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TINJAUAN PUSTAKA

Omega-3 for Inflammatory Bowel Disease: Is it worthy? – A Literature Review

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Abstrak

Tujuan: Memberikan pemahaman mengenai potensi terapeutik asam lemak omega-3 dalam penanganan Inflammatory Bowel Disease (IBD). **Metode:** Artikel ini disusun berdasarkan metode tinjauan literatur. Sumber data diperoleh dari artikel-artikel ilmiah yang dipublikasikan di jurnal internasional berbahasa Inggris. Proses pencarian literatur dilakukan melalui mesin pencari Google Scholar dan PubMed. **Hasil:** Inflammatory Bowel Disease (IBD), yang mencakup kondisi seperti Ulcerative Colitis (UC) dan Crohn's Disease (CD), merupakan kelompok gangguan inflamasi kronis yang mempengaruhi saluran pencernaan. Dalam beberapa tahun terakhir, asam lemak omega-3 telah menjadi titik perhatian dalam diskusi IBD, terutama karena sifat anti-inflamasinya. Penelitian epidemiologi menunjukkan bahwa diet kaya omega-3 dapat meningkatkan kemungkinan remisi klinis pada pasien IBD. Sebagai contoh, pasien UC yang mengonsumsi salmon Alaskan dalam jumlah tinggi menunjukkan penurunan marker inflamasi dibandingkan dengan kelompok kontrol. **Kesimpulan:** Bukti saat ini menunjukkan bahwa makanan alami yang kaya omega-3, seperti salmon, memiliki potensi manfaat dalam penanganan Inflammatory Bowel Disease.

Kata kunci: *Omega-3; Inflammatory Bowel Disease; Ulcerative Colitis; Crohn's Disease*

Abstract

Objective: *To provide insights into the therapeutic potential of omega-3 fatty acids in the management of Inflammatory Bowel Disease (IBD).* ***Methode:*** *This article is structured based on a literature review approach. Data sources were derived from scientific articles published in international English-language journals. Literature search processes were conducted using the Google Scholar and PubMed search engines.* ***Results:*** *Inflammatory Bowel Disease (IBD), which includes conditions such as Ulcerative Colitis (UC) and Crohn's Disease (CD), represents a group of chronic inflammatory disorders affecting the gastrointestinal tract. In recent years, omega-3 fatty acids have gained prominence in IBD discussions due to their anti-inflammatory properties. Epidemiological studies indicate that a diet rich in omega-3 can increase the probability of clinical remission in IBD patients. For instance, UC patients consuming high amounts of Alaskan salmon demonstrated decreased inflammatory markers compared to the control group.* ***Conclusion:*** *Current evidence suggests that naturally omega-3-rich foods, like salmon, offer potential benefits in the management of Inflammatory Bowel Disease*.

Keywords: *Omega-3; Inflammatory Bowel Disease; Ulcerative Colitis; Crohn's Disease*

INTRODUCTION

The term "inflammatory bowel diseases" (IBDs) refers to a group of chronic inflammatory conditions of the digestive tract, primarily Crohn's disease and ulcerative colitis.[1] When it's challenging to differentiate between these two conditions, it is classified as indeterminate colitis (IC).[2] IBDs, predominantly consisting of ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders that frequently relapse and affect the digestive system. It is estimated that in the United States, there are over 3 million sufferers, 2.5 million in Europe, and 75,000 in Australia, placing significant pressure on public health systems.[3] Over the past two decades, the incidence of IBD in the Asia-Pacific region has seen a notable increase. IBD is more commonly found among high socioeconomic status groups, non-smokers, oral contraceptive users, and those who consume a low-fiber diet. IBD typically manifests at a young age, around 25-30 years old, with its prevalence being almost equal between men and women. Of all IBD patients involving the colon, about 10% are diagnosed with IC. IBD can lead to a decreased quality of life, increased morbidity, and often results in complications requiring medical and surgical interventions.[2]

Omega-3 polyunsaturated fatty acids (ω-3 PUFAs), which comprise eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been proven in many clinical trials to have positive effects as adjuncts in the treatment of IBD. The consumption of ω3FA is linked to anti-inflammatory qualities that may aid in the healing of the intestinal mucosa and reduce IBD symptoms that are already present. Oily fish (tuna, salmon, mackerel, or sardines), as well as fish or olive oil supplements, can be regularly consumed to ensure adequate intake of important ω3FAs.[4] A recent meta-analysis of observational studies showed that fish consumption was inversely associated with the risk of CD. Moreover, there was a strong inverse association between dietary n-3 PUFAs intake and the risk of UC [5].

According to the scoping review, a higher intake of omega-3 polyunsaturated fatty acids (PUFAs) found in fish was associated with a lower risk of developing Crohn's disease (CD) as they can inhibit the formation of proinflammatory leukotrienes and prostaglandins. Specifically, a higher intake of docosahexaenoic acid (DHA) from the ω-3 series was inversely associated with the development of CD. However, the review did not provide a clear conclusion on whether omega-3 increases or decreases IBD as a whole.[6] Huang et al. (2022) research found that the consumption of omega-3 fatty acids from dietary sources and supplements is linked to a decrease in the levels of inflammatory markers such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α) within the body.[1] The study conducted by Astore et al. (2022) employed the Mendelian Randomization (MR) approach to evaluate the causal relationship between omega-3 fatty acids and Inflammatory Bowel Disease (IBD). The analysis results indicated that elevated levels of circulating omega-3 fatty acids are associated with a reduced risk of IBD. Furthermore, the study identified several Single Nucleotide Polymorphisms (SNPs) that serve as genetic instruments for omega-3 fatty acids. These findings support the view that omega-3 fatty acids play a causal role

in reducing the risk of IBD. Therefore, omega-3 fatty acids can be considered as a potential tool in the prevention and treatment of IBD.[7]

From the data presented in the mentioned research, it is evident that omega-3 can play a significant role in managing inflammation in IBD through its anti-inflammatory properties, modulation of immune response, and influence on gut microbiota. Integrating omega-3 into the nutrition plan of IBD patients can assist in alleviating symptoms, enhancing quality of life, and supporting improved disease management. This article will focus on the role of omega-3 for IBD patients, both in prevention and therapy of IBD.

METHOD

The type of research conducted was a literature review of research articles published internationally. The search was conducted on Google Scholar and PubMed journal databases using the keywords: "Omega-3", "Inflammatory Bowel Disease", "Omega-3 and Inflammatory Bowel Disease", "Omega-3 and IBD", "Omega-3 fatty acids and inflammatory bowel disease", "eicosapentaenoic acid and inflammatory bowel disease," "docosahexaenoic acid and inflammatory bowel disease" and "Effects of omega-3 on IBD".

RESULTS AND DISCUSSION

Omega-3 Polyunsaturated Fatty Acids

Fatty acids (FAs), notably omega 3 and omega 6, hold a significant role in autoimmune diseases and immune cell metabolism. While omega 6 fatty acids are viewed as pro-inflammatory agents, omega 3 fatty acids are perceived as anti-inflammatory compounds.[8–10] Omega-3 polyunsaturated fatty acids (omega-3 PUFAs), encompassing EPA, DHA, and ALA, which are crucial dietary elements, offer potential health advantages for humans. DPA serves as an intermediary between EPA and DHA. EPA and DHA predominantly originate from marine organisms or deep-sea fish, such as salmon, sardines, and mackerel.[4,11]

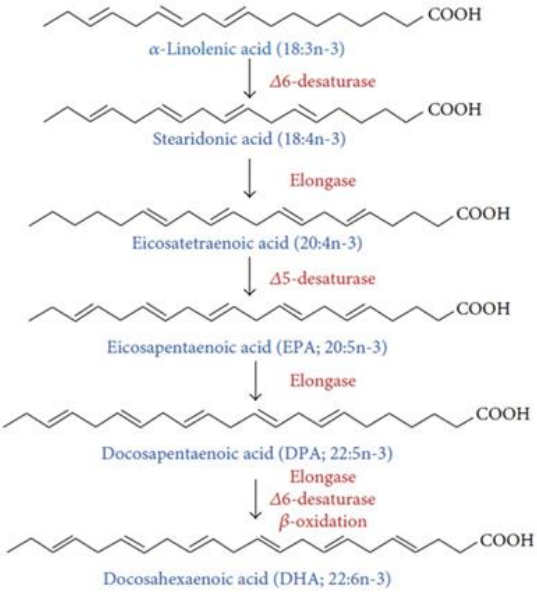

Figure 1. Synthetic pathway of omega-3 polyunsaturated fatty acids.[15]

The human body lacks the ability to synthesize omega-3 PUFAs, necessitating their direct intake through diet or conversion from ingested ALA. Only a small portion of ALA can be transformed into EPA, DPA, or DHA, thereby underscoring the necessity of dietary supplements or pharmaceutical preparations to provide adequate unsaturated fatty acids. In addition to functioning as an energy source for the body, omega-3 PUFAs play a pivotal role in the development of infant brains and in mitigating inflammation.[12] Incorporating omega-3 PUFAs into the diet has the potential to reduce LDL-cholesterol, prevent myocardial infarctions, and lessen the morbidity and mortality associated with cardiovascular diseases.[13] Omega-3 PUFAs are commonly ingested through food or supplements, and their consumption is believed to confer supplementary beneficial effects throughout the entire body, increasing the significance of investigating the impact of omega-3 PUFAs on gut microbes. The abundance of human gut microbes exhibits a positive correlation with the concentration of omega-3 PUFAs in the bloodstream.[14] Currently, omega-3 PUFAs have emerged as a focal point in nutritional biochemistry research and assume pivotal roles in the regulation of gut microbes and gut immunity.[15]

Structure and Molecular Mechanism of Omega-3 Polyunsaturated Fatty Acids

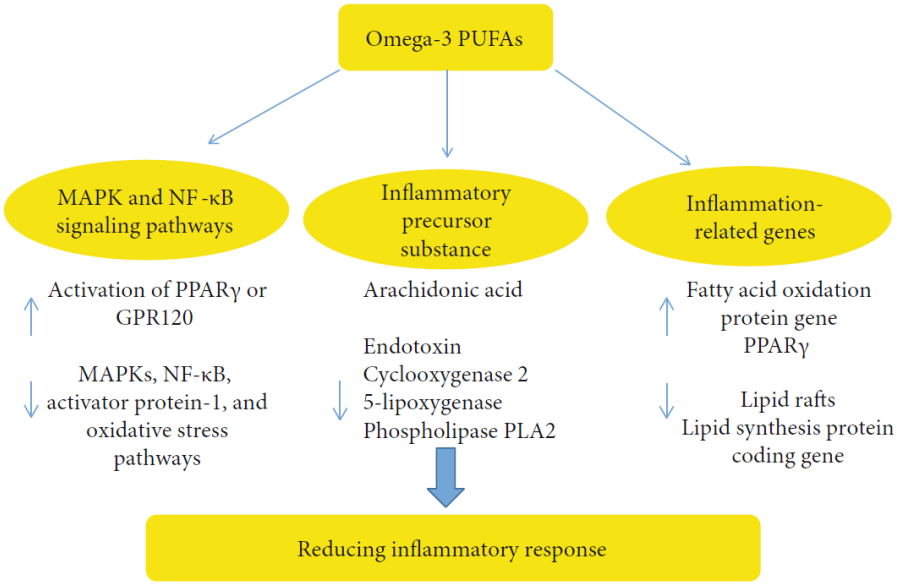

Figure 2. Omega-3 PUFAs reduce inflammation through three main pathways.[15]

Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) are well-known as common dietary supplements, yet their mechanism of action in maintaining intestinal barrier function remains somewhat unclear. This lack of clarity has limited the assessment of their effectiveness. Based on previous research, several of their mechanisms are currently understood. Fundamentally, fatty acids are carbon-chain structures of varying lengths synthesized within the cytoplasm

from a substance called Acetyl-CoA. There are two main families of fatty acids: omega-3 (ω-3) with alpha-linolenic acid (ALA; C18:3n-3) and omega-6 (ω-6) with linoleic acid (LA; C18:2n-6). Both types of fatty acids cannot be produced by the body and must be obtained from food. They are referred to as essential fatty acids. In general, PUFAs are involved in cell signaling, immune system regulation, and forming structural components of cell membrane phospholipids. During infections or injuries, PUFAs are released from the cell membrane to produce lipid-based signaling molecules known as eicosanoids. This family of eicosanoid molecules regulates initiation, development, and resolution stages of the inflammatory response. Due to the higher ω-6/ω-3 PUFAs ratio in animal diets, eicosanoids are largely derived from arachidonic acid (ARA; C20:4n-6) through enzymatic reactions by cyclooxygenase (COX) and lipoxygenase (LOX). The COX pathway (COX-1/-2/-3) produces series 2 prostaglandins (PGs) and thromboxanes (TXBs), while the LOX pathway (5-/12-/15-LOX) produces hydroxyeicosatetraenoic acid (HETE), lipoxin (LX), leukotriene (LT) series 4, and other oxidative derivatives. The same applies to ω-3 ALA derivatives, particularly eicosapentaenoic acid (EPA; C20:5n-3), which generates series 3 PGs and TXBs via the COX-2 pathway, and hydroxyeicosapentaenoic acid (HEPE) and series 5 LTs via the LOX pathway (5-/12-/15-LOX).[16,17]

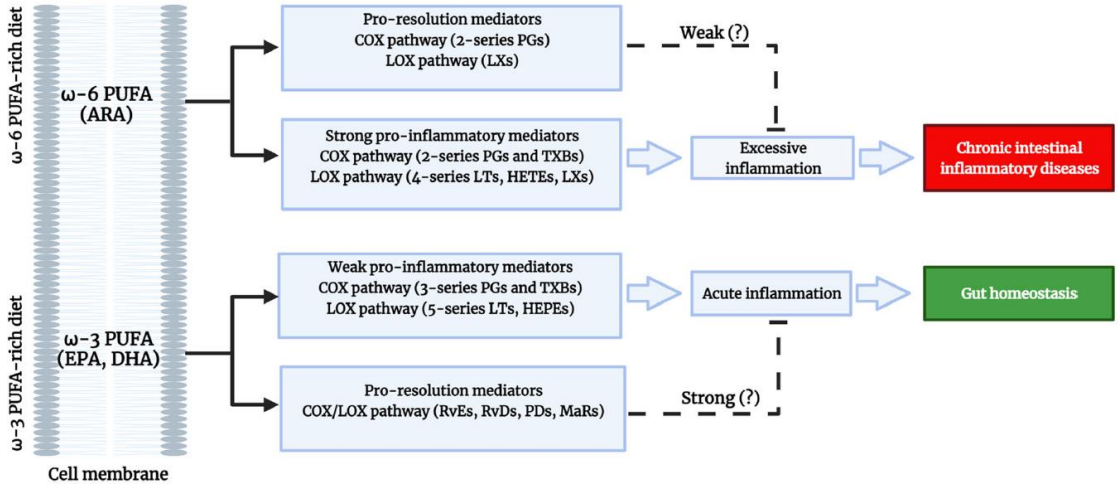

Figure 3. Eicosanoid Families of Omega-3 and Omega-6 Polyunsaturated Fatty Acids Involved in Intestinal Inflammation and Resolution.[16]

Proinflammatory eicosanoids derived from ARA have been widely reported to alter gut microbiota composition and play a central role in the pathogenesis of IBD. Therefore, NSAIDs predominantly aim to inhibit ARA and its derivatives, primarily through the COX pathway. On the other hand, EPA and docosahexaenoic acid (DHA; C22:6n-3) can replace ARA in cell membranes and produce weaker eicosanoids that stimulate inflammation resolution up to 100-fold. Furthermore, newly discovered molecules derived from EPA, such as the E-series resolvins (RvEs), and DHA, such as the D-series resolvins (RvDs), maresins (MaRs), and protectins (PDs), act as inflammation inhibitors. These molecules

not only halt inflammation but also clear inflammatory remnants and stimulate antimicrobial defenses to maintain gut environmental balance. Furthermore, recent findings reveal that ARA-derived PG derivatives (PGD2, PGE2) and LX(A4) exhibit both proinflammatory and proresolving characteristics in a process termed 'class-switching'. This pivotal discovery ultimately confirms that both ω-3 and ω-6 PUFAs yield anti-inflammatory eicosanoids that support the inflammation resolution process. However, abundant data indicate that ω-3 PUFA is the most potent anti-inflammatory agent compared to ω-6 PUFA. This may be attributed to significant differences in the magnitude of eicosanoid actions involved in the resolution phase.[16,17]

The Role Omega-3 in Inflammator Bowel Disesase

Numerous epidemiological studies have highlighted the significance of dietary fats, such as monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), in the development of UC and CD. A high consumption of linoleic acid (LA, n-6) is recognized as a contributing factor in hastening the advancement of both conditions. On the other hand, sufficient intake of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) may inhibit the progression of these diseases. Research indicates that omega-3 fatty acids can influence the peroxisome proliferator-activated receptor/nuclear factor of activated T cells (PPAR-g/NFAT) pathway, promoting the healing of intestinal mucosa.[18,19] An animal study demonstrated that diets rich in omega-3 fatty acids diminished the expression of COX-2 in the colon and lowered IL-6 and TNF-a production. In a separate rat study, Mbodji et al. found that combining n-3 polyunsaturated fatty acids (n-3 PUFAs) with 5-ASA therapy was notably more effective in inhibiting nuclear factor kappa B (NF-kB) activation compared to just 5-ASA. This combination also reduced the required dose. A systematic review and meta-analysis by Mozaffari et al., encompassing 12 studies with 282,610 participants, identified a negative correlation between long-chain n-3 PUFA intake and UC risk. They also observed a similar inverse relationship between fish consumption and CD incidence.[5,18] Conversely, another review did not establish a clear benefit of omega-3 supplementation for IBD patients. Earlier research suggests that n-3 PUFAs play a role in the production of both inflammatory and anti-inflammatory eicosanoids, like prostaglandins and leukotrienes. Essentially, n-3 PUFAs competitively inhibit the transformation of arachidonic acid into leukotrienes, lipoxins, and prostaglandins. They can also counteract inflammation by obstructing the creation of other inflammatory cytokines and by impacting T-helper 1 (Th1) lymphocyte activity, leukocyte chemotaxis, adhesion molecule expression, and leukocyte-endothelial interactions. Moreover, n-3 PUFAs have been identified as precursors in the creation of resolvins, maresins, and protectins, which are crucial for resolving inflammation. There's a possibility that

IBD patients lack essential fatty acids, and introducing n-3 PUFA interventions might benefit them by altering arachidonic acid compounds and/or diminishing oxidative stress. However, given the varied findings, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines currently do not advocate for n-3 PUFA supplementation in IBD patients.[18–20]

Omega-3 PUFAs have significantly altered the biochemical structure of lipid rafts. These are the dynamic regions of the cell membrane rich in sphingolipids and cholesterol, where specific signaling proteins gather. These lipid microdomains hold a crucial role in both the activation and differentiation of CD4+ T cells, as well as downstream processes in B cell activity. Several pieces of evidence from both in vitro and in vivo studies have indicated that n-3 PUFAs have displaced a considerable number of signaling proteins that are essential for the activation of CD4+ T cells. Additionally, n-3 PUFAs have been observed to inhibit the polarization of CD4+ T cells into Th1 and Th17 cells, likely achieved through alterations in the IL-6/gp130/STAT3 pathway. Conversely, n-3 PUFAs or specialized pro-resolving mediators (SPMs) have exhibited the ability to enhance humoral immunity by influencing the development of B cells in the bone marrow, facilitating B cell activation, and promoting the production of antibodies in response to antigens. While it is necessary to validate these findings and provide further clarity on the underlying mechanisms, there is a plausible speculation that n-3 PUFAs could contribute to mitigating autoimmune and chronic inflammatory diseases [21].

Omega-3 Supplementation in Inflammatory Bowel Disease

A significant number of IBD patients express interest in omega-3 supplementation, either through omega-3 rich foods or via fish oil capsules. Research has indicated that a diet high in omega-3 can potentially lead to clinical remission in these patients. For instance, a study focused on the consumption of Alaskan salmon revealed that UC patients who ingested 600 mg of Atlantic salmon weekly exhibited lower SCCAI scores after 8 weeks compared to their counterparts who didn't. Another year-long study involving 230 participants found that those maintaining a diet with an omega-3 to omega-6 ratio nearing 1 had higher remission rates than those on a predominantly omega-6 diet. However, it's crucial to note that not all sources of omega-3 have proven beneficial. One particular study associated a high intake of alpha-linolenic acid, a precursor to long-chain n-3 PUFA, with an elevated risk of UC recurrence, while n-3 PUFA intake without supplements showed protective effects. Sources of alpha-linolenic acid include seeds like chia, hemp, and flax. Yet, this conclusion is based on a single study, warranting cautious interpretation.[22]

While fish oil, a form of omega-3 supplementation, is popularly consumed for various chronic ailments, including IBD, its clinical efficacy remains uncertain. Multiple trials have explored the impact of fish oil on UC, yielding mixed results. One randomized, placebo-controlled trial deduced that omega-3 supplements were beneficial for short-term prevention (3

months) of UC relapse, but this effect diminished after a 3-year period. Another research found no significant difference in UC relapse rates between the omega-3 supplemented group and the control group. Furthermore, a meta-analysis of three trials and a recent systematic review, both examining omega-3's role in UC remission and relapse prevention, found no tangible benefits, leading us to refrain from recommending omega-3 supplementation for UC.[22]

In the context of CD, recent research echoes the findings related to UC, suggesting that omega-3 supplementation might not be beneficial. Notably, the outcomes of EPIC-1 and EPIC-2, two extensive multicenter RCTs studying CD relapse with a daily 4 g omega-3 dosage, concluded its inefficacy in preventing relapses. A meta-analysis, which reviewed six trials involving 1039 patients, identified only a marginal advantage in relapse prevention through maintenance supplementation, though the studies varied significantly in their design. Given the prevailing evidence, we currently advise against n-3 PUFA supplementation for IBD patients. However, based on preliminary studies suggesting potential benefits, we advocate for a balanced diet enriched with omega-3s. Specifically, we emphasize the consumption of foods abundant in DPA and DHA omega-3s, such as salmon and mackerel.[22]

Supplementation of the diet with extra-virgin olive oil, which is higher in mono-unsaturated fats than PUFAs, protected against inflammation in the dextran sodium sulfate model of colitis. Studies also have examined varying the ratios of n-6 and n-3 PUFAs in animal models167; inflammation could be attenuated significantly if rats were pretreated for months with one third of fat from n-3 and the rest as n-6 (linoleic acid: a-linoleic acid of 2). In this study, however, animals received only 10% of their calories from fat, which is much less than the typical American diet. The issue with translating many of these studies to our patients is that animal work generally involves pretreatment of rats/mice with a particular diet and does not clarify whether these fats help in established inflammation. [23]

CONCLUSION

Inflammatory Bowel Disease (IBD), including Ulcerative Colitis (UC) and Crohn's Disease (CD), is a chronic gastrointestinal disorder. Recent studies highlight the potential anti-inflammatory benefits of omega-3 fatty acids for IBD patients. For instance, UC patients consuming Alaskan salmon showed reduced inflammation. However, the role of omega-3 is complex. While some sources, like alpha-linolenic acid, might increase UC relapse risk, consistent omega-3 intake without supplements appears protective. The efficacy of fish oil supplements remains debated, with mixed clinical trial results. Current evidence leans towards naturally omega-3-rich foods, like salmon, as beneficial. Balancing omega-3 and omega-6 intake might also promote remission. Further research is essential for definitive recommendations.

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CONFLICT OF INTEREST

There is no conflict of interest in writing this article.

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