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Dear Dr. Rodry R Mikhael,

Good day. Thank you for your submission of the manuscript "**Seluang Fish (Rasbora sp.) Oil Improves Interleukin 17 Levels in Rheumatoid Arthritis**" to The Indonesian Biomedical Journal.

Regarding the [regulation about submission fee](#) for our journal, herein we attach the invoice for submission #2085. Please complete the payment before **October 10, 2022**.

Please let us know once you have done with the payment process (make sure you send us the payment proof), so that we can proceed your manuscript to the initial check.

Thank you. If you have any questions, please contact us.

Best Regards,

—

Secretariat of The Indonesian Biomedical Journal

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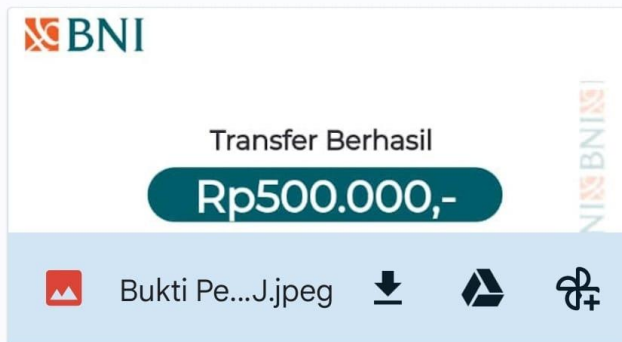
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Dear secretariat of INABJ journal,
here we attach the payment proof for our article
submission

thank you
regards
Rodry Mikhael

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Dear Author,

Thank you for the submission fee payment. We will soon proceed manuscript #2085 for initial check after we confirm the payment to our finance staff. The initial check process usually will take about 2-3 days. We will contact you back when we have done with the process.

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Noted with thanks.

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Ok, thank you.



Balas



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[InaBJ] M2022174 Manuscript
Initial Check  Kotak Masuk



Secretariat of InaBJ 5/10/2022



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Dear Dr. Rodry R Mikhael,

Good day. Thank you for your submission of the manuscript "**Seluang Fish (Rasbora sp.) Oil Improves Interleukin 17 Levels in Rheumatoid Arthritis**". Your manuscript has been coded as **M2022174**, please note this code for your reference to communicate with us regarding this manuscript in the future.

Before your manuscript is sent to our reviewers, it has been initially checked. For a detailed list of corrections, please find it in the manuscript attached. Please **mark/highlight the revised part of the manuscript**, so that the editor will notice the changes.

Please send us an email of your corrected manuscript before **October 9, 2022** so that we can proceed with the peer-reviewing process. If you have any questions, do not hesitate to contact us.

Thank you. Please let us know if you have any questions. We wish you a nice day.

Best Regards,

—



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15.34

Voij 4G LTE1 Voij LTE2



rodtobing 8 Okt
kepada Sekretariat



Dear Editor of The Indonesian
Biomedical Journal

Thank you for your email. Here we
attach our revised manuscript titled
**"Seluang Fish (*Rasbora sp.*) Oil
Improves Interleukin 17 Levels in
Rheumatoid Arthritis"**.

(code **M2022174**). We have
corrected the manuscript and the
details have been highlighted so the
editor can mark the results of the
correction. If there is anything that
needs to be added or corrected,
please tell us.

Regards
Rodry Mikhael

On Wed, Oct 5, 2022 at 3:49 PM Sekretariat of InaBJ
<secretariatnabj@gmail.com> wrote:

[Tampilkan kutipan teks](#)



15.36

Voij 4G LTE1 Voij LTE2



Secretariat of InaBJ 28 Okt

kepada tobing28, saya ▾



Dear Mr. Rodry Mikhael,

Good day. We have reached a decision regarding your submission to The Indonesian Biomedical Journal, "**Seluang Fish (Rasbora sp.) Oil Improves Interleukin 17 Levels in Rheumatoid Arthritis**".

Our decision is to: **Resubmit for Review**.

This manuscript is interesting, however it needs major revisions before it can be published, since we found a lot of unclear information about the preparation of Seluang fish oil. Find the files attached to see our reviewer's detailed comments. Please revise this manuscript according to reviewers' suggestions, and provide us a revised version of your manuscript and a response letter to the reviewer before **November 11, 2022**.

Make sure you proofread the manuscript before sending it back. Mark/highlighted the revised part of the manuscript, so that the editor will notice the changes. You are also obligated to fill the attached Response Form for Reviewer's Comments with your response or the answer to reviewers' question/comments. Please do not hesitate to contact us if you have any questions.

When you are done, you can upload it in:

<https://inabj.org/index.php/ibj/author/submissionReview/2085>, or simply send us an email.



M2022174 Revision (Round 2)



Tambahkan label



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kepada Sekretariat, Rodrymik... ▾



Dear Editor and Reviewer of Indonesia Biomedical Journal

Thank you for your willingness in reviewing our submitted manuscript (M2022174). Based on your correction in round 2, here we make our revised manuscript, with detailed corrections and comments based on your review and advice. This revision has been discussed and agreed upon by all authors.

We hope that this manuscript will be accepted by all the reviewers and the editorial team of InaBJ. Please tell us if there is anything that needs to be corrected.

Regards,

Rodry Mikhael



M2022174...ments.xlsx



← [InaBJ] M2022174 Editor Decision -
Resubmit for Review



Secretariat of InaBJ

ke Saya & 1 lainnya

📧 28/10/2022 16.29



Dear Mr. Rodry Mikhael,

Good day. We have reached a decision regarding your submission to The Indonesian Biomedical Journal, "**Seluang Fish (*Rasbora sp.*) Oil Improves Interleukin 17 Levels in Rheumatoid Arthritis**".

Our decision is to: **Resubmit for Review.**

This manuscript is interesting, however it needs major revisions before it can be published, since we found a lot of unclear information about the preparation of Seluang fish oil. Find the files attached to see our reviewer's detailed comments. Please revise this manuscript according to reviewers' suggestions, and provide us a revised version of your manuscript and a response letter to the reviewer before **November 11, 2022.**

Make sure you proofread the manuscript before sending it back. Mark/highlighted the revised part of the manuscript, so that the editor will notice the changes. You are also obligated to fill the attached Response Form for Reviewer's Comments with your response or the answer to reviewers' question/comments. Please do not



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Secretariat of InaBJ 31 Okt

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Thank you for your response.

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Dear Editor, Indonesian Biomedical Journal

Greetings,

we want to ask some question regarding our submission

1. how much the similarity cut-off allowed for manuscript submission, to avoid plagiarism in InaBJ? because we want to check for plagiarism before manuscript re-submission

2. Based on the previous review, we were asked to make a picture that explains the working mechanism of Seluang fish oil/vitamin D and proinflammatory cytokines. Should we make our own pictures or can we use picture from other articles?

Thank you for your attention

regards

Rodry mikhael



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kepada Sekretariat



Dear Editor and Reviewer, Indonesia Biomedical Journal.

Greetings from Palembang

Thank you for your willingness in reviewing our submitted manuscript (M2022174) about Seluang Fish Oil efficacy in Rheumatoid Arthritis.

Here we make our re-submission manuscript, with detailed corrections inside based on your review and advice. Also, we add a letter from the author regarding the manuscript submission.

We hope that this manuscript will be accepted by all the reviewers and the editorial team of InaBJ.

Please tell us if there is anything that needs to be corrected.

Regards,

Rodry Mikhael

On Fri, Oct 28, 2022 at 4:29 PM Sekretariat of InaBJ <secretariatnabj@gmail.com> wrote:

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← [InaBJ] M2022174 Editor Decision
Round 2 - Revisions Required



Secretariat of InaBJ

ke Saya



11/11/2022 16.17

Dear Mr. Rodry R Mikhael,

Good day. We have reached a decision regarding your submission to The Indonesian Biomedical Journal, "**Seluang Fish (*Rasbora sp.*) Oil Improves Interleukin 17 Levels and Disease Activity in Rheumatoid Arthritis**".

Our decision is to: **Revisions Required.**

Thank you for your revision in the previous round, however, we still find that this manuscript still needs some revisions. Find the file attached to see our editor's detailed comments. Our editor also did some editorial revision to your manuscript, please let us know if there's any statement that you do not agree with.

Please revise this manuscript according to the suggestions before **November 21, 2022**. Mark/highlighted the revised part of the manuscript, so that the editor will notice the changes.

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Please let us know when you have received this



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kepada Secretariat, Rodrymik... ^



Dari rodtobing • rodrymikhael1990@gmail.com

Kepada Secretariat of InaBJ •
secretariatinabj@gmail.com
Rodrymikhael Lumbantobing •
tobing28@yahoo.com

Tanggal 19 Nov 2022 07.27

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Dear Editor and Reviewer of Indonesia Biomedical Journal

Thank you for your willingness in reviewing our submitted manuscript (M2022174). Based on your correction in round 2, here we make our revised manuscript, with detailed corrections and comments based on your review and advice. This revision has been discussed and agreed upon by all authors.

We hope that this manuscript will be accepted by all the reviewers and the editorial team of InaBJ. Please tell us if there is anything that needs to be corrected.

Regards,

Rodry Mikhael



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VoLTE1 VoLTE2 4G



[InaBJ] M2022174 Proof

Reading & Article in Press



Kotak Masuk



Secretariat of InaBJ 9/12/2022

Dear Authors, Thank you for your contribution to The Indonesian Biomedical Journal. In this



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kepada Secretariat

Dear Editor Indonesian Biomedical Journal.
Thank you for your email.
We will read the manuscript , fill the attached form
and send it back to the journal.
Regards.
Rodry Mikhael

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M2022174 article response



Kotak Masuk



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Dear Editor of The Indonesian Biomedical Journal We have read the manuscript and



Secretariat of InaBJ 12/12/2022

Dear Dr Rodry Mikhael, Thank you for your proofreading approval. We have now



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Dear Editor of Indonesian Biomedical Journal.
We have received your email and we approve this correction

Thank you and best regards,

Rodry Mikhael

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VoLTE1 VoLTE2 4G



Decision - Manuscript



Accepted  Kotak Masuk



Secretariat of InaBJ 21/11/2022



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Dear Dr. Rodry R Mikhael,

Good day. We have reached a decision regarding your submission to The Indonesian Biomedical Journal, "**Seluang Fish (*Rasbora sp.*) Oil Improves Interleukin 17 Levels and Disease Activity in Rheumatoid Arthritis**".

Our decision is to: **Accept Manuscript.**

Your manuscript will be sent to our publisher for typesetting and you should receive the proofreading in due course. We will let you know once your manuscript is available to be accessed in our [Article in Press](#) section.

Congratulations on your interesting research, and thank you for allowing us to publish this valuable material. Please let us know once you have read this email. We wish you a nice day.

Best Regards,

--

Secretariat of The Indonesian Biomedical Journal

Prodia Tower 9th Floor

11 Kramat Raya No. 150 Jakarta 10430





[InaBJ] M2022174 Publication
Fee Invoice  Kotak Masuk



Secretariat of InaBJ 21/11/2022

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Dear Dr. Rodry Mikhael,

Good day. Our editor has decided that your manuscript "**Seluang Fish (*Rasbora* sp.) Oil Improves Interleukin 17 Levels and Disease Activity in Rheumatoid Arthritis**" is acceptable for publication, please complete the payment for publication fee.

Regarding [the regulation about publication fee](#) for our journal, herein we attach the invoice for submission M2022174. Please complete the payment before **November 28, 2022**. Let us know once you have done with the payment process (by sending us the payment proof).

Thank you. We will be waiting to hear from you.
We wish you a nice day.

Best Regards,

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Fax. +62-21-3144181



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VoLTE1 VoLTE2 4G




[InaBJ] M2022174 Editor

Decision - Manuscript



Accepted  Kotak Masuk



Secretariat of InaBJ  21/11/2022

Dear Dr. Rodry R Mikhael, Good day. We have reached a decision regarding your



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Dear Editor, Indonesian Biomedical Journal

Greetings from Palembang

Thank you for your acceptance in our manuscript submission.

Please let us know when the article has been published.

Regards.

Dr.Radiyati Umi Partan, SpPD KR/ Dr. Rodry Mikhael

[Tampilkan kutipan teks](#)



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[InaBJ] M2022174 Proof
Reading & Article in Press ▶



Kotak Masuk



Secretariat of InaBJ 9/12/2022

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Dear Authors,

Thank you for your contribution to The Indonesian Biomedical Journal. In this opportunity, we would like to inform you that your manuscript "**Seluang Fish (Rasbora sp.) Oil Improves Interleukin-17 Levels and Disease Activity in Rheumatoid Arthritis**" is now available online in our [Article in Press](#) section.

We have done some editorial changes to the manuscript. Hence, we need your assistance to check if there's any mistake in our printing and please state your agreement and fill the form attached before **December 19, 2022**. If you find any mistake in the design, please do not hesitate to let us know.

Please find the attachment to view the draft of the manuscript and the proof reading form. When you completed all your corrections/comments, please send your commented copy and send it along with your filled "**Proof Reading Approval by Author**" to our email address in secretariat@inabj.org.

To complete the metadata during publication, we



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To complete the metadata during publication, we also need your assistant to inform us **the email address of the following coauthors:**

1. Radiyati Umi Partan
2. Triawan Adinata
3. Surya Darma
4. Muhammad Reagan
5. Rina Kriswiastiny
6. Yulianto Kusnadi
7. Eddy Mart Salim

Thank you for your kind attention and cooperation. We will be waiting to hear from you.

Best Regards,

--

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Dear Editor of The Indonesian Biomedical Journal
We have read the manuscript and proposed some minor grammatical changes (highlighted in the PDF article). Otherwise, the article looks good to us. The proofreading approval has been filled and signed by the author.

The email address of each author are listed below

1. Radiyati Umi Partan (radiandinadr@yahoo.co.id)
2. Triawan Adinata (triawan.adinata@gmail.com)
3. Surya Darma (sdarma71@yahoo.com)
4. Muhammad Reagan (muhammadreagan@gmail.com)
5. Rina Kriswiastiny (rinakriswiastiny@yahoo.com)
6. Yulianto Kusnadi (yk_raihan@yahoo.com)
7. Eddy Mart Salim (eddysalim13@yahoo.com)

Thank you
Best regards
Rodry Mikhael



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[InaBJ] New Issue Published (InaBJ Vol.15 No.1) Kotak Masuk



Secretariat of InaBJ 23 Feb

kepada Anna, ferry, Hamsu, H...  

Dear Authors,

The Indonesian Biomedical Journal has just published its latest issue (Vol.15 No.1, February 2023) at <https://inabj.org/index.php/ibj/issue/view/50>. We invite you to check it as your manuscripts are included in this issue.

Thank you for allowing us to publish your article.
We will be waiting for your next submission.

Best Regards,

—

Secretariat of The Indonesian Biomedical Journal

Prodia Tower 9th Floor

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by

Submission date: 23-Mar-2023 06:33AM (UTC-0400)

Submission ID: 2044346577

File name: 2085-6272-1-PB-1.pdf (1.81M)

Word count: 6100

Character count: 31470

RESEARCH ARTICLE

Seluang Fish (*Rasbora* sp.) Oil Improves Interleukin-17 Levels and Disease Activity in Rheumatoid ArthritisRadiyah Umi Partan¹, Rodry Mikhael^{1,*}, Triawan Adinata¹, Surya Darma¹, Muhammad Reagan¹,
Rina Kriswiastiny¹, Yulianto Kusnadi², Eddy Mart Salim³¹Division of Rheumatology, Department of Internal Medicine, Dr. Mohammad Hoesin General Hospital, Jl. Jenderal Sudirman KM 3.5, Palembang 30126, Indonesia²Division of Endocrinology, Department of Internal Medicine, Dr. Mohammad Hoesin General Hospital, Jl. Jenderal Sudirman KM 3.5, Palembang 30126, Indonesia³Division of Allergy-Immunology, Department of Internal Medicine, Dr. Mohammad Hoesin General Hospital, Jl. Jenderal Sudirman KM 3.5, Palembang 30126, Indonesia

*Corresponding author. E-mail: rodrymikhael1990@gmail.com

Received date: Oct 3, 2022; Revised date: Nov 20, 2022; Accepted date: Nov 21, 2022

Abstract

BACKGROUND: Vitamin D has a role in downregulating the proinflammatory cytokines as well as promoting the antiinflammatory pathway in rheumatoid arthritis (RA). Seluang fish (*Rasbora* sp.) has potency as a new source of vitamin D. Previous study had proven Seluang fish oil efficacy in systemic lupus erythematosus. However, there are no trials that prove its efficacy in RA yet. Hence, this study was conducted to find out the ability of Seluang fish oil to improve proinflammatory cytokines, vitamin D levels, and disease activity in RA.

METHODS: A clinical trial with a randomized and double-blind method was done in two groups, each one consisting of 17 RA subjects. One group was given 500 µL of a Seluang fish oil capsule (contains 665 IU cholecalciferol), while the other group was given a placebo daily, for 12 consecutive weeks. Measurements of the RA disease activity score 28 erythrocyte sedimentation rate (DAS28-ESR) and DAS28 C-reactive protein (DAS28-CRP), as well as measurement

of interleukin (IL)-6, IL-17, and vitamin D levels by using immunoassay method were performed before and after the supplementation.

RESULTS: Significant alterations in the lower levels of IL-17 were observed in the Seluang fish oil group ($p=0.031$), but not in the placebo group ($p=0.320$). Reduction of DAS28-ESR ($p=0.000$) and DAS28-CRP ($p=0.000$) score demonstrated that the Seluang fish oil supplementation was useful in reducing RA disease activity. No significant shift was observed in either vitamin D ($p=0.967$) or IL-6 levels ($p=0.076$) after Seluang Fish Oil supplementation.

CONCLUSION: Seluang fish oil is effective in lowering IL-17 levels, DAS28-ESR, and DAS28-CRP, but not in improving vitamin D level or lowering IL-6 level in RA patients.

KEYWORDS: rheumatoid arthritis, seluang fish oil, interleukin-6, interleukin-17, vitamin D, DAS28

Indones Biomed J. 2023; 15(1): 61-8

Introduction

Rheumatoid arthritis (RA) is a global problem in rheumatology. As a chronic autoimmune disorder, it causes joint pain and stiffness as well as extra-articular

manifestations that impair patients' quality of life. The number of people with RA in Indonesia is between 0.5-1% of the population, which is increasing every year.(1) This disease is characterized by the presence of immunoglobulin against the component of citrullinated protein. RA is initiated by the peptide citrullination followed by the formation of



autoantibodies, namely **rheumatoid factor (RF)** or **anti-citrullinated peptide antibody (ACPA)**, which is present in approximately 71.4 % of cases.(2) The clinical findings that happen to people with RA are due to the inflammatory process, the build-up of immune complexes, and synovitis. The presence of RF (or ACPA) is caused by several cytokines, namely interleukin (IL)-4, IL-5, and IL-10. They will trigger the proliferation of B lymphocytes, thus producing an autoantibody. These cytokines are produced by T-helper2 cells. The condition sets off the inflammatory process interfered by **IL-1, IL-6, IL-17, and tumor necrosis factor (TNF)- α** . It can damage joints as well as extra-articular organ involvement, such as scleritis, rheumatoid nodules, vasculitis, as well as Felty syndrome, and deliver the clinical findings in RA.(2) Previous studies found that elevated levels of IL-6 and IL-17 are related to higher symptoms in RA.(3,4)

One of the clinical conditions that worsen RA symptoms is vitamin D deficiency. Vitamin D (1,25 OH-cholecalciferol) helps to control how cells in the immune system work, and how they are regulated. Similar to other types of autoimmune rheumatic disorder, such as **systemic lupus erythematosus (SLE)** and **juvenile idiopathic arthritis (JIA)**, RA patients often have a mild or severe reduction in vitamin D levels. When immunosuppressant drugs called glucocorticoids are given, vitamin D levels drop due to the reduced hydroxylation process of cholecalciferol.(5-7) Its supplementation can slow down the immune response, which stops the chain reaction of inflammation, and helps RA patients' clinical problems.(8-10) So, providing vitamin D supplements for RA patients has become a key part of the treatment.(1)

Management of RA is necessary to obtain remission or low-disease activity. A previous multicenter study found that the number of patients that achieve remission in RA is 62.3% based on **disease activity score 28 C-reactive protein (DAS28-CRP)**, and 35.5% based on **DAS28 erythrocyte sedimentation rate (DAS28-ESR)**. Factors that contribute in achieving remission in RA include young patients, less comorbidity, and the use of biologic agents.(11) Clinical remission in RA is related to the improvement of T regulatory (Treg) balance, while vitamin D supplementation showed benefits in increasing Treg number and function. (12) Therefore, a clinical smart step in managing RA aims to find possible natural sources of vitamin D. Seluang fish (*Rasbora* sp.) is a kind of freshwater river species fish that can be discovered in South Sumatra, Indonesia. Seluang fish are a part of daily consumption in South Sumatra, as well as in other regions in Indonesia. This fish is at the

bottom of its food chain, so it doesn't get the heavy metals that tend to build up in the top consumers.(13) A previous study found that the extraction of Seluang fish oil contains 2043.34 IU/mL of Vitamin D (cholecalciferol) and is high in both zinc and calcium.(14,15) Previous trials have shown the ability of Seluang fish oil supplementation in improving vitamin D levels, and reducing disease activity along with proinflammatory cytokines in SLE, but there are no studies regarding its efficacy in RA.(7,16) Thus, this research was conducted to investigate the capability of Seluang fish oil to improve IL-6, IL-17, vitamin D levels, as well as improving DAS28-ESR and DAS28-CRP for RA patients.

Methods

Study Participants

A randomized clinical trial using double-blind method was carried out at the **Rheumatology Clinic of Dr. Mohammad Hoesin General Hospital**, Palembang, starting from October to December 2021. Male and female RA patients aged 18-60 years old that met the **American College of Rheumatology (ACR) 2010 criteria** were enrolled as the subjects of this study.(17) Informed consents were obtained from all the subjects. Subject that suffered from any comorbidities, acute or chronic infection, other autoimmune disorders, as well as subject that received vitamin D therapy within the preceding month were excluded.

All RA subjects took standard medications as guided by the latest ACR Guidelines, or the Indonesia Rheumatology Association (IRA) guidelines. These drugs include dglucocorticoid and/or disease modifying anti rheumatic drugs (DMARD), such as 7.5-25 mg/week of methotrexate, 10-20 mg/day of leflunomide, or another DMARD (sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine) or targeted therapy (tocilizumab) based on physician discretion.(1,18) The study was conducted according to the protocols established by the Declaration of Helsinki, and this study has been approved by Dr. Mohammad Hoesin General Hospital Ethics Committee (No. 92/kepkrsmh/2021). The research protocol was submitted to the Indonesia Ministry of Health National Clinical Registry (No. 1671021P311172021090800005).

Seluang Fish Oil Preparation and Processing

About 30 kg of fresh Seluang Fish (*Rasbora* sp.) were acquired from a fish store in Palembang, in October 2021 and kept cold in -25°C to reduce biochemical changes during the transport to the Biotechnology Laboratory, Faculty of

Medicine, Universitas Sriwijaya, Palembang. The fish were cleaned and washed before boiled using the wet rendering technique, then the grinded fish were put together with water at a ratio of 1:10. Then, the fish were boiled in a double jacketed kettle at a temperature of 85-95°C for 60 minutes. Fish oil floated on the surface of the bouillon was set apart and carried out for purification by screening process. The filtrate of fish oil was obtained and stored in a coolant temperature of 4°C for 12 hours. The cooled oil would form layers that consisted of water, free fatty acid, phosphatide, and fish oil. The fish oil was separated and packed into capsules containing 500 µL oil. The extracted oil contains cholecalciferol (2043.34 IU/mL), calcium (65.96 mg/L) and zinc (1.8 mg/L).^(14,15) This oil's efficacy and safety had been studied in the laboratory using an animal model.⁽¹⁹⁾ As a newly developed complementary medicine, its efficacy and safety had been studied in SLE patients with doses one capsule per day for 12 weeks and the result has been published previously.^(7,16) All processes were performed and supervised by Biotechnology Laboratory staff, Faculty of Medicine, Universitas Sriwijaya.

Randomization and Intervention

Subjects were put in a 1:1 in two groups through block randomization (www.randomization.com) after they gave their informed consent. The intervention group received one capsule (500 µL) Seluang fish oil every day, which contains approximately 665 IU of cholecalciferol, while the control groups received one capsule of placebo every day. Both placebo and Seluang fish oil capsules are identical in color and taste.⁽¹⁵⁾ Subjects in both groups also received standard immunosuppressant for RA, namely glucocorticoid and/

or DMARDs, based on physician discretion. These drugs were taken once to three times per day (for glucocorticoid) to three times a week (for methotrexate), according to ACR or IRA guidelines. Subjects were prohibited from taking any supplement or any form of vitamin D to reduce bias.

Figure 1 described the timeline and group allocation for this study. After the first visit, the regular visits at 4, 8, and 12 weeks were carried out. The experiments were conducted for twelve weeks, and the expected outcomes were a change in DAS28-ESR and DAS28-CRP scores, as well as changes in IL-6, IL-17, and vitamin D levels after 12 weeks of supplementation in both groups.^(7,16)

Measurement of IL-6, IL-17, and Vitamin D Levels

Around 3 milliliters (mL) of blood were drawn from each subjects, before and after the intervention (at week-12). Following that, an ethylenediaminetetraacetic acid (EDTA) tube containing the blood was centrifuged for ten minutes at 5000 rpm. The plasma was kept at -20°C. The measurement of IL-6 level was carried out with quantitative electrochemiluminescence (ECLIA) method by Elecsys IL-6 (Cat. No.: No.05109442190, Roche Diagnostics GmbH, Mannheim, Germany). IL-17 level was measured quantitatively using Quantikine nzyme-Linked Immunosorbent Assay (ELISA) Human IL-17 kit (Cat. No.: D1700, Lot: P316011, R&D Systems, Minneapolis, MN, USA). Meanwhile, the vitamin D level was measured with a chemiluminescent microparticle immunoassay standardized laboratory method using Liaison 25-OH Vitamin D Total (Cat. No.: 310600, Abbott Laboratories, Chicago, IL, USA). All examinations were carried out at Prodia Clinical Laboratory, Jakarta, according to the kit protocols.

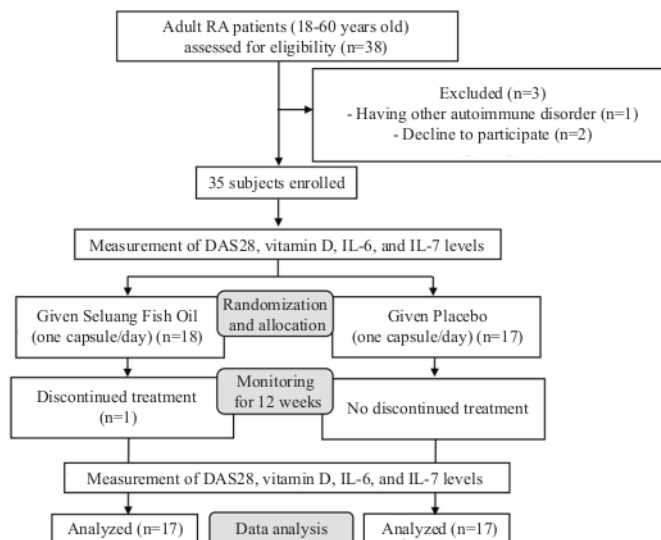


Figure 1. Study design of current study. A total of 35 subjects fulfilled the enrollment criteria and participated at the beginning of the study. However, during the follow up one subject in the Seluang Fish Oil group declined to participate, hence only 17 subjects in each group were included for the final analysis.

Clinical Determination of RA Disease Activity

Determination of disease activity status among RA subjects was accomplished by developing the DAS28 score, that consist of DAS28-CRP and DAS28-ESR. These scores are generated from the calculation of the number of tender joint count (TJC), swelling joint count (SJC), pain scales (as measured by visual analog scale (VAS)), and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) using the following formula (1,18):

$$\text{DAS28-ESR} = 0.56 \times \sqrt{\text{TJC}} + 0.28 \times \sqrt{\text{SJC}} + 0.07 \times \ln(\text{ESR}) + 0.014 \times (\text{VAS})$$

$$\text{DAS28-CRP} = 0.56 \times \sqrt{\text{TJC}} + 0.28 \times \sqrt{\text{SJC}} + 0.36 \times \ln(\text{CRP} + 1) + 0.014 \times (\text{VAS}) + 0.96$$

Statistical Analysis

The SPSS 25.0 program (IBM Corporation, Armonk, NY, USA) was used for data analysis. The subjects' characteristics were presented as frequency, mean±standard

deviation (SD), or median (min-max). Significant difference between the baseline data of the two groups' mean scores was examined by the unpaired T-test or the Mann-Whitney U test. Meanwhile, same groups' scores (for pre and post comparison) were examined using paired T-test or the Wilcoxon test to decide whether there was significant improvement after supplementation or not. A *p*-value of <0.05 was determined to be statistically significant.

Results

Baseline Characteristics

Among the subjects, there was similar conditions between the Seluang fish oil group and the placebo group before the treatment (Table 1). Among all subjects, 14 subjects (41.2%)

Table 1. Characteristics of subjects in both groups at the beginning of the study.

Characteristics	Seluang Fish Oil (n=17)	Placebo (n=17)	<i>p</i> -value
Female, n (%)	16 (94.1%)	16 (94.1%)	1.00 ^a
Age (years), median (min-max)	45 (19-57)	52 (19-57)	0.092 ^b
Duration of RA (months), median (min-max)	24 (2-132)	36 (12-288)	0.140 ^b
Hemoglobin (g/dL), mean±SD	12.15±1.12	12.59±1.16	0.268 ^c
Leucocyte (x10 ³) (/μL), mean±SD	10.60±3.70	9.60±2.70	0.387 ^c
Platelet (x 10 ³) (/μL), median (min-max)	353 (308-586)	327 (222-482)	0.085 ^b
Blood Glucose (mg/dL), median (min-max)	88 (79-184)	107 (87-140)	0.085 ^b
Ureum (mg/dL), median (min-max)	19 (9-34)	24 (11-58)	0.394 ^b
Serum creatinine (mg/dL), median (min-max)	0.69 (0.52-0.96)	0.68 (0.5-1.24)	0.760 ^b
SGOT (AST) (U/L), median (min-max)	18 (8-28)	18 (11-155)	0.610 ^b
SGPT (AST) (U/L), median (min-max)	16 (6-24)	18 (9-128)	0.281 ^b
Calcium (mg/dL), mean±SD	8.88±0.46	8.96±0.51	0.582 ^c
Vitamin D (ng/mL), mean±SD	22.61±9.38	21.68±8.42	0.763 ^c
Vitamin D Status, n (%)			
Vit D Deficiency (<20 ng/mL)	6 (42.9%)	8 (57.1%)	0.765 ^d
Vit D Insufficiency (20-29.9 ng/mL)	9 (56.3%)	7 (43.8%)	
Vit D Sufficient (≥30 ng/mL)	2 (50%)	2 (50%)	
IL-17 (pg/mL), median (min-max)	7.17 (4.62-18.60)	7.17 (4.51-32.59)	0.812 ^b
IL-6 (pg/mL), median (min-max)	7.59 (1.78-57.25)	11.21 (1.5-100.30)	0.865 ^b
DAS28-ESR, mean±SD	4.82±0.94	4.94±1.02	0.910 ^c
DAS28-CRP, median (min-max)	3.85 (2.44-6.45)	4.1 (3.15-5.54)	0.122 ^b
RA Medication, n (%)			
Methotrexate	16 (94.1%)	13 (76.5%)	0.051 ^a
Leflunomide	4 (23.5%)	3 (17.6%)	
Methylprednisone	15 (88.2%)	14 (82.4%)	
Hydroxychloroquine	0 (0%)	2 (11.8%)	
Sulfasalazine	1 (5.9%)	0 (0%)	
Azathioprine	0 (0%)	1 (5.9%)	
Cyclosporine	0 (0%)	1 (5.9%)	

^aFisher exact test; ^bMann-whitney test; ^cUnpaired T-test; ^dPearson Chi-square test.

Table 2. Comparison of disease activity of RA after 12 weeks of supplementations.

Characteristics	Seluang Fish Oil (n=17)			Placebo (n=17)		
	Before	After	p-value	Before	After	p-value
TJC, median (min-max)	8 (1-21)	2 (0-14)	0.004 ^{a*}	9 (3-28)	4 (0-16)	0.001 ^{a*}
SJC, median (min-max)	2 (0-11)	0 (0-4)	0.007 ^{a*}	3 (0-10)	0 (0-4)	0.002 ^{a*}
VAS, mean±SD	6.59±2.32	3.47±2.85	0.000 ^{b*}	6.76±1.48	4.47±2.00	0.003 ^{b*}
ESR (mm/hour), mean±SD	62.47±28.14	42.52±23.09	0.004 ^{b*}	50.35±31.19	42.11±29.32	0.033 ^{b*}
CRP (mg/L), median (min-max)	5.00 (1.60-200.00)	8.90 (0.50-47.50)	0.733 ^a	5.00 (1.30-74.20)	2.30 (0.30-59.70)	0.093 ^a
DAS28-CRP, mean±SD	3.81±1.09	2.83±1.05	0.000 ^{b,**}	4.19±0.69	2.90±0.84	0.000 ^{b,**}
DAS28-ESR, mean±SD	4.82±0.94	3.57±1.19	0.000 ^{b,**}	4.94±1.02	3.64±1.00	0.000 ^{b,**}

^aWilcoxon test; ^bPaired t-test; marked significant result with p-value of * $p < 0.05$; ** $p < 0.001$

had vitamin D deficiency, 16 subjects (47.1%) had vitamin D insufficiency, and 4 subjects (11.8%) had sufficient level of vitamin D. There were no significant discrepancies in medication and disease duration for RA in both groups. Seeing as all of the RA subjects showed equality of baseline characteristics, there was no opportunity for bias.

RA Disease Activity

In Table 2, there were significant improvements of disease activity (as determined with DAS28-ESR and DAS28-CRP) after 12 weeks of supplementation, with both group showing $p=0.000$ for DAS28-ESR and DAS28-CRP alterations. These benefits were measured by a reduction in DAS28-ESR and DAS28-CRP scores as well as their components, with the exception of CRP levels.

Plasma Cytokine Levels

There was equality of IL-6 and IL-17 value in both of the groups at baseline. However, as shown in Figure 2, the addition of Seluang fish oil treatment was substantially more successful, as measured by the reduction of IL-17 levels in the Seluang fish oil group (7.17 (4.62-18.6) vs. 4.95 (3.86-17.08) pg/mL; $p=0.031$) while compared to the

placebo group (7.17 (4.51-32.59) vs. 4.84 (3.78-33.25) pg/mL, $p=0.320$).

In contrast, the researchers found that subjects in the Seluang fish oil group didn't experience a significant reduction of IL-6 levels (7.59 (1.78-57.25) vs. 3.44 (1.5-79.9) pg/mL; $p=0.076$), while there was significant difference in the placebo group (11.21 (91.5-100.3) vs. 3.76 (1.5-53.6) pg/mL; $p=0.020$). There were no undesirable effects reported in both groups during this study.

Plasma Vitamin D Levels

Before the intervention, the average vitamin D levels of the subjects were 22.61±9.38 ng/mL in the Seluang fish oil group and 21.68±8.42 ng/mL in the placebo groups, and showed no significant difference ($p=0.763$). As shown in Figure 2, even after the supplementation in both groups, there was no significant shift of vitamin D levels in the Seluang fish oil group (22.61±9.38 vs. 22.56±9.81 ng/mL; $p=0.967$) and the placebo group (21.68±20.00 vs. 20.98±6.75 ng/mL; $p=0.647$). There was also no remarkable dissimilarity in values of vitamin D between the Seluang fish oil and placebo groups at the end of the study (22.56±9.81 vs. 20.98±6.75 ng/mL, respectively; $p=0.588$).

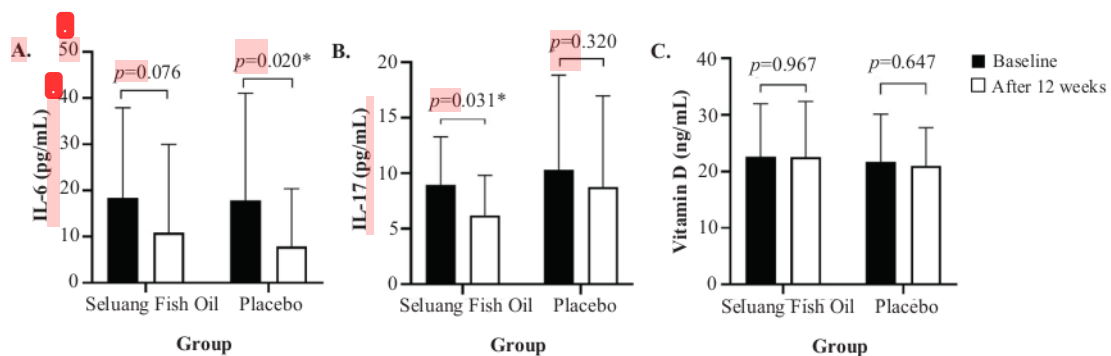


Figure 2. Comparison of changes in IL-6, IL-17 and vitamin D levels in Seluang Fish Oil and placebo groups. Vitamin D level was analyzed with paired T-test, while IL-6 and IL-17 level were analyzed with Wilcoxon test. *marked significant result with $p < 0.05$.

Discussion

Seluang fish oil is thought to be effective against RA because it contains a high concentration of cholecalciferol. As a molecule with sterol compound, vitamin D plays an indispensable role in the modulation and adjustment of the immune system.(20,21) As shown in Figure 3, vitamin D will inhibit the gene that encodes nuclear factor-kappa B (NF-κB), which is a factor that helps transcript genes for cytokines, including proinflammatory cytokines.(22) Its suppression makes the IL-2 gene less active and stops IL-2 being produced. When IL-2 cytokines are stopped from spreading, T lymphocyte cell growth slows down. Serum concentrations of many factors that have proinflammatory properties, such as CRP, TNF-α, interferon (IFN)-γ, IL-1, IL-6, and IL-17 have been shown to go down when vitamin D is taken. These are also used to elevate the function of IL-4, IL-5, and IL-10, as well as the total antioxidant capacity, repair the balance between Th1/Th2 cells and stabilize Treg cells that release several regulatory mediators in inflammation like transforming growth factor (TGF)-β.(23,24)

Our findings are similar to what was presented in earlier research; 41.2% of subjects with RA suffered from vitamin D deficiency, which was classified as ≤20 ng/mL.(25,26) Those with Indonesian ethnicity tend to have darker skin and higher melanin content that inhibits the skin synthesis of vitamin D, compared to East Asian or European people. Also, the RA patients were predominantly women, who were usually dressed in hijab which can reduce sunlight exposure. However, we didn't measure subjects' daily habits relating to vitamin D deficiency.

The predominance of the female gender in this study is also similar to prior studies.(25,26) There is a role of hormonal status in females, especially estrogen, which act as an immunomodulator and maintain autoreactive T cells. During the post-menopausal period, the decrease of estrogen level will increase proinflammatory cytokines such as IL-6, IL-1β and TNF-α, thus trigger RA symptoms.(27)

The clinical severity of RA, as measured by the reduction of DAS28-ESR and DAS28-CRP, was shown to be lower in both Seluang fish oil and placebo groups after intervention. It is estimated due to the effect of the immunosuppressant therapy which is being used in both groups during the study. A meta-analysis found that taking vitamin D supplements for 3 to 6 months resulted in an improvement of disease clinical activity in RA.(8) However, our study failed to prove the increase of Vitamin D levels in patients after 12 weeks of Seluang oil supplementation. This is opposite to other studies that recorded a remarkable increase in vitamin D levels after Seluang fish oil supplementation in SLE patients.(7,16,28) The concentration of vitamin D in Seluang fish oil that was used in our study is 665 IU/day, which is different from the previous study that use 500 IU/weekly to 300000 IU/day of vitamin D.(8) Although no consensus exists regarding the precise vitamin D dose for correction in patients with autoimmune disorder, indefinite doses up to 6000 IU/day of vitamin D can be given to correct vitamin D deficiency.(29) Our study results are similar to a previous meta-analysis that also found no significant increase of cholecalciferol after supplementation of vitamin D in RA. However, their study had heterogeneity in duration and dose of vitamin D supplementation.(8) It is also hypothesized that the lack of increase in vitamin D levels in this trial were related

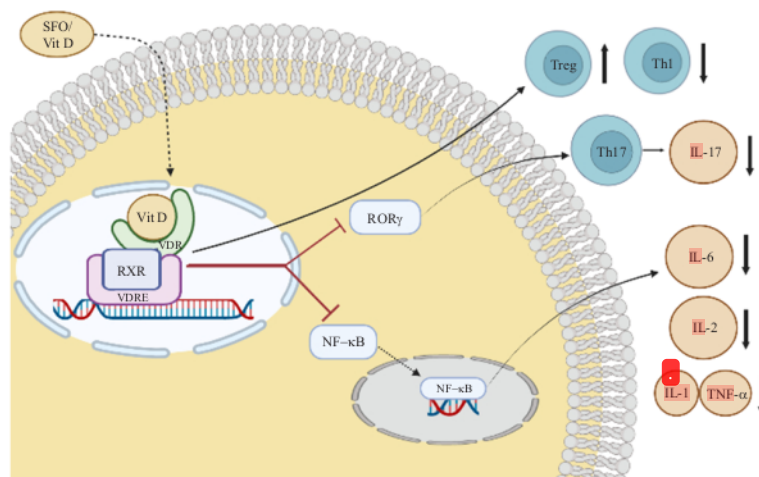


Figure 3. Mechanism of proinflammatory cytokines suppression by Seluang fish oil (contains 2043.34 IU/mL cholecalciferol). IL: interleukin; Vit D: vitamin D; VDR: vitamin D receptor; VDRE: vitamin D response element; NF-κB: nuclear factor kappa B; RORγ: RAR related orphan receptor gamma; RXR: retinoid X receptor; SFO: seluang fish oil; TNF: tumor necrosis factor. (Figure was created using BioRender).

to the low amount of vitamin D levels in both groups before supplementation. Although higher doses have been administered in previous studies, only a few investigations have been performed on vitamin D supplementation in Indonesian RA subjects.(26)

One type of cytokine that plays a significant role in RA pathophysiology is IL-6. In addition, Th17 cells, along with other innate immune cells, are responsible for the production of a significant amount of the pro-inflammatory cytokine IL-17. Compared to normal people, RA patients have higher baseline concentrations of proinflammatory cytokines in their joint fluid and synovium.(30)

In this study, reduction of IL-6 levels in both groups were observed. Systemic parameters including IL-6 and CRP were not remarkably altered after vitamin D administration, as reported by several studies.(25,31,32) In another trial, participants taking Seluang fish oil for SLE had lower IL-6 levels, while participants with RA had greater baseline cytokine levels to begin with.(33) Contrarily, it was found that vitamin D augmentation increased IL-6 levels in multiple sclerosis patients.(34) The effect on IL-6 levels may be different from what researchers have observed in the past, depending on sample size, how much of the supplement was taken and for how long. A study showed that 50.000 IU/week of vitamin D addition in RA treatment did not reduce IL-6 levels significantly, also showing no correlation between vitamin D and IL-6 levels.(25)

A statistically significant decrease of IL-17 levels was found after Seluang oil supplementation for 12 weeks. This supports another study that proved the advantages of vitamin D supplementation in reducing IL-17 levels in various autoimmune disorders, such as SLE, psoriasis and multiple sclerosis.(35-37) The mechanism of improving IL-17 status was through enhancing Th17/T reg balance, and also the down-regulating effect could be caused by inhibition of RAR related orphan receptor gamma (ROR γ), the main factor for IL-17 synthesis and transcription (Figure 3).(38) Vitamin D promotes Th2 cytokines which also has a negative regulator effect on Th17 differentiation.(6,30)

This study has a small number of samples, and neither the effects of being exposed to the sun nor the effects of eating nutritious foods were investigated. There was no indication of the subjects' RA status, whether it was in the early or late stages, which was something that could have played a role in the findings. Last but not least, both the quantity and duration of the vitamin D delivery found in this study were shorter compared to earlier studies.(8) Further studies are needed with a longer duration or higher dose of supplementation of Seluang fish oil in RA.

Conclusion

This study figured out the effectiveness of Seluang fish oil supplementation for improving disease activity and IL-17 levels in RA subjects, suggesting that this fish (or its oil product) has potency as a supplement for RA management. There was no remarkable reduction in IL-6 levels or increase in vitamin D levels after Seluang fish oil supplementation.

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Authors Contribution

RUP and EMS were involved in planning, designing, and supervising the work. RUP, RM, TA, SD, MR, RK, and YK performed data acquisition, data analysis, and statistical analysis. RUP, RM, and TA performed the manuscript preparation and designed the figures. All authors discussed and agreed on the manuscript submission.

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