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Review Article

The Effect of Omega-3 Fatty Acids in Ulcerative Colitis: A Systematic Review

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ABSTRACT

The beneficial effects of Omega-3 poly-unsaturated fatty acids (n-3) as nutritional components is related to its anti-inflammatory effects. In spite of anti-inflammatory effects, controversial results of omega-3 fatty acids have been observed in the treatment of ulcerative colitis (UC). This systematic review was undertaken to assess the therapeutic effects of omega-3 fatty acids supplementation on UC. A search in PubMed database with specified MeSH terms was conducted and the RCT was selected that were published up to November 12th, 2017 and in English language evaluating the effect of oral supplementation of n-3 fatty acids in adult Patients suffering from active and inactive UC. The trials assessing the improvement of UC and reporting the index as a result (8 trials), but trials with consumption of dietary supplements enriched with n-3 fatty acids were excluded. These trials evaluated the improvement of UC through intervention by using n-3 fatty acids with different outcomes such as clinical response, disease activity index (DAI), endoscopic and histology scores, reduction in corticosteroids consumption in patients achieving remission after treatment and time in remission. The evaluation data indicated reduction in corticosteroids dosage in UC patients during fish oil treatment in all three related trials that assessed this index. Only one of these trials reported statistical significant changes in dosage requirement of corticosteroids. Based on controversial results that were obtained from this systematic review, it was not expressed conclusively that taking omega -3 PUFA supplements in the treatment of UC is helpful and need more studies in this field.

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Introduction

Ulcerative colitis (UC) is one of the major idiopathic subgroup of inflammatory disorders of the gastrointestinal tract that can occur exclusively in mucosal layer of the colon in continuous form (1, 2). UC is relatively common in more developed countries. Its prevalence is high in Western countries (with a prevalence rate of 249 per 100,000 in North America) and the continuing incidence rate rising around the world (3). The

highest annual incidence of UC has been reported as 24.3 per 100,000 in Europe, 19.2 per 100,000 in North America, and 6.3 per 100,000 in Asia and the Middle East. Accordingly, the increasing incidence and prevalence rates, by time and place around the world, show its necessity as a global disease (4).

UC can occur any time in life, but is usually diagnosed before age 30, and equally occur in men and women (5). The causes of UC are not fully understood, but multiple factors such as genetic and environmental factors play important roles in its severity and pathogenesis (5). The pathological findings, correlated with UC are an increase in oxidative stress, inflammatory mediators, intestinal permeability and sulphide production and an abnormality in colonic milieu and content of the mucosal layer and decreased oxidation of short chain fatty acids and methylation, but we should note that none of them is not considered as initial trigger for UC (5).

Although treatment with medication such as 5-ASA agents, immunosuppressive agents and steroids are the most important therapeutic methods, but it is associated with several side effects. Due to these therapeutic side effects, people are going to have nutritional supports in addition to their therapy (6). In this systematic review, the effects of omega-3 poly-unsaturated fatty acids that may result in finding new strategies for treatment in the future will be reviewed. The beneficial effects of omega-3 poly-unsaturated fatty acids (n-3) as nutritional components is related to the anti-inflammatory effects, that can change the component of fatty acids synthesis in cell membrane and decrease arachidonic acid that produce pro-inflammatory cytokines in cyclooxygenase and 5-lipoxygenase pathways (7, 8).

In these pathways, production of interleukin-1b (7), interleukin-8 (8), thromboxane A2, leukotriene B4, prostaglandin E2 and tumour necrosis factor (TNF) and scavenge free radicals as pro-inflammatory cytokines are reduced (7) with reduced activation of NF-KB, chemotaxisity of leukocyte and T-cell reactivity (8) that can have a significant role in pathogenesis of UC. Various forms of n-3 obtained from various sources such as eicosa pentanoic acid (EPA or 20:5) and docosa hexanoic acid (DHA, 22:6) (longer chain n-3) found in marine sources like fish oil and alpha linolenic acid (ALA, 18:3) that is another source of n-3 with a shorter chain, and in nuts and vegetable oils. Additionally longer chain n-3 can be made from ALA by endogenous process, the benefits of which is in doubt (7).

The second effect of the omega-3 poly-unsaturated fatty acids (n-3 PUFA) return to its role as an antioxidant agent that is considered as a defensive mechanism and can reduce the severity of the inflammatory response. In normal situations when the level of free oxygen radicals is not still high, n-3 can act as a free radical scavenger, but in terms of high oxidative stress situation (like inflammation) fatty acids oxidation is increased; however, these problems depend on the level of intracellular antioxidant like vitamin E. Oxidative stress in UC patients is caused by high concentration of free oxygen radicals or reactive oxygen species (ROS) produced from different ways (5, 9).

Increase in oxidative stress can make harm with the oxidation in intestinal cells through chain reaction that leads to breakage of macromolecules like nucleic acid, proteins and lipid structure, such as lipid peroxidation that can cause the loss of PUFAs and the loss of enzymatic activity and receptors in intestinal membrane that lead to disruption of membrane integrity and ultimately change the performance of epithelial cells. These damages play an important role in the acceleration of UC, in order to prevent these tissues from damaging the defensive mechanism occurring in the intestinal mucosa (5, 9). According to controversial results of the effects of omega-3 fatty acids on the treatment of ulcerative colitis reported in some articles (10), in this review, our aim was to discuss the therapeutic effect of omega-3 fatty acids in patients with UC.

Materials and Methods

For this systematic review, we searched for articles investigating the effects of n-3 fatty acids on both active and inactive UC in PubMed database with these MeSH terms: “ulcerative colitis”, “Colitis”, “inflammatory bowel disease”, “gastrointestinal disease”, “gastroenteritis”, “intestinal disease” AND “randomized controlled trial” AND “omega-3 fatty acids”, “n3 fatty acids”, “n-3poly unsaturated fatty acids” ,“n-3 PUFA”, “pufan-3”, “n-3 fatty acids”, “n-3 oil” NOT “animal models” , and “cancer”.

Our criteria for considering articles were type of participants, interventions and outcome measures. Studies were included in this systematic review were the randomized controlled trials (RCT), in English language and were published up to November 12th and included adult patients with active or inactive ulcerative colitis, and trials with evaluating oral supplementation of omega-3 poly-unsaturated fatty acids. Trials with dietary supplements enriched with n-3 fatty acids were excluded because other components in dietary supplements may affect our results and trials with assessing the improvement of UC with reporting one or more index as a result, such as clinical response, disease activity index (DAI),

endoscopic score, histology score and reduction in corticosteroids requirement in patients achieving remission after treatment and time to remission.

Results

Tottaly, 483 articles in the initial search were recruited, 464 of which were excluded due to their irrelevant titles and six studies were excluded by reading the abstracts; two articles were excluded due to involving dietary supplements, enriched with n-3 fatty acids through intervention, and two of them were removed due to lack of access to their full texts, and one study was excluded because of the consumption of sulfasalazine as the placebo group. Then, eight articles were included in this systematic review were summarized in Table 1.

Trials with specified criteria to assess the improvement of UC with one or more outcomes such as clinical response, DAI, endoscopic and histology scores, reduction in corticosteroids requirement in patients achieving remission after treatment and time in remission were included in this review (Table 2-6).

Table 1: Features of the studies of the effects of n-3 fatty acids on ulcerative colitis.

Study	Participants	Duration	Interventions a) n-3 fatty acid b) Placebo group
Aslan, 1992	11 patients with mild/ moderate UC	8 months	a) Max-EPA (Fish oil capsules): 2·7 g EPA¶ 1·8 g DHA daily b) Corn oil (10.3 g of oleic acid, 2.1 g of palmitic acid, 1.8 g of linoleic acid)
Almallah, 1998	18 patients with active UC	6 months	a) 15 ml of fish oil: 3·2 g EPA¶ 2·4 g DHA daily b) sunflower oil: 2.6 g of oleic acid and 7.9 g of linoleic acid
Stenson, 1992	18 patients with active UC	4 months	a) Max-EPA (18 capsules) provided a total of 3.24 g of EPA, 2.16 g of b) vegetable oil (18 capsules) 12.36 g oleic acid, 2.52 g palmitic acid, 2.16 g linoleic acid
Lorenz, 1989	39 patients with active UC	7 months	a) Max EPA, 11 mL/d b) Olive oil, 11 mL/d
Hawthorne, 1992	96 patients in remission or 'going into remission'	4 weeks	a) Hi EPA, 20 mL/ b) Olive oil, 20 mL/d
Loeschke, 1996	64 patients in remission or minimally active	2 years	a) Fish oil capsules, 5.1 g/d b) Corn oil, 5.1 g/d daily
Greenfield, 1993	43 patients	9 months	a) Max EPA (fish oil), 12 g/d followed by 6 g/d b) Olive oil, 12 g/d followed by 6 g/d b) Super evening primrose oil, 3 g/d followed by 1.5 g/d
Middleton, 2002	63 patients with quiescent disease	12 months	a) GLA 1.6 g, EPA 270 mg, DHA 45 mg, per day b) Sunflower oil, 500 mg/day

Table 2: Results of n-3 fatty acids on clinical scores in ulcerative colitis.

Study	Measure of clinical scores	Outcomes
Aslan, 1992	Disease Activity Index (DAI)**	Decrease in (DAI) scores in the group treated with fish oil, DAI scores changed from 2.76 to 1.23 and in the placebo group DAI scores decrease from 1.65 to 1.59 after treatment.
Almallah, 1998	UC Activity Index*	Reduction in clinical score in group, that were treated with fish oil (range 1 to 5) in comparison with baseline clinical score (range 5 to 12, $P<0.05$).
Loeschke, 1996	UC Activity Index*	Reduction in the group that was treated with fish oil at 3 months. But no significant difference between groups at months 6 to 24.
Lorenz, 1989	UC Activity Index*	No significant difference between groups in disease Activity Index

*Sum of average number of bowel movements per day, plus 1 point for presence of each of the following: general malaise, abdominal pain, rectal bleeding, anorexia, abdominal tenderness, complications, and pyrexia. **Sum of 1) stool frequency, 2) rectal bleeding, 3) sigmoidoscopic appearance of mucosa, and 4) physician's assessment of disease activity; 0–3 points for each variable, with 0 for no abnormality.

Table 3: Results of n-3 fatty acids on endoscopic score in ulcerative colitis.

Study	Measure of endoscopic score	Outcomes
Almallah, 1998	Sigmoidoscopic score*	Decrease in sigmoidoscopic scores in treatment with fish oil at months 3 and 6 (Improvement) Sigmoidoscopic score at baseline was (interquartile range: 10 to17) and after 6 months decreased to (range: 4 to 6, P=0.013). In the placebo group sigmoidoscopic score was (range: 7 to 17) then changed in to (range: 7 to 14) at 6 months.
Stenson, 1992	Sigmoidoscopic scores*	No significant changes reported for endoscopic scores in fish oil and placebo groups. Endoscopic score baseline in the fish oil group was 7.36 (SD±2.86) then decreased -2.09 points (95% CI: -4.63 to 0.45; P=0.06) after 4 months of treatment with fish oil.
Lorenz, 1989	Gross morphologic appearance**	No significant difference for endoscopic scores between groups when restricted to UC.

*24-point scale that is a sum of 1) erythema, 2) edema, 3) granularity, 4) mucopus, 5) friability, and 6) bleeding; 0–3 points for each variable, with 0 - no abnormality. **Scale of 0–3 where 1 for mild inflammation with loss of vascular pattern plus or minus granularity or localized apthous ulcers, 2 for severe inflammation with contact bleeding, and 3 for more severe disease with friability, ulcers, or spontaneous bleeding.

Table 4: Results of n-3 fatty acids on histologic score in ulcerative colitis.

Study	Measure of histologic score	Outcomes
Aslan, 1992	Biopsy score	No significant difference between groups (n-3fatty acid and control group) at 3 months
Almallah, 1998	Histologic score	Improvement in histologic score that was treatment with fish oil (P=0.016).
Stenson, 1992	Histologic score	Greater improvement in histology index with fish oil (P=0·002).
Lorenz, 1989	Histologic score	Difference in histologic score between n-3 fatty acid and control group at 3-month.
Greenfield, 1993	Histology	reported no significant difference between groups (n-3 fatty acid and control group) at 6-month

Table 5: Results of n-3 fatty acids on corticosteroid requirement in ulcerative colitis.

Study	Corticosteroid requirement
Aslan, 1992	8 of 11 (72%) patients reduced in dosage requirement of Corticosteroids (anti-inflammatory) drugs during fish oil treatment. (no p-value reported).
Stenson, 1992	Decreased 6.8 mg/d in prednisone dose during fish oil treatment although no statistically significant changes in dosage requirement of Corticosteroids (prednisone) in both groups (P>0.2).
Hawthorne, 1992	Decreased in prednisolone dose from 10 mg/d at baseline to 5 mg/d at 1 month to 0 mg/d at 2 months in group that treatment with n-3 and for olive oil group from 10 mg/d at baseline at 8 mg/d at 1month to 5 mg/d at 2-month (P=0.01).

Table 6: Results of n-3 fatty acids on relapse rate in ulcerative colitis.

Study	Relapse rate
Middleton, 2002	No significant difference in relapse rates 55% for fish oil and 38% sunflower oil groups over 24 months.
Hawthorne, 1992	230 days (Median number of days) in remission for group that was treatment with fish oil and 208days for group that was treatment with olive oil (no difference) Or Relapse rate 42% with fish oil, 48% with olive oil (P=0·54) over 6 month.
Greenfield, 1993	No difference in relapse rate, 6% for the Max EPA, 13% for olive oil and 5% for super evening primrose oil groups at 6 months.
Loeschke, 1996	Relapse rates 58% for fish oil and 55% corn oil groups over 24 months (No difference; P>0.1).

Different outcomes that have been used to evaluate the effects of interventions in UC patients were presented.

Clinical Response

Clinical responses were reported in four studies (Table 2) and two of them reported a decline in clinical score in the group treated with fish oil (11, 12) and one study (13) reported no significant difference between groups in DAI. A study (11) reported a reduction in clinical scores in the group treated with fish oil (1 to 5) as compared with baseline clinical score (5 to 12, $P < 0.05$). One study (12) reported a decrease in DAI score in for patients treated with fish oil, while DAI scores changed from 2.76 to 1.23 and in the placebo group, DAI scores decreased from 1.65 to 1.59 after the treatment.

In fact, 56% decline in DAI score was reported in the group treated with fish oil, compared with 4% in the placebo group ($P<0.05$). No significant difference was reported between groups in DAI (13). Another study (14) reported a reduction in clinical response in the group treated with fish oil for three months. No significant difference between groups was found during three months.

Endoscopic Score

One study (11) reported a decrease in sigmoidoscopic scores in treatment with fish oil. Decrease in sigmoidoscopic scores were reported in the group treated with fish oil at months three and six (11). sigmoidoscopic score at baseline was 10 to 17 (interquartile range) and after six months decreased to 4-6 ($P=0.013$). In the placebo group, sigmoidoscopic score was 7-17 and then changed to 7-14 after six months.

No significant change was reported by two studies (13, 15) for endoscopic scores in fish oil and placebo groups. Endoscopic score baseline in one study for the fish oil group was 7.36 (SD±-2.86) (15) which then decreased -2.09 points (95% CI -4.63 to 0.45; $P=0.06$) after four months of treatment with fish oil. No significant difference for endoscopic score was found between groups when restricted to UC (13) (Table 3).

Histologic Score

In 3 studies (11, 13, 15), an improvement in histologic score was reported when treatment with fish oil was undertaken (Table 4). One study (11) reported an improvement in histologic score after 6 months treatment with fish oil (mean scores at 6 months were 5 and 8 for fish oil, $P=0.016$). Another study (15) revealed a greater improvement in histology index with fish oil ($P=0·002$). A difference in histologic score was found between n-3 fatty acid (0.85 units at three months) in the control group (13). No significant difference between groups (n-3 fatty acid and comparative group) at three and six months were noted in two studies (12, 16).

Reduction in Corticosteroid Requirement in Patients

Decrease in corticosteroids doses during treatment with fish oil were reported in three studies (12, 15, 17, results are summarized in Table 5), although no significant changes in dosage requirement of corticosteroids (prednisone) were visible in two of them (12, 15). One study (12) reported a reduction in dosage requirement of corticosteroids (anti-inflammatory drugs) during fish oil treatment in 8 out of 11 patients (72%). Another one (17) demonstrated a decrease in prednisolone dose from 10 mg/d at baseline to 5 mg/d AFTER one month to 0 mg/d after two months in the group that treated with n-3 and for olive oil group from 10 mg/d at baseline at 8 mg/d after one month to 5 mg/d after two months ($P=0.01$). In one study, a decrease of 6.8 mg/d in median prednisone dose during fish oil treatment was shown, although no significant changes in dosage requirement of corticosteroids (prednisone) during treatment with placebo were noticed ($P>0.2$) (15).

Achieving Remission After Treatment

One study (11) reported nine patients (100%) achieving remission in the group that were treated with fish oil and none of them (0 out of 9) in the placebo group (RR=19.00, 95% CI=1.27 to 284.24, $P=0.03$).

Time in Remission or Relapse Rate

No significant difference in relapse rate was reported with all of four studies (14, 16-18, results are summarized in Table 6). One study (17) revealed 230 days (Median number of days) remission for the group that was treated with fish oil and 208 in the group that was treated with olive oil (no significant difference), relapse rate of 42% with fish oil, and 48% with olive oil ($P=0·54$). In one study (16), it was shown that no difference in relapse rate was visible, 6% for the Max EPA (Fish oil capsules), 13 % for olive oil and 5% for super evening primrose oil groups after six months. Another one (14) reported a relapse rate of 58% for fish oil and 55% for corn oil over 24 months (no significant difference ($P>0.1$)). The other one (18) reported relapse rate of 55% for fish oil and 38% for sunflower oil over 24 months (no significant difference).

Discussion

The beneficial effect of omega-3 poly-unsaturated fatty acids (n-3) as nutritional components is related to its anti-inflammatory effects and its role as an antioxidant agent (19). In this systematic review, the results showed that treatment with omega-3 PUFA supplement can lead in reduction of corticosteroids dosage requirement in patients with UC. All three studies that assessed this outcome were reports of this entry (12, 15, 17), but only one study showed significant changes in dosage requirement of corticosteroids (17). From four studies that evaluated the relapse rate, all of them showed no significant difference in relapse rate after treatment.

It seems that the second role of the omega-3 PUFA as an antioxidant agent can be changed. In normal situation, when the levels of free oxygen radicals is not still high, n-3 can act as a free radical scavenger; but in terms of high oxidative stress conditions (like inflammation), the fatty acid oxidation is increased and may cause cell damage, but these problems are dependent on the intracellular antioxidant levels (20).

According to the results of some researches, an increase in the intake of antioxidants can reduce oxidation and lead to inflammation and damages. The consumption of omega-3 PUFA and antioxidants was shown to be more efficient in comparison to consumption of omega-3 PUFA alone in prevention and treatment of UC; but this evidence needs more research to be confirmed. In a study that an oral supplement enriched with fish oil was administered, soluble fibers and antioxidants for corticosteroid sparing in patients with UC showed an improvement that may be due to the effect of other components of this supplement, so it is necessary to undertake further researches to show the possible effects of the antioxidants with w3 supplementation in UC improvement (20).

Controversial results of the effect of omega-3 fatty acids supplement on the outcomes have been reported in some articles. The selection of the oil type is important as one study indicated that oleic acid content in olive oil as the placebo can improve UC in animal models. In addition, the use of oils with high levels of w6 fatty acids instead of w3 can change the component of fatty acids synthesis in cell membrane and increase arachidonic acid and lead to inflammation. So the basal level of w6 in comparison to w3 fatty acids in UC patients and the amount that they receive through diet, must be checked before any intervention. Finally, the level of vitamin E as an intracellular antioxidant can reduce lipid peroxidation in cell membrane, so that vitamin E deficiency can influence the results. It seems to be helpful to assess vitamin E deficiency in UC patients and if it is necessary, it must be supplemented before any intervention. Due to inconsistence outcomes that were obtained from this systematic review, we cannot express conclusively that taking omega-3 PUFA supplements in treatment of UC is helpful and still it needs more studies to be conducted in this field.

Conflict of Interest

None declared.

References

1 Hosseinzadeh F, Salehi M, Tanideh N, et al. The Healing Effect of Grape Seed Oil Enema with or without Sesame Oil in Acetic Acid Induced Ulcerative Colitis of Rats. *World J Plast Surg.* 2017;6:176-82. PMID:28713708.

2 Mehrabani D, Ziaei M, Hosseini SV, et al. The effect of calendula officinalis in therapy of acetic Acid induced ulcerative colitis in dog as an animal model. *Iran Red Crescent Med J.* 2011;13:884-90. PMID:22737434.

3 Charlebois A, Rosenfeld G, Bressler B. The Impact of Dietary Interventions on the Symptoms of Inflammatory Bowel Disease: A Systematic Review. *Crit Rev Food Sci Nutr.* 2016;56:1370-8. DOI:1080/10408398.2012.760515. PMID:25569442.

4 Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *J Gastroenterology.* 2012;142:46-54.e42. DOI:1053/j.gastro.2011.10.001.

5 Safarpour AR, Hosseini SV, Mehrabani D. Epidemiology of inflammatory bowel diseases in iran and Asia; a mini review. *Iran J Med Sci.* 2013;38:140-9. PMID:24031103.

6 Mehrabani D, Bahrami F, Hosseini SV, et al. The Healing Effect of Teucrium polium in Acetic Acid-Induced Ulcerative Colitis in the Dog as an Animal Model. *Middle East J Dig Dis.* 2012;4:40-7. PMID:24829634.

7 Turner D, Zlotkin SH, Shah PS, et al. Omega 3 fatty acids (fish oil) for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev.* 2007;(2):CD006320. DOI:1002/14651858.CD006320.pub2. PMID:17443620.

8 Cabré E1, Mañosa M, Gassull MA. Omega-3 fatty acids and inflammatory bowel diseases – a systematic review. *Br J Nutr.* 2012;107:S240–52. DOI:1017/S0007114512001626. PMID:22591898.

9 Ioannidis O, Varnalidis I, Paraskevas G, et al. Nutritional modulation of the inflammatory bowel response. *Digestion*. 2011;84:89–101. DOI:1159/000323456. PMID:21494040.

10 Owczarek D, Rodacki T, Domagała-Rodacka R, et al. Diet and nutritional factors in inflammatory bowel diseases .*World J Gastroenterol*. 2016;22:895-905. DOI:3748/wjg.v22.i3.895. PMID:26811635.

11 Almallah YZ, Richardson S, O'Hanrahan T, et al. Distal procto-colitis, natural cytotoxicity, and essential fatty acids. *Am J Gastroenterol*. 1998;93:804–9. DOI:1111/j.1572-0241.1998.229_a.x. PMID:9625132.

12 Aslan A, Triadafilopoulos G. Fish oil fatty acid supplementation in active ulcerative colitis: a double-blind, placebo-controlled, crossover study. *Am J Gastroenterol*. 1992; 87:432–7. PMID:1553930.

13 Lorenz R, Weber PC, Szimnau P, et al. Supplementation with n-3 fatty acids from fish oil in chronic inflammatory bowel disease: a randomized, placebo-controlled, double-blind cross-over trial. *J Intern Med Suppl*. 1989;731:225–32. DOI:1111/j.1365-2796.1989.tb01461.x. PMID:2650694.

14 Loeschke K, Ueberschaer B, Pietsch A, et al. n-3 fatty acids only delay early relapse of ulcerative colitis in remission. *Dig Dis Sci*. 1996;41:2087–94. DOI:1007/bf02093614. PMID:8888725.

15 Stenson WF, Cort D, Rodgers J, et al. Dietary supplements with fish oil in ulcerative colitis. *Ann Intern Med*. 1992;116:609–614. DOI:7326/0003-4819-116-8-609.

16 Greenfield SM, Green AT, Teare JP, et al. A randomized controlled study of evening primrose oil and fish oil in ulcerative colitis. *Aliment Pharmacol Ther*. 1993;7:159–66. DOI:1111/j.1365-2036.1993.tb00085.x. PMID:8485269.

17 Hawthorne AB, Daneshmend TK, Hawkey CJ, et al. Treatment of ulcerative colitis with fish oil supplementation: a prospective 12 month randomised controlled trial. *Gut*. 1992;33: 922–8. DOI:1136/gut.33.7.922.

18 Middleton SJ, Naylor S, Woolner J, et al. A doubleblind, randomized, placebo-controlled trial of essential fatty acid supplementation in the maintenance of remission of ulcerative colitis. *Aliment Pharmacol Ther*. 2002;16:1131–5. DOI:1046/j.1365-2036.2002.01286.x. PMID:12030955.

19 Yates CM, Calder PC, Ed Rainger G. Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. *Pharmacol Ther*. 2014;141:272–282. DOI:1016/j.pharmthera.2013.10.010. PMID:24201219.

20 Seidner DL , Lashner BA, Brzezinski A, et al. An oral supplement enriched with fish oil, soluble fiber, and antioxidants for corticosteroid sparing in ulcerative colitis: a randomized, controlled trial. *Clin Gastroenterol Hepatol*. 2005;3:358-69. PMID:15822041.