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Review Article

The effect of seafood oil omega-3 supplementation on ulcerative colitis remission: A systematic review

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Abstract

Background and aims: Ulcerative colitis (UC) is a prevalent and long-term condition that causes inflammation, irritation, and ulcers in the colon. This systematic review aimed to evaluate the effect of seafood oil omega-3 supplementation on UC remission.

Methods: PubMed, EMBASE, Web of Science, and Scopus databases were extensively searched on 25.5.2022 according to the PRISMA checklist. The studies were imported into EndNote X9. Data were extracted in Excel form, including the first author's name, study setting, year of publication, sample size, sea oil type, intervention, and outcomes.

Results: Seafood oil omega-3 supplementation reduced the levels of leukotriene B4, interleukin (IL)-2, IL-8, IL-1β, thromboxane A2, prostaglandin E2, scavenges-free radicals, and tumor necrosis factor-α (TNF-α). In addition, supplementation with this oil could decrease free radicals at the cellular level and subsequently increase antioxidant activity, which also mediates the inflammatory process itself.

Conclusion: Most studies showed that omega-3 extracted from seafood can reduce inflammation and oxidative stress (OS) in intestinal cells. It also could improve clinical symptoms and scores of histological, sigmoidoscopic, and simple clinical colitis activity index (SCCAI). However, some studies reported no positive effects in this regard and confirmed that these compounds have no effect on improving UC symptoms.

Keywords: Omega-3, Fish oil, Ulcerative colitis, Inflammatory bowel disease

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Introduction

Ulcerative colitis (UC) is a recurrent, idiopathic, and chronic disease that is considered a subtype of inflammatory bowel disease (IBD). UC is characterized by the inflammation of the gastrointestinal tract, commonly the innermost part of the colon (1), and leads to abdominal pain, bloating, diarrhea and rectal bleeding, digestive disorders, weight loss, and ultimately an impaired health-related quality of life at younger ages (2,3). Thus, it can disrupt the daily activities of affected people, including their work, school, social relationships, and daily life (4,5). Mild to moderate symptoms are most frequently reported, but in some cases, they can cause severe cases that require immediate medical attention and hospitalization (6,7). Despite significant advances in UC treatment, some patients are resistant to common treatments (8). On the other hand, these treatments are expensive and sometimes cause severe side effects. For example, corticosteroids are the most common drugs prescribed for the treatment of the disease and are associated with acne, moon face, oedema, glucose intolerance, sleep and mood disturbance, dyspepsia, posterior subcapsular cataracts, osteoporosis, myopathy, and susceptibility to infection (9). Therefore, the use of newer drugs and the study of alternative and natural therapies will be necessary for overcoming the UC treatment challenges (10). Given that food enters the digestive system, it can be mentioned that diet can affect exacerbate or reduce the symptoms of UC, one of the most important of which is seafood (2). Studies show that seafood omega-3, which consists of eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are inversely associated with UC symptoms (11-13). Nonetheless, given insufficient data and controversial results to recommend the use of omega-3 fatty acids for the remission of UC reported in a previous systematic review and a meta-analysis (14,15), this meta-analysis aimed to investigate the effect of seafood oil omega-3 supplementation on UC remission.

Materials and Methods

Data sources and search strategy

This systematic review method followed PRISMA 2020 statement (http://prisma-statement.org/prismastatement/Checklist.aspx) so that according to the instructions, an extensive search was undertaken on 25.5.2022 in PubMed, EMBASE, Web of Science, and Scopus databases. In this study, the following keywords were used for searching:

((“ulcerative colitis” OR “colitis gravis” OR “idiopathic proctocolitis” OR “inflammatory bowel disease”) AND (“fish oil” OR “seal oil” OR “marine oil” OR “omega-3” OR

"n-3 fatty acid" OR "ω-3 fatty acid" OR "docosahexaenoic acid" OR "docosahexaenoic" OR "eicosapentaenoic" OR "icosapentaenoic acid" OR "eicosapentaenoic acid")).

Study selection

The records were imported into EndNote X9 (July 31, 2018, Thomson Reuters) to manage references and remove duplicate publications. Two researchers independently screened the records in terms of titles and abstracts according to the study inclusion and exclusion criteria. The clinical trial studies that addressed the effects of marine oil omega-3 supplementation on UC remission were included in the systematic review. Not retrieving the full text of the articles and being published in non-English languages were considered the exclusion criteria. The full texts of all screened publications were independently evaluated, and any disagreement between the authors was resolved by discussion. A PRISMA flow diagram of the search strategy was used as well.

Data extraction and quality assessment

Studies were independently extracted and selected by two researchers. The data were extracted from the articles and recorded in Excel form, including the first author's name, study setting, year of publication, sample size, sea oil type, intervention, and outcomes.

Results

Search results, study characteristics of selected studies

The PRISMA flow diagram including database searches is illustrated in Figure 1. The initial electronic search in the mentioned databases retrieved 3314 titles/abstracts. From all retrieved publications, 1854 records were deleted due to duplicate titles. Some other titles/abstracts were excluded (n = 8) as well; two manuscripts were out of the aim of the study (16,17), one IBD study was generally reviewed (18), three records did not have the desired methodology (19-21) and the full text of 2 others could not be retrieved (22,23), and finally, 25 articles were selected for the assessment.

Although there are various drugs such as immunosuppressive agents, 5-ASA agents, and steroids to cure UC, each of them has its own side effects. The results of the study demonstrated that the beneficial effects of omega-3 unsaturated fatty acids (EPA and DHA) are related to the anti-inflammatory effects of these compounds. These effects are induced by making changes in the synthesis of fatty acids in the intestinal cells. In addition to reducing pro-inflammatory factors, omega-3 can be effective in improving UC symptoms by reducing the level of free radicals and antioxidant activities. Based on data in Table 1, the results of the reviewed studies mainly emphasized that omega-3 sea oils remission effects on UC are associated with the reduction of clinical symptoms, disease-related complications, and the reduction of inflammatory cytokines and oxidative stress (OS).

Several mechanisms are associated with the favorable effects of seafood omega-3 on UC. The main mechanisms are as follows:

1. Anti-inflammatory effects

Several pathways are engaged in the inflammation and pathogenicity of UC, including increased interferon-γ, tumor necrosis factor-α (TNF-α), interleukins (ILs) (IL-4, IL-5, IL-9, IL-17, and IL-22), and reduced levels of IL-10 and transforming growing factor-β (32,49). The main favorable effects of omega-3 as supplementation on UC are related to anti-inflammatory effects. They can induce a change in the synthesis cycle of fatty acids in the cell membrane and reduce arachidonic acid that synthesizes pro-inflammatory cytokines in 5-lipoxygenase and cyclooxygenase pathways (15). The syntheses of leukotriene B4 (LTB4), IL 8, and IL1B, as well as thromboxane A2, prostaglandin E2, scavenges free radicals, and TNF are all decreased in these pathways (15,38,50). Moreover, they can decrease the chemotaxis of T-cell and leukocyte reactivity and the activation of NF-κB (50,51). In this study, seafood omega-3 suppressed the synthesis of leukotriene B4, which is an important mediator of inflammation and a stimulus for neutrophil chemotaxis in IBD (26,27).

2. Radical scavenging effect

Marine oil omega-3 induces various mechanisms to suppress the OS onset and consequently reduce the severity of the inflammatory response. They could have favorable effects by scavenging free radicals, reducing prooxidative enzymes and cytokines, and increasing the antioxidative capabilities of cells (52). Marine oil omega-3 antioxidant activity is related to the level of intracellular antioxidants such as vitamins D and E, mucosal immune response, and genetic susceptibility (52).

OS in UC patients occurred due to the high concentration of reactive oxygen species (ROS) produced in different mechanisms. Increasing OS can harm the oxidation in intestinal cells via a chain reaction that causes the breakage of macromolecules such as proteins, nucleic acid, and lipid structure, as well as lipid peroxidation which can cause the loss of polyunsaturated fatty acids (PUFAs) and the loss of enzymatic activity and receptors in the intestinal membrane, leading to the infraction of membrane integrity and finally disrupting the action of epithelial cells (15,36). The infiltration of the mucosal tissue with activated phagocytic immune cells causing the production of ROS and nitrogen species leads to a shift toward prooxidants. It disrupts cellular homeostasis by distracting key macromolecules and attributing to cell injury and elevated permeability of the mucosal barrier, thus precipitating and maintaining ongoing inflammation (53). Thus, antioxidants such as marine oil omega-3 can downregulate the inducible isoforms of nitric oxide, myeloperoxidase, lipoxygenases, cyclooxygenase, and nicotinamide adenine dinucleotide phosphate oxidase.

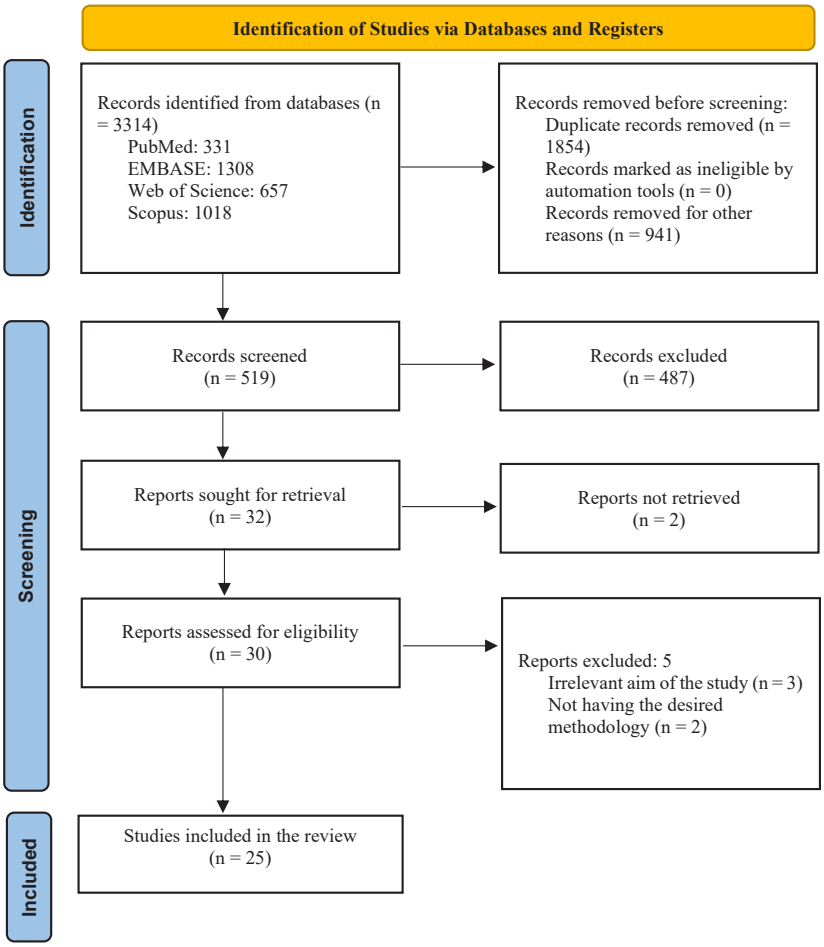

Figure 1. Flow diagram for including studies in the systematic review

Table 1. Characteristics of clinical trials included in this systematic review

First Author	Year	Country	Sample Size	Marine omega-3	Intervention	Outcome
Lorenz (24)	1989	Germany	39	Fish oil	3 of the 1.2 mL fish oil capsules for 3 months. After 4 weeks, they received capsules for 7 months	Clinical disease activity did not change statistically. A moderate fall in inflammatory lipid mediators by dietary n-3 fatty acids and a little morphological improvement in chronic IBD were observed
Salomon (25)	1990	USA	10	Fish oil	15 capsules of EPA (containing 2.7 g) daily in three divided doses for 8 weeks	Although some patients had an improvement in their symptoms, there was no change in some patients, and at least their condition did not worsen
Hawthorne (26)	1992	UK	87	Fish oil	Fish oil, 10 mL twice daily for a year	Fish oil supplementation in UC patients works somewhat like corticosteroids but does not affect maintenance therapy. In addition, it synthesized detectable amounts of leukotriene B5 and suppressed leukotriene B4
Stenson (27)	1992	USA	18	Fish oil	Fish oil containing 18 Max-EPA (EPA 3.24) capsules daily and DHA, 2.16 g) for 4 months	Supplementation decreased rectal dialysate levels of leukotriene B4 and produced a modest corticosteroid-sparing effect on UC patients, but there was no benefit in maintenance therapy
Greenfield (28)	1993	UK	43	Fish oil	Max-EPA at 3 months by 3-fold and 6 months by 4 folds	Improvements were observed in the acute histology index and total histology
Loeschke (29)	1996	Germany	64	Fish oil	2 capsules contained fish oil (5.1 g/d n-3 fatty acids) for 3 months	Actuarial relapse-free survival was ameliorated only during months 2 and 3
Campbell (30)	1997	USA	24	Fish oil	The formula includes supplemental oligosaccharides fish oil, and gum arabic for 7 days	EPA and DHA were increased in plasma phospholipids and the red blood cells
Almallah (31)	1998	UK	18	Fish oil	Patients received either fish oil extract (DHA, 2.4 g and EPA, 3.2 g) daily for 6 months	Reduced the histological scores and sigmoidoscopic scores and finally improved disease activity
Almallah (32)	2000	UK	18	Fish oil	15 mL of fish oil extract (5 mL 3 times a day) for 6 months	Reduced NK cell cytotoxic activity, IL-2, and sIL2R
Almallah (33)	2000	UK	18	Fish oil	Fifteen mL of the fish oil extract (5 mL 3 times a day). This provided a total of 3·2 g of EPA and 2.4 g of DHA for 6 months	Reduced the number of cells expressing HLA and CD3 and the percentage of cells containing IgM and improved the histological score

Table 1. Continued.

First Author	Year	Country	Sample Size	Marine omega-3	Intervention	Outcome
Dichi (34)	2000	Brazil	10	Fish oil	5.4 g/d of fish oil omega-3 fatty acids (18 capsules) for 2 months, and then 2 g/d of sulfasalazine for 2 months	CRP, ESR, and platelet count increased. Moreover, an increase in fecal nitrogen and a reduction in a sigmoidoscopy score were observed
Middleton (35)	2002	UK	58	Fish oil	Patients received either DHA, 45 mg, per day, 500 mg/d) and trial medication (gamma-linolenic acid (1.6 g, EPA, 270 mg) for 12 months	No statistical differences were in the relapse rate and the intake of dietary constituents or adverse events between the groups
Barbosa (36)	2003	Brazil	18	Fish oil	4.5 g/d (30 capsules) of fish oil omega-3 fatty acids (omega-3) for 2 months	No significant changes were found in any laboratory indicator or the histology scores and sigmoidoscopy. The ESR and oxidative stress represented a decrease
Seidner (37)	2005	USA	121	Fish oil	18 oz of formula for 6 months	A reduction in the dose of prednisone was required to control clinical symptoms for 6 months
Brunborg (38)	2008	Norway	38	Fish oil + seal oil	10 mL of the seal oil (n = 18) or cod liver oil (n = 20) was given orally 3 times/day for 14 days.	No significant changes were observed; but, in both groups, the changes in the plasma level of leukotriene B4, joint pain parameters, and serum fatty acid profile were favorable and reduced LTB4 plasma levels
Bjørkkjaer (39)	2009	Norway	18	Fish oil + seal oil	Seal and whale oils were prescribed 10 mL × 3 daily through a nasoduodenal feeding tube for 10 days in IBD patients	Decreased IBD-related joint pain and disease activity. The seal oil reduced the PGE2 level in the plasma
Grimstad (40)	2011	Norway	12	Fish oil	200 gr of Atlantic salmon fillet 3 times/ week for 8 weeks	The anti-inflammatory fatty acid index was significantly elevated in biopsies and plasma. Based on AIFAI and SCCAI results and a tendency of reduced levels of CRP and homocysteine, UC symptoms improved.
Scaioli (41)	2015	Italy	35	Fish oil	All patients took 2 g EPA-FFA daily as 2 capsules (500 mg PUFAs) 2 times/day with food for 8 weeks	The plasma n-3 PUFA levels in IBD patients were significantly increased, and the RBC n-6 PUFA content in IBD patients represented a decrease
Prossomariti (42)	2017	Italy	19	Fish oil	2 g/day (90 days supplementation with two 500 mg capsules twice a day) of EPA-FFA	Reduced promoted goblet cell differentiation, modulated intestinal microbiota composition, and mucosal inflammation in UC patients
Scaioli (43)	2017	Italy	60	Fish oil	EPA-FFA (500 mg, 2 bid) for 6 months	Fecal calprotectin levels significantly decreased and ameliorated the symptom of the disease
Scaioli (44)	2018	Italy	60	Fish oil	Patients were administered either 2 g daily of EPA-FFA (2 x 500 mg gastro-resistant sustained-release capsules, twice daily) for 6 months	Decrease fecal levels of calprotectin
Bernabe-García (45)	2020	Mexico	214	Fish oil	75 mg of DHA/kg body weight for 14 days	Decreased necrotizing enterocolitis, the number of patients who needed treatment, and the level of treatment failure
Abhari (46)	2020	Iran	70	Algal oil	4.3 g (4800 mg) of omega-3 (4 capsules of 1200 mg)/day for 2 months	Decreased the levels of oxidative and inflammatory markers while increasing antioxidant markers in the serum
Arslan (47)	2002	Norway	10	Seal oil	Seal oil (10 mL) was given 3 times/day	No change was found in intestinal permeability, calprotectin concentration in gut lavage fluid, and lipid peroxidation. Reduced IBD-associated joint pain
Bjørkkjaer (48)	2004	Norway	19	Seal oil	Ten mL of seal oil 3 times daily for 10 days	Decreased the duration of morning stiffness, intensity of pain, number of tender joints, and the doctor's scoring of rheumatic disease activity

Note. LTB4: Leukotriene B4; IgM: Immunoglobulin M; IBD: Irritable bowel disease; UC: Ulcerative colitis; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; HLA: Human leukocyte antigens; CD3: Cluster of differentiation 3; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; PGE2: Prostaglandin E2; SCCAI: Simple clinical colitis activity index; PUFAs: Polyunsaturated fatty acids; AIFAI: Anti-inflammatory fatty acid index; RBC: Red blood cells.

They can also prevent the formation of free radicals by enhancing glutathione peroxidase, catalase, superoxide dismutase, paraoxonase, and peroxiredoxins (46,47,53).

3. Clinical and laboratory response

Some studies indicated that seafood omega-3 reduces the histological score, simple clinical colitis activity index (SCCAI), and sigmoidoscopic scores, and finally improves patients' situation (31,33,34,36). Other studies reported that corticosteroid doses during treatment with the fish oil were decreased as well (37,40). In summary, seafood-derived omega-3 PUFAs can improve the clinical and laboratory findings of the disease and interact with the gut microbiota to promote the homeostasis of the gut immune system. Therefore, in general, dietary supplements with fish oil play a role in improving IBD disease outcomes (12). The overall effects of omega-3 seafood are illustrated in Figure 2.

Discussion

This systematic review aimed to investigate the effect of omega-3 marine oil on UC remission. Most studies showed that omega-3 extracted from seafood can reduce inflammation and OS in intestinal cells. It also improves the clinical symptoms and scores of histological, sigmoidoscopic, and SCCAI. However, some studies did not report such positive effects; they demonstrated that these compounds have no effect on improving UC symptoms. Turner et al revealed that there was no difference in the relapse rate between the fish oil omega-3

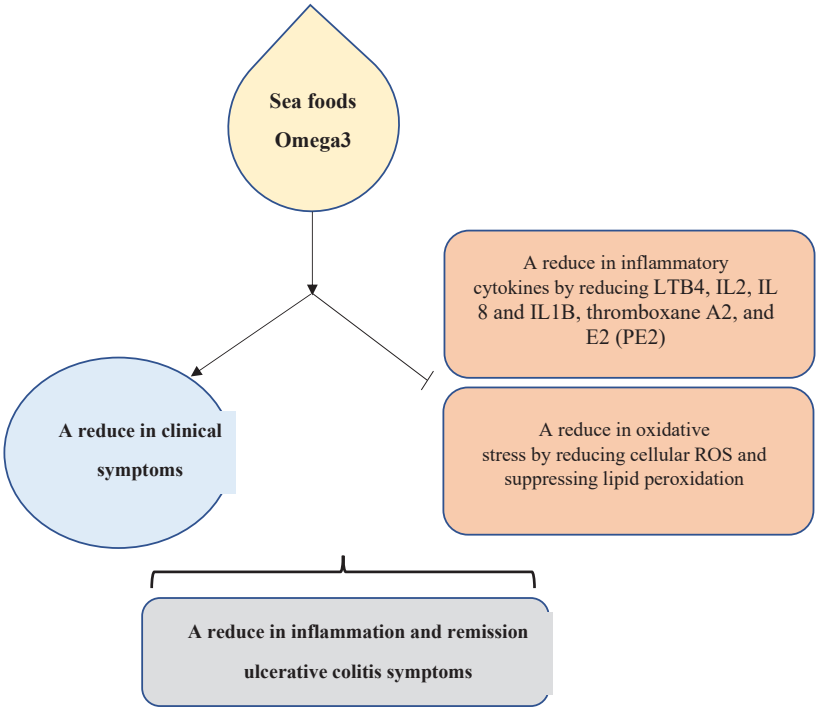

Figure 2. Effects and Mechanisms of Seafood Omega-3 Supplementation on the UC. *Note*. UC: Ulcerative colitis; LB4: Leukotriene B4; IL2: Interleukin 2; PE2: Prostaglandin E2

supplementation group and control groups. They further indicated that higher rates of symptoms of the upper gastrointestinal tract and diarrhea were observed in the intervention group. Therefore, insufficient data were obtained to recommend the use of omega-3 fatty acids for remission symptoms in UC patients (14). Another review represented that diet and nutritional supplements that contribute to the development of an optimal gut microbial community hold promising effects on reducing intestinal inflammation associated with IBD. More studies are probably needed to determine the mechanisms of these nutritional supplements, including fish oil (12). One study evaluated the effects of omega-3 fatty acids on UC and reported controversial results in this regard while not conclusively stating that taking omega-3 PUFA supplementation is beneficial in the treatment of UC. This study highlighted the need for further studies in this area (15). The reasons for the difference in the results of the studies and some existing discrepancies can be due to different dosages of supplementation, different methodologies of the studies, poor absorption of sea omega-3, different chemical formulations, and poor patient adherence to the treatment (54).

Omega-3 and its relevant PUFAs are generally safe with benign side effects, including dyspepsia, diarrhea, nausea, eructation, gas, arthralgia, and fishy taste (55).

One of the limitations of the present study was the investigation of omega-3 from seafood, which may have different doses of omega-3 or different bioavailability rates based on the type of fish or seafood. On the other hand, a comprehensive and detailed review of the studies conducted according to the purpose of the study was one of the strengths of this study.

Conclusion

Overall, it was found that omega-3 extracted from seafood can reduce inflammation and OS in intestinal cells. It could also improve the clinical symptoms and scores of histological, sigmoidoscopic, and SCCAI. However, some studies reported no positive effects but indicated that these compounds have no effect on improving UC symptoms. More studies are needed to obtain clearer and more accurate results on the effects of omega-3 extracted from seafood on UC.

Author Contributions

Conceptualization: Hossein Mardani-Nafchi.
Data curation: Atieh Mohammadi-Nafchi.
Investigation: Hossein Mardani-Nafchi.
Methodology: Hossein Mardani-Nafchi.
Project administration: Hossein Mardani-Nafchi.
Resources: Atieh Mohammadi-Nafchi.
Supervision: Atieh Mohammadi-Nafchi.
Writing – original draft: Hossein Mardani-Nafchi, Atieh Mohammadi-Nafchi.
Writing – review & editing: Hossein Mardani-Nafchi, Atieh Mohammadi-Nafchi.

Conflict of Interests

We declare that we have no conflict of interests.

Ethical Approval

Not applicable.

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Nil.

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