

# Omega-3 Polyunsaturate Fatty Acid Supplementation Potential to Improve Activity Components of Rheumatoid Arthritis: A Systematic Review

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## ABSTRACT

**Introduction:** Rheumatoid arthritis (RA) is a chronic disease that causes deformity in most productive age and can lead to death as disease activity increases. Omega-3 polyunsaturated fatty acids have the potential to complement available therapies in reducing disease activity. Currently, the effect of omega-3 PUFAs on disease activity components is still unclear. The current systematic reviews determine the effect of omega-3 PUFAs' supplementation on the components of RA disease activity.

**Methods:** This research is guided by the PRISMA guidelines systematically. Literature was searched in the databases: PubMed, MDPI, and Clinicaltrials.gov. The inclusion criteria used were: giving omega-3 PUFAs, free full-text, RCT, in English or Indonesian, assessing disease activity and its components; while the exclusion criteria were: unpublished, comparisons were inappropriate. Assessment of literature quality with the Cochrane Collaboration's tool. The study included six studies from 1994 to 2017.

**Results:** The effect of omega-3 PUFAs is diversity in changes of disease activity in 4 of 5 studies. There are significant reductions in the number of joint pains in the literature by daily doses above 2.9 grams or at lower doses taking longer; and swollen joints in 2 studies that were only affected in doses above 2.9 grams. There are significant reductions in pain severity in the studies. Change increases with higher doses. There are variable LED and CRP changes.

**Conclusion:** Depending on their dose and administration duration, omega-3 PUFAs can directly and indirectly affect disease activity through the influence of most of its components, namely: the number of joints affected and the degree of pain.

**Keywords:** Fish oil; omega-3 PUFAs; autoimmune; joint pain; DAS28

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## INTRODUCTION

Rheumatoid Arthritis (RA) is an inflammatory autoimmune disease that usually attacks the joints. This autoimmune disease affects about 1% of the world's population, is dominated by the adult population of productive age ranging from 20-40 years (WHO, 2021). The risk factors for RA are genetic susceptibility and environmental exposure. Environmental exposure in the form of cigarette smoke or infection can trigger injury to self-proteins or process, which is commonly called as the formation of autoantigens, such as through citrullination and carbamylation mechanisms (Lin et al., 2020). Changes in self-protein could not be recognized and tolerated in certain genetic groups, both the HLA group (HLA-DR4, HLA-DRB1) and non-HLA groups (PTPN22, TRAF1, STAT4, CTLA-4, PAD14) (Abbas et al., 2018). Failure of this tolerance mechanism is followed by activation of innate and adaptive immune systems through activation of autoreactive T cells and autoreactive B cells. Innate and adaptive immune system follows the blood flow to the joints. In joints, these activated immune cells trigger the release of pro-inflammatory cytokines, activation of macrophages, activation of synovial cells,

and the formation of autoantibodies. Injured body cells are recognized as foreign bodies. This mechanism continues in the body of patients with RA as a process of forming chronic inflammatory autoimmune. This chronic inflammatory process has the potential to be stopped through diet or supplementation of omega-3 PUFAs, which are capable of eliciting an immunomodulatory effect, through the competitive inhibitory role of cyclooxygenase and lipooxygenase enzymes (Calder, 2010). Another mechanism of omega-3 PUFAs studied in inhibiting chronic inflammation is the control of CD4 T cells, monocytes, and major histocomplex class II. This treatment is expected to be able to prevent or control joint manifestations in the form of pain, swelling, stiffness, to deformities, such as boutonniere deformity and swan neck deformity. Early and adequate management is needed to prevent further extra-joint manifestations of RA. The success of therapy can be observed in the disease activity components such as the number of painful joints, the degree of pain, the number of swollen joints, ESR, and CRP (Lin et al., 2020). This study investigated the effect of omega-3 PUFAs supplementation on the components of RA disease activity.

## METHODS

The literature reviewed in this study were those using randomized controlled trial method. The included literature must be in free full-text in Indonesian or English. In addition, unpublished literature, editorials, and reviews have been excluded. Study eligibility was selected based on the PICO frameworks in Table 1.

Table 1. Study eligibility

Criteria	Explanation
Population	Patients with RA aged 18 years and over.
Intervention	Omega-3 PUFA supplementation includes $\alpha$ -linolenic acid, eicosapentaenoic acid, and/or docosahexaenoic acid.
Comparison	Placebo or supplementation other than omega-3 PUFAs
Outcome	1. AR disease activity scores were categorized into mild, moderate, and severe degrees. 2. Components of the assessment of the AR disease activity score.

The literature search in this study used the Pubmed, clinicaltrials.gov, and MDPI electronic databases published until April 2021. The literature search used the Boolean Operators OR and AND with the search terms (“Omega-3 PUFAs” OR “Omega-3 Polyunsaturated fatty acids”) AND (Disease Activity) AND (Rheumatoid Arthritis OR Inflammatory arthritis).

Literature assessment in randomized controlled trials used the Risk of Bias 2 assessment form from the Cochrane Risk of Bias Tool. The data obtained were then collected in a collection sheet in Microsoft Excel. The data were analyzed descriptively and systematically to answer research questions.

## RESULTS

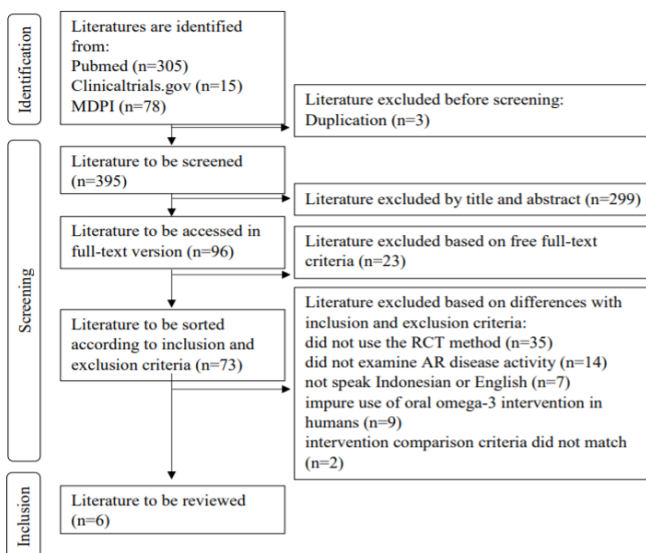


Figure 1. Study selection using PRISMA

Six pieces of literature were obtained and then evaluated for risk of bias (Geusens et al., 1994; Dawczynski et al., 2009, 2011; Reed et al., 2014; Rajaei et al., 2015; Veselinovic et al., 2017). It was found that 5 of the 6 literature had a low risk of bias and the rest had concerns of bias but were considered in the analysis. The details of the literature assessment are summarized in Figure 2.

	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall	
(Dawczynski, 2011)	+	+	+	+	+	+	
(Veselinovic, 2017)	+	+	+	+	+	+	Low risk
(Geusens, 1994)	!	+	+	+	+	!	Some concerns
(Dawczynski, 2009)	+	+	+	+	+	+	High risk
(Rajaei, 2016)	+	+	+	+	+	+	
(Reed, 2014)	+	+	+	+	+	+	

Figure 2. Differences in the improvement of total joint pain in omega-3 and comparison groups

It was found that 5 of 6 studies were conducted on the European continent, the rest on the Asian continent (Geusens et al., 1994; Dawczynski et al., 2009, 2011; Reed et al., 2014; Rajaei et al., 2015; Veselinovic et al., 2017). All were randomized, double-blind, placebo-controlled clinical trials. The literature was published in the range of 1994 to 2017.

The number of research subjects in this systematic study were 384 patients, consisting of 334 women (87%) and 50 men (13%). The mean age in the literature ranges from 42.4 to 63.1 years. All study subjects were diagnosed with RA with the ACR (American College of Rheumatology) criteria. The drugs were corticosteroids and NSAIDs. The dose was ensured to be stable at least 4 weeks before intervention in 5 of the 6 reviewed literature (Geusens et al., 1994; Dawczynski et al., 2009, 2011; Reed et al., 2014; Veselinovic et al., 2017). While DMARD use has been confirmed to be stable, the dose was at least 8 weeks prior to intervention in 5 of 6 literature. Only the literature by Rajaei does not include data on the history of use of pharmacological therapy (Rajaei et al., 2015).

Overall, from 6 included literature, omega-3 PUFAs were given for a minimum of 12 weeks and a maximum of 48 weeks (Geusens et al., 1994; Dawczynski et al., 2009, 2011; Reed et al., 2014; Rajaei et al., 2015; Veselinovic et al., 2017). A study by Dawczynski that lasted 48 weeks showed that as many as 6 people (13%) dropped out in the first 32 weeks due to side effects of DMARDs (Dawczynski et al., 2009). The mean daily dose of omega-3 PUFAs administered to the included studies varied, with the lowest dose being 2.2 grams and the highest dose being 3.9 grams (Geusens et al., 1994; Dawczynski et al., 2009, 2011; Reed et al., 2014; Rajaei et al., 2015; Veselinovic et al., 2017).

Findings of 5 studies were included in this systematic review using DAS28 (Dawczynski et al., 2009, 2011; Reed et al., 2014; Rajaei et al., 2015; Veselinovic et al., 2017). A significant change in disease activity was found after the administration of omega-3 PUFAs.

Four literature showed a significant reduction in joint pain, both in the intervention group and in the comparison group (Geusens et al., 1994; Dawczynski et al., 2009; Rajaei et al., 2015; Veselinovic et al., 2017). After 12 weeks of administration with 3 to 3.9 grams of omega-3 PUFAs daily, there was a significant difference in the value of reducing joint pain compared with the comparison group (Rajaei et al., 2015; Veselinovic et al., 2017).

Table 2. Characteristics of research interventions

No	(First researcher, year)	Omega-3 administration duration (weeks)	Dosage and frequency of administration of omega-3
1	(Veselinovic, 2017)	12	Distributed 3 types (1) 3000 mg omega-3 PUFA/day (1 capsule = 600mg); (2) 1200 mg n-3 PUFA + 1300 mg PMO/day; (3) without supplementation. The two groups studied, group 1 dan 3 (comparative).
2	(Dawczynski, 2011)	12	Distributed 3 types (1) 3000 mg omega-3 PUFA/day ; (2) 3150- mg GLA/day; (3) 1575 mg n-3 PUFA dan 1800 mg GLA/day; (4) 3000 mg olive oils. The two groups studied, group 1 dan 4 (comparative).
3	(Geusens, 1994)	48	Distributed 3 types (6 capsules each group) total daily dose = (1) 2.6 g n-3 LC PUFA , (2) 1.3 g n-3 LC PUFA + placebo (3 g olive oils), (3) 6 g olive oils. Evaluate grup 1 dan 3 (comparative).
4	(Dawczynski, 2009)	48	Distributed 2 types = (1) 1.1 g ALA, 0.7 g EPA, 0.1 g DPA and 0.4 g DHA in milk; (2) placebo. The two groups studied, group 1, group 2
5	(Rajaei, 2015)	12	Distributed 2 types of capsules (3 capsules per group)= (1) 1.8 gram EPA and 2,1 gram DHA; (2 placebo)
6	(Reed, 2014)	36	(1) 6 capsules of BSO (1.8 gm GLA) and 7 capsules of SSO daily; (2) 7 fish oil capsules (2.1 g EPA/1.4 g DHA) and 6 daily SSO capsules; (3) 6 capsules of BSO and 7 capsules of fish oil daily. Examined groups 2 and 1 (comparative).

Table 3. Changes in disease activity

(First Researcher, Year)	Classification of Disease Activity	Disease activity of the group of omega-3 PUFAs		Disease activity of the comparison group		Conclusions in the literature
		Before intervention	After intervention	Before intervention	After intervention	
(Veselinovic, 2017)	DAS 28	Moderate-severe (4.99±8.2)	Mild-moderate (3.91±0.80)	Moderate (Moderate-severe) (4.66 ± 0.80)	Moderate (4.23 ± 0.66)	Significantly different (p≤0.001)
(Dawczynski, 2011)	DAS 28	Moderate (moderate-severe) (4.7 ± 0.9)	Moderate (mild-moderate) (3.8 ± 1.2)	Moderate (4.4 ± 0.6)	Moderate (mild-moderate) (3.7 ± 1.2)	Significantly different in omega-3group
(Dawczynski, 2009)	DAS 28	Moderate (moderate-severe) (4.45 ± 1.05)	Moderate (mild-severe) (4.32 ± 1.11)	Moderate (mild-severe) (4.18 ± 1.11)	Moderate (moderate-severe) (4.24 ± 0.80)	Significantly different (p≤0.01)
(Rajaei, 2015)	DAS 28	Moderate -severe	Mild-moderate	Moderate-severe	Moderate	Significantly different (p≤0.05)
(Reed, 2014)	DAS 28	Moderate-severe (5.2 ± 0.8)	Mild-moderate (3.64 ± 0.6)	Moderate (moderate-severe) (5 ± 0.8)	Moderate (mild-moderate) 3.67 ± 0.5	Not significantly different

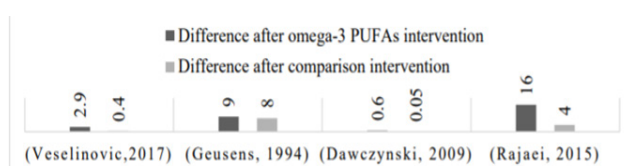


Figure 3. Differences in the improvement of total number of joint pain in omega-3 and comparison groups

A significant reduction in the number of swollen joints occurred in all three included studies, both in the intervention group omega-3 PUFAs and the comparison

group (Dawczynski et al., 2009; Rajaei et al., 2015; Veselinovic et al., 2017). After giving omega-3 PUFAs starting from 3 grams to 3.9 grams/day for 12 weeks, it was found that the reduction in the number of swollen joints was better than the comparison group (Rajaei et al., 2015; Veselinovic et al., 2017). Different results were obtained in the administration of omega-3 PUFAs at a dose of 2.3 grams/day for 48 weeks, which resulted in lower number of swollen joints in the comparison group (Dawczynski et al., 2009).

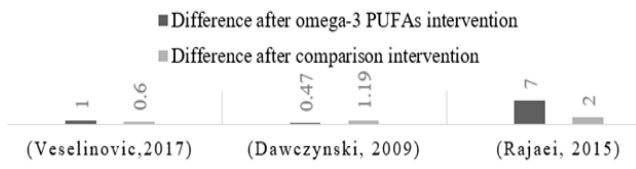


Figure 4. Differences in the improvement of total number of swollen joint in omega-3 and comparison groups

Pain scales were not always included in the study that provided data on disease activity scores. These four studies showed a significant reduction in the intervention group receiving omega-3 PUFAs (Geusens et al., 1994; Dawczynski et al., 2011; Rajaei et al., 2015; Veselinovic et al., 2017). Similar results were found in the comparison group, except those in Rajaei's study where the degree of pain was constant (Rajaei et al., 2015).

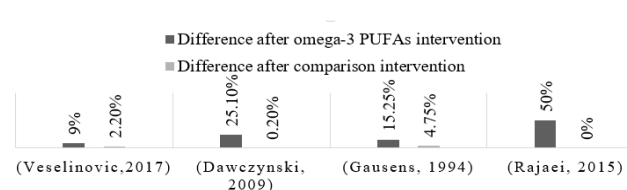


Figure 5. Differences of LED repair (mm/h) in omega-3 and comparison group

To determine the disease activity score, the results of the LED and CRP laboratory tests were considered, which were derived from supporting examinations data. The LED data were reviewed from 4 included literature (Geusens et al., 1994; Dawczynski et al., 2009; Rajaei et al., 2015; Veselinovic et al., 2017). CRP assessment data were reviewed from 2 literature (Dawczynski et al., 2009; Veselinovic et al., 2017).

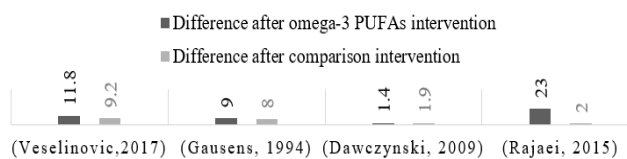


Figure 6. Differences in the pain degree improvement (%) in omega-3 and comparison groups

The entire literature showed a significant decrease in ESR and CRP outcomes, both in the intervention group and in the comparison group, except for the study conducted by Dawczynski which tended to remain constant (Dawczynski et al., 2009).

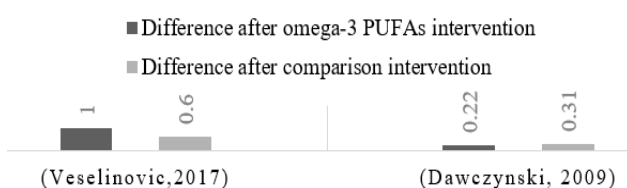


Figure 7. Differences in CRP improvement (mg/dl) in omega-3 and comparison group

## DISCUSSION

This review found that the maximum intervention of omega-3 PUFAs was 48 weeks. This was in accordance with the findings of a systematic review by Nelson with 14 literature that the maximum intervention time is 48 weeks (Nelson et al., 2020).

The literature reviewed in this study showed that the lowest administered dose of omega-3 PUFAs was 2.2 grams and the highest was 3.9 grams. However, a research by Akintoye in the form of a placebo-controlled trial with 1516 multinational patients showed that doses of omega-3 PUFAs above this limit can cause mild bleeding (Akintoye et al., 2018). This systematic review found that lower doses of marine omega-3 PUFAs showed the only minimal impact.

From the reviewed literature, we found that daily administration of 3 to 3.9 grams of omega-3 PUFAs for 12 weeks resulted in significant difference in the joint pain reduction between the intervention and the comparison groups. The reduction in joint pain in the included studies is in line with a meta-analysis of a randomized controlled trial by Goldberg and Katz that omega-3 PUFAs can reduce the number of painful joints with a minimum dose of 2.9 grams and within a minimum of 12 weeks (Goldberg and Katz, 2007). However, this meta-analysis differs from 2 other included studies that also had a positive effect with doses of omega-3 PUFAs below 2.9 grams/day (2.3 grams to 2.6 grams) for 48 weeks (Geusens et al., 1994; Dawczynski et al., 2009). This difference can occur at the daily dose of omega-3 PUFAs below 2.9 grams, but it is still above the 1.5 gram dose, and the effect has only been shown in the longer intervention time. Although the smaller dose had a positive effect on the number of painful joints, the most significant difference in the reduction in the number of joint pains was still found in the study with the highest daily dose of omega-3 PUFAs, which was 3.9 grams/day (Rajaei et al., 2015).

The studied literature showed that there were different results in the reduction of the number of swollen joints after the administration of omega-3 PUFAs from 3 - 3.9 grams/day for 12 weeks and at a dose of 2.3 grams/day for 48 weeks (Dawczynski et al., 2009; Rajaei et al., 2015; Veselinovic et al., 2017). This difference was in line with a meta-analysis of randomized controlled studies examining the effect of omega-3 PUFAs at a dose of at least 2.9 grams and for at least 12 weeks (Goldberg and Katz, 2007). In this meta-analysis, the administration of omega-3 PUFAs in doses exceeding 2.9 grams for more than three weeks could potentially reduce the number of swollen joints. This decrease in the number of joints affected, both the number of painful joints and the number of swollen joint, may occur due to the anti-inflammatory effect of omega-3 PUFAs by lowering RA.

The reviewed studies also showed significant reduction in pain scales among the groups receiving omega-3 PUFAs intervention. Research by Rajaei had the most significant pain reduction value, which was a decrease of 50% from the pre-intervention value. The research by Rajaei was the only included literature whose research was carried out in the Asian continent. The dose used in this study was the highest dose which was found to be directly proportional to the decrease in the degree of pain among the included studies that provided data on the patient's pain scale. These data were supported by a meta-analysis study from Goldberg and Katz which stated that the administration of omega-3 PUFAs above 2.7 grams/day can reduce

pain complaints in patients with inflammatory arthritis (Goldberg and Katz, 2007). In addition, decreased NSAID consumption in the intervention group omega-3 PUFAs was found in a systematic review by Miles and Calder (Miles and Calder, 2012).

Significant decrease in ESR and CRP outcomes was also found in the studied literature. However, the study of Dawczynski et al. (2009) showed constant ESR and CRP outcomes. This was in line with research by Lourdudoss, which also used omega-3 PUFAs in non-supplements (Lourdudoss et al., 2018). In this study, the levels of CRP and ESR as markers of systemic inflammation were not affected by supplementation of omega-3 PUFAs in a population of early-stage AR patients.

There were several limitations of this study. First, there was limited number of included literatures, especially those that provide data on the results of supporting examinations. Second, the types of omega-3 PUFAs used were diverse. In addition, there might have been the presence of the influence of non-supplementary diet, but it was not studied. Then, there was limited amount of research literature taken from developing countries, but epidemiologically the number of cases in these countries continues to increase. Fourth, the complete assessment components might have caused bias in drawing conclusions. Then, the wide range of participants' sex comparisons might have led to bias towards some components of disease activity. Finally, some of the included literature did not include a history of treatment, so that there could be bias in concluding.

## CONCLUSION

Supplementation of omega-3 PUFAs decreased AR disease activity scores, reduces the number of painful joints and swollen joints at doses above 3 grams/day for at least three months or at lower doses over a longer period of time; reduced the degree of pain, and reduced the results of ESR and CRP investigations when given at doses above 3 grams/day.

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## CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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## AUTHOR CONTRIBUTION

All author have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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