the diet of asthmatic patients with perilla oil (n-3) or corn oil (n-6). The study revealed that, leucocytes from the corn oil supplemented group generated a greater amount of LTB4 and LTC4 than the perilla oil supplemented group, and the anti-inflammatory benefits in the latter were also reflected through their improved respiratory function parameters of peak expiratory flow (PEF) in the mornings, forced expiratory volume (FEV) and forced vital capacity (FVC) [25]. On deeper investigation of the mechanisms of n-3 fatty acid-mediated actions, it was found that mice exposed to cigarette smoke to mimic lung injury caused by smoke and pulmonary toxicants, on treatment with the resolvin RvD1, exhibited potent anti-inflammatory and resolution of inflammation in the lungs when supplied after the final smoke exposure. The same study also made use of blood monocytes, small airway epithelial cells, and primary human lung fibroblasts, which were treated with cytokine IL-1β or an extract of cigarette smoke along with RvD1 in in vitro. RvD1 inhibits the release of pro-inflammatory mediators by primary human cells in a dose-dependent manner, attenuates neutrophilic lung inflammation and release of pro-inflammatory cytokines, along with the upregulation of the anti-inflammatory cytokine IL-10 [26]. Lipoxins and resolvins serve as

natural agonists in resolution of pulmonary inflammation. Briefly, lipoxins are arachidonic acid derivatives generated via multistep enzymatic reactions mediated by lipoxygenases to produce trihydroxy-tetraene-containing eicosanoids. On the other hand, resolvins are endogenous autacoids, derived from EPA and DHA as E-series (RvE) and D-series (RvD) resolvins, respectively. The intracellular signaling pathways resolvins adopt to bring about their actions, involve NF-Kβ and kinases. Resolvins can control the NF-Kβ signaling pathway, for e.g. RvE1 is an agonist in the signal transduction mechanism to inhibit TNF-α induced activation of NF-Kβ in a concentration-dependent manner. It can also suppress pro-inflammatory LTB4-mediated BLT1 signaling by lowering activation of NF-Kβ. The mechanism of NF-Kβ repression is relevant for resolution of inflammation in pulmonary diseases, as it induces granulocyte apoptosis. With respect to kinases, the pro-inflammatory reactions involved in chronic inflammatory lung diseases, are mainly regulated by phosphatidylinositol 3-kinase (PI3-K) and the MAPK family member extracellular signal regulated kinase (ERK). *In vitro*, RvE1 increases phosphorylation of kinases, which has a protective effect of controlling apoptotic programs in cells. RvE1 also mitigates attenuates inflammatory pain by indirectly inhibiting the ERK signaling pathway [27].

2.2 Irritable bowel disease (IBD)

Inflammatory/irritable bowel disease is a broader term used to describe the disorders that involve the inflammation of the gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) are both related to IBD and result from interactions between gene, environment, and gut microbiota. Crohn's disease is characterized by chronic inflammation which relapses and remits, ultimately affecting the entire gastrointestinal tract, whereas ulcerative colitis inflammation is mostly confined to the colon-rectum junction. The pathogenesis of the disease mostly involves predisposing genetic, environmental, and immunologic factors [28, 29]. More than 200 gene regions have been identified that confer risk for Crohn's disease or ulcerative colitis in the European population [30]. The currently available drugs to treat IBD work by targeting receptors of T-cell activation (e.g., visilizumab, abatacept), prebiotics, probiotics targeting the intestinal flora antibiotics, adhesion molecule blockers (e.g., MLN-02, alicaforsen, natalizumab), cytokines (e.g., interleukin 10) [31]. Despite the advent of new therapeutic agents in recent years, current treatments are modestly successful with notable side effects [32]. Also, epidemiologic studies reported that increased animal fat/n-6 PUFA intake with the prevalence of both CD [33, 34] and UC [35]. Hence it is necessary to understand the role of n-3 PUFA and its metabolites in disease prevention of IBD. The potential role of n-3 PUFA in inflammation has garnered interest in fatty acid profiling in various metabolic and inflammatory diseases. Like other diseases, the inflammatory state in IBD is a result of the eicosanoid pathway with elevated levels of LTB4, LTC4, and thromboxanes (A1 and A2) in the inflamed intestinal mucosa [4]. Many clinical studies conducted with fish oil or EPA supplementation reported the inhibitory effect on inflammatory molecules production [36–38]. Animal model studies are in line with results of clinical studies concluded that n-3 PUFA ameliorated the intestinal inflammation [39–41]. The immunomodulatory and anti-inflammatory effects of n-3 PUFA are reported either directly [42, 43] or indirectly by the generation of PUFA metabolites containing hydroxyl groups i.e. resolvins, hydroxy fatty acids etc. [44]. Although there is a reasonable amount of data available on anti-inflammatory effect of n-3 PUFA, limited reports available in their use on IBD patients; hence deeper research in the aspects of dose, and mechanistic understanding is needed to replace or enhance the effect of currently available drugs along with nutritional intervention.

2.3 Psoriasis

Psoriasis is an inflammatory skin disease, affecting about 2% of the general population, characterized by hyperproliferation and poor differentiation of keratinocytes, increased vascularization of the skin, leukocyte infiltration and fibroblast activation [45]. It is a skin disease considered to be resulting from T-cell-mediated inflammation, wherein the inflammatory reaction is controlled by diet, lifestyle, and environmental cues such as infections and stress. Although the etiology remains unknown, accumulating evidence indicates that cytokines, mainly tumor necrosis factor α (TNF-α), IL-17 and IL-23, play essential roles in the development [6]. In the psoriatic lesions, inflammatory dermal dendritic cells (DCs) produce IL-23 that enhances the production of T cytotoxic 17 cells (Tc17) or IL-17 from T helper 17 cells (Th17) in the skin, leading to epithelial hyperplasia and inflammatory cell infiltration [46]. A documented and conclusive cure for psoriasis does not exist, some of the commonly used treatments to reduce the severity of disease and lessen the impact are phototherapy, topical and systemic therapies in moderate-to-severe psoriasis and drugs are corticosteroids, methotrexate, tar, cyclosporine, and emollients. Nevertheless, almost all the mentioned treatments are accompanied by major adverse effects [47]. Among nutritional components regulating the pathophysiology of psoriasis, PUFAs proved to be promising in the treatment of many skin diseases as safe, including psoriasis [48]. Calorie restriction or weight loss may also influence the severity of the disease. However randomized control trial study conducted by Guida et al. concluded that calorie restriction (20 kcal/kg/day) along with n-3 PUFA (2.6 g/day) enriched diet improved the clinical response of immune-modulating drugs in obese psoriatic patients [49]. Many clinical studies have demonstrated that the administration of fish oil or n-3 PUFA ethyl esters in psoriatic animal model/patients ameliorated the degree of skin inflammation [44–48, 50]. However, the reports on the exact mechanism are limited. A recent study conducted by Sawada et al. using metabolite produced by n-3 PUFA such as resolvinE1 (RvE1) in imiquimod (IMQ)-induced murine psoriasis mouse model concluded that RvE1 remarkably suppressed the epidermal hyperplasia and inflammatory cell infiltration in the psoriatic skin. These suppressive effects are due to the antagonistic effect of RvE1 on BLT1 production, a receptor of LTB4 and decrease in mRNA expression of cytokines (IL-17 and IL-23) indicating the novel mechanism of psoriatic pathogenesis and potential of RvE1 as an adjuvant in the psoriatic therapy [51].

2.4 Chronic obstructive pulmonary disease (COPD)

COPD is a chronic inflammatory lung disease triggered by exposure to toxic particles and gases, especially, cigarette smoke. Some of the predominant characteristics of COPD include parenchymal destruction, poorly reversible, persistent airflow limitation, and chronic bronchitis. A COPD patient shows some visible symptoms like cough, chest tightness dyspnoea, excess sputum production, and wheezing [52]. COPD is coordinated by a complex network of inflammatory mediators, such as inflammatory enzymes, lipid mediators (eicosanoids, namely prostanoids and leukotrienes, LTs), interleukins (ILs), and adhesion molecules, which may moderate airway inflammation through chemotactic and autocrine or paracrine effects [3]. Eicosanoids are produced by cells resident in the lung and airways, such as fibroblasts, epithelial cells, myofibroblasts, and smooth muscle cells, also by inflammatory cells that have migrated from the circulation to the airways, such as macrophages, mast cells, neutrophils, platelets, eosinophils, and T-lymphocytes [53]. Activated macrophages release cytokines such as IL-8, IL-6, IL-10, TNF-α, and LTB4, which can attract and activate various inflammatory cells.

Smooth muscle cells, fibroblasts, and myofibroblasts play a key regulatory role in airway remodeling by generating different structural components, such as collagen and proteoglycans [54]. Although the mediators involved in structural remodeling of the bronchial wall remains unknown, chemokines, cytokines, and growth factors are thought to have a crucial role. Observational clinical studies suggest that n-3 PUFA levels in COPD are inversely related to systemic inflammation and directly related to clinical outcomes [55–57]. Interventional studies using n-3 PUFAs alone in COPD do not exist; however, many trials are currently underway, which may generate valuable data in the coming years [58–60]. An animal study in pneumonia model of mice, revealed RvE1 metabolite of n-3 PUFA decreased levels of several pro-inflammatory chemokines and cytokines in the lung, and improved survival [61]. However, currently, there is a paucity of data regarding the potential of n-3 PUFAs to be used therapeutically in COPD. Recent studies, conducted using omega-3 PUFAs in COPD has used nutrient combinations, in a manner that the exact effects of omega-3 PUFAs cannot be elucidated.

2.5 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a low grade chronic inflammatory autoimmune disease affecting the joints and bones. RA and systemic lupus erythematosus (SLE) are multisystem autoimmune diseases featuring the production of a variety of auto-antibodies, and resulting in higher immune-mediated inflammation. Prevalence of RA is known to affect 17.6 million people worldwide [7] with the huge economic burden to mankind. Pathogenesis of RA in early phase focused on auto-antibodies and immune complexes [62], however, the nature of T-cell mediated antigen-specific responses, T-cell-independent cytokine species, and aggressive tumor-like behavior of rheumatoid synovium have also been reported. Immune complex theory strongly suggests increased neutrophils accumulation in synovial fluid results in engulfment of immune complex and release proteolytic enzymes [62]. A better understanding of the intracellular targets that regulate cytokines in RA can potentially lead to new therapeutic interventions. For instance, studies reported activation of NF-κB in the synovium of RA patients [63] and mitogen-activated protein (MAP) kinases are identified as vital regulators of cytokine and metalloproteinase production. The mechanistic approach to currently available drugs is partially understood and mostly targeting the eicosanoid pathway, and reports are scarce about gene targets on CD28, AP-1, and MAP kinases. Investigators have examined the effect of dietary fatty acid supplementation in different autoimmune diseases, and the effects of both n-6 and n-3 PUFA on RA have been reported [64]. Resolvins derived from EPA and DHA are anti-inflammatory and resolve inflammation, serving as important mediators in regulating various homeostatic functions, including gastric mucosal integrity. Kremer and co-workers reported that a dose of 90 mg/kg/day EPA/DHA (3:2 ratio) showed a shorter period to respond than 45 mg/kg/day [65]. Clinical studies have ambiguity in results, few observed reductions in both tender joints by 36% and swollen joint to 38% in patients, whereas the placebo group showed no improvement in these parameters [66]. Fish oil supplementation in women patients showing a decrease in the production of serum nuclear factor-kappa B (Nf-kB) ligand/osteoprotegerin ratio [67]. Cell culture-based investigations have reported that EPA and DHA prevent the proliferation of human T cells and their generation of IL-2 [68]. Animal studies also reported a beneficial effect of marine n-3 PUFA in RA [69, 70]. Finally, supplementation with dietary n-3 PUFA and its ability to inhibit TNF-α and IL-1b synthesis is rational. Considering the emphasis on recommendations to increase dietary n-3 PUFA intake for health benefits, the possible therapeutic potential of fish oil/n-3 PUFA on autoimmune diseases need to be clearly defined.

2.6 Conjunctivitis

Conjunctivitis is an ocular inflammatory condition of the membrane lining the eyelid, which provides a shelter to the open surface of the sclera [71]. It is said to be the most common cause of "red eye," and the infection, either acute or chronic can originate from three different sources, based on which it is commonly classified: viral, allergic, and bacterial conjunctivitis. The type of conjunctivitis may be determined by a diagnostic investigation which takes into account, the patient's age, time of the year, and physical examination findings [72]. Identification of the pathogen which elicits the inflammatory response is necessary to decide on the required treatment module, since some bacterial conjunctivitis forms are self-limiting, while those caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae* demand aggressive antibiotic therapy, and primarily good eyelid hygiene [71]. The visual symptoms of inflammation at the ocular surface, include, lid and conjunctival edema–redness, tearing, extreme itching, and photophobia during the acute phase cause immense discomfort, thereby necessitating treatment [73]. Effective pharmacological cure comprises antihistamines, mast cell stabilizers, and non-steroidal anti-inflammatory drugs [74]. The excess wateriness experienced during conjunctivitis and also early dry eye disease is because of enhanced goblet cell mucin secretion into tears, which otherwise produce a regulated amount of mucins only to protect the eye. This phenomenon is due to the action of inflammatory mediators, cysteinyl leukotrienes LTB4, LTC4, LTD4, and LTE4, and prostaglandin PGD2, which stimulate conjunctival goblet cell mucous secretion. Thus, mitigation of this LTD4 effect can aid in reducing mucin secretion, and this has been achieved previously by the action of Resolvins D1 (RvD1) and E1 (RvE1) [2]. The finding of Dartt and co-workers [2] indicates that lipids including fatty acids or lipid mediators play a role in suppression of systemic inflammation as well as local, such as in the case of inflammatory conjunctivitis. The connection between the quality of fat consumed and conjunctivitis was drawn from the results of a Japanese study, which states that meat intake is directly proportional to the prevalence of rhinoconjunctivitis in young adult Japanese women, while no correlation was seen between fish intake and rhinoconjunctivitis [75]. Though, there are not many reports from similar controlled clinical trials that specifically correlate meat intake with incidence of conjunctivitis, to ascertain such claims. The study does raise questions on the role of fats present in meat that possibly trigger the pathways in inflammation. The true potential of n-3 PUFA as an anti-inflammatory in managing conjunctivitis was elucidated through other detailed investigations of their actions and mechanisms at molecular levels. A primary mode of action is that of the resolvin mediated responses, as mentioned earlier. The process of resolution of inflammation is an active process facilitated by pro-resolution lipid mediators. Not only D-series resolvins RvD1, which are produced in the cornea but also aspirin-triggered RvD1 (ATRvD1) have exhibited regulation of inflammatory responses to histamine in allergic conjunctivitis. The effect is implemented by a cross-talk between two types of G protein-coupled receptors (GPCRs). When RvD1 interacts with its receptor GPR32, it prevents the histamine-stimulated H1 receptor-mediated rise in intracellular Ca^{2+}, thereby blocking H1 receptor-mediated responses. Consequentially, this activates extracellularly regulated–protein kinase (ERK) 1/2 [76]. In addition to resolvins, another class of lipid mediators that can mimic these anti-inflammatory actions in conjunctivitis includes lipoxins, especially, lipoxin A4 that has benefits similar to that of ATRvDI and can activate ALX/FPR2 receptor to regulate conjunctival goblet cell secretion, which is particularly useful in maintaining ocular surface homeostasis, and managing the dry eye syndrome [77]. Another evidence of polyunsaturated fats aiding in the treatment of conjunctivitis emerged on evaluating the impact of the feeding of omega-3 and omega-6 PUFA on human leukocyte antigen-DR (HLA-DR) marker of conjunctival

inflammation in dry eye patients; it was observed that increased intake of both these fatty acids suppressed the expression of HLA-DR [78]. With this, it is evident that dietary supplementation of n-3 PUFA has a modulatory effect on conjunctivitis. Their efficacy has been tested in mammals such as dogs affected with keratoconjunctivitis sicca, where EPA + DHA + antioxidants in defined proportion was used as an adjuvant [79]. Furthermore, their use of topical treatment has also been suggested in the literature. Based on data from animal preliminary human studies, protectins (NPD1) and DHA turn out to be a safe, effective treatment for dry eye through a topical application [80]. Ultimately, investigators have also proposed formulations for active use in therapy, one such patented formulation by Aleo et al. [81], clearly provided the n-3 and n-6 PUFA proportion for creating an ophthalmic composition suitable for ocular inflammation.

2.7 Hepatitis

Hepatitis is the inflammation of the liver with symptoms that generally include right upper abdominal pain, headache, fatigue and malaise, myalgia, altered sense of smell or taste, nausea and vomiting, coryza, photophobia, diarrhea (may have pale stools and dark urine) [5]. Hepatitis treatment can be managed better without any inconveniences, with the help of dietary interventions, which not only limit the progression of hepatitis but can also be used as a novel therapy. Considering the abundant evidence of n-3 PUFA and their anti-inflammatory effect in most liver maladies, including fatty liver disease, cirrhosis, and acute liver failure, their role in immune-mediated liver diseases is not fully exploited. Fatty acids belonging to the n-3 family have been shown to suppress hepatitis via an autophagy-dependent mechanism and are particularly helpful for therapy in autoimmune hepatitis [82]. In this regard, the n-3 PUFA mediators resolvin D1 and E1 can be particularly useful, as they inhibit concanavalin A-induced liver injury and restricting the progression of hepatitis to liver cancer in mice through suppression of NF-kβ/AP-1 activity [83]. The actions of n-3 PUFA were evaluated in a macrophage-dependent acute D-galactosamine/lipopolysaccharide (D-GalN/LPS) hepatitis model in the transgenic fat-1 mice. The findings clearly stated that the n-3 PUFA supplementation dampened the severity of the inflammatory liver injury and histological liver damage in fat-1 mice. The balance in n-6/n-3 PUFA ratio was improved, and levels of serum alanine aminotransferase and TNF-α and IL-1β cytokine production were lowered. The effect was confirmed through the lowered hepatic gene expression of all the pro-inflammatory cytokines, thus proving their anti-inflammatory benefits in the framework of liver inflammation [84]. The most striking feature of n-3 PUFA therapy in HCV was discovered when the efficacy of EPA was evaluated against ribavirin (RBV) associated hemolytic anemia. When EPA was supplemented with the standard combination therapy of peginterferon (PEG-IFN) and ribavirin (RBV), patients receiving EPA, required reduced RBV doses compared to the non-EPA group, and also showed decreased RBV-induced hemolysis, although rates of virological response are yet to be elucidated [85]. Therefore, it is encouraging that EPA can lower dependency on drugs in even such morbid disorders. Some of the other adverse effects of RBV treatment which have been effectively countered by n-3 PUFA include lowering of the impairment of the filterability of erythrocytes of chronic HCV patients in whom erythrocyte filterability was caused due to oxidative membrane damage induced by RBV which led to hemolytic anemia [86]. This finding further ensures the maintenance of the lymphocyte levels and improvement in hemoglobin levels in the patients of PEG-IFN and RBV treatment [87]. Thus, n-3 PUFA and their mediators can be recommended for concurrent administration with the recommended standard interferon and antibiotic therapy, to facilitate recovery, ameliorate adverse effects, and prevent mortalities in chronic cases.

2.8 Rhinitis

Allergic rhinitis (AR) is a highly prevalent heterogeneous disorder, caused by pollens, molds, dust mites, and animal dander, but often goes undiagnosed as a condition of rhinitis. The symptoms of AR, which include sneezing, itching, nasal congestion, and rhinorrhea are mostly IgE mediated and triggered through mucosal infiltration and action on eosinophils, plasma cells, and mast cells, [7]. Some other discomforts experienced by the patients in chronic rhinitis include sinusitis, eustachian-tube dysfunction, sleep disturbances, and forces the patient to breathe through the mouth. AR may not appear as a serious ailment but is clinically relevant as it triggers numerous complications, is a potential risk factor for asthma, deteriorates the quality of life and efficiency at work. The range of pharmaceutical options available to manage a rhinitis episode includes intranasal corticosteroids, which are effective and safe. The most common drug type is that of first-generation antihistamines, but they are well-known to cause sedation, psychomotor retardation, and decreased academic performance. AR is tackled most effectively from its natural history, using immunotherapy by targeting allergens singly [88]. Various dietary factors have been associated with allergic rhinitis, such as dietary antioxidants in vegetables may reduce wheezing symptoms, but fats such as butter and margarine tend to aggravate the symptoms [89]. The exact mechanism by which saturated fats alter airway inflammation has neither been fully understood nor has it received much attention. Yet, reports suggest that accumulation of saturated fatty acids is associated with changes in levels of serum cholesterol and arachidonic acid content in the cell membranes, which together modify the lymphocyte function. These observations and other epidemiological data led to the conclusion that saturated fats aggravate rhinitis, asthma and related conditions [90]. Since saturated fats were implicated in worsening rhinitis, the effect of unsaturated fats on allergic sensitization and allergic rhinitis was also investigated by many researchers. It was found that the presence of unsaturated fatty acids in membranes of red blood cells (RBC) in the form of EPA and the diet as ALA, lower sensitivity and incidence of rhinitis [8, 91]. Fish consumption during pregnancy as well as childhood was associated with a lowered risk of any respiratory illnesses—allergic rhinitis, wheezing or asthma in childhood and later, and long chain n-3 PUFA supplementation was also not related to the risk of postpartum hemorrhages in mothers as well [92, 93]. An insight into the mechanism by which this effect is achieved suggests that n-3 PUFA supplementation during pregnancy boosts levels of placental DHA and specialized pro-resolving lipid mediators (SPM) precursors without aggravating inflammatory gene expression [94]. Also, adjunctive supplementation of fish quickens the effects of routine pharmacotherapy in AR subjects by lowering AR related symptoms and serum levels of Ig E, which is crucial since IL-5 and Ig E are found in higher concentrations in nasal secretion and sputum of AR patients [95]. With such abundant information pointing towards the preventive and prophylactic effects of polyunsaturated fatty acids on the rhinitis, the dietary incorporation of n-3 PUFA, as well as their use as adjuvant therapy for lowering the incidence and severity of a rhinitis episode, can be strongly recommended. These fatty acids have also demonstrated a potential to slow down the progression of chronic rhinitis, thereby improving quality of life and productivity at work.

3. Summary and conclusion

Taken together, findings from in-vitro and in-vivo studies of inflammatory diseases suggest that n-3 PUFA could be potential therapeutic molecules to combat

inflammatory diseases as described in this chapter. The results from mechanistic studies reveal the effects of LC-PUFAs (n-6 and n-3) on human health are highly favorable. However, the relation between the two families of LC-PUFAs on the mechanisms of action needs to be further understood as the presence of these two fatty acids in the diet play a significant effect on the metabolism of other. The inflammatory mechanism involved in the pathogenesis provides novel candidature targets for cost-effective pharmacological and nutraceutical drugs. Despite a better understanding of the beneficial effects of LC-PUFAs, there is a lack of data on attempts to replace or supplement with currently available drugs. Investigating the synergistic potential of various food bioactive molecules with existing clinically proven drugs could be the most effective therapy to ameliorate many of these inflammatory diseases.

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