1. PROSES SUBMIT

UNTUK INDONESIA ADIL & BERADAB

wiwied ekasari <wiwied-e@ff.unair.ac.id>

FABAD A-599 Manuscript received

2 messages

FABAD Ankara <fabadankara@gmail.com> Thu, Nov 21, 2019 at 3:19 PM
To: wiwied-e@ff.unair.ac.id

Dear Dr. Wiwied Ekasari,

Your manuscript was received and given the code A-599. Please use this code in the subject of your e-mails for further inquiries.

Regards.

Prof. Dr. Nesrin Gökhan Kelekçi
FABAD Journal of Pharmaceutical Sciences
Editor

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wiwied ekasari <wiwied-e@ff.unair.ac.id> Thu, Nov 21, 2019 at 5:14 PM
To: FABAD Ankara <fabadankara@gmail.com>

Dear
Prof. Dr. Nesrin Gökhan Kelekçi
FABAD Journal of Pharmaceutical Sciences

Thank you for your information
I hope my manuscript code A-599 can be accepted in your journal

Best regard
Dr. Wiwied Ekasari

[Quoted text hidden]

2. PROSES REVIEW

wiwied ekasari <wiwied-e@ff.unair.ac.id>

FABAD A-599 revision

2 messages

FABAD Ankara <fabadankara@gmail.com> Thu, Dec 5, 2019 at 8:18 PM
Reply-To: rebbie.sumpay@hindawi.com
To: wiwied-e@ff.unair.ac.id

Dear Dr. Wiwied Ekasari,

Your manuscript entitled "Antimalarial Activity of Multiple Dose on *Plasmodium berghei* Infected Mice and Heme Detoxification Inhibitory Activity of *Helianthus annuus* L. Leaf Extract" (code: A-599) has been evaluated by the reviewers and the comments are given in the attached file. As you will see from the comments of the referees, manuscript revision is required. Please find the reviewer's comments below for your submitted manuscript.

Kindly effect the recommended corrections and send it back within two weeks. The revised version of your manuscript will be sent to the reviewers again, which means that a further evaluation of your contribution will be made. Final decision about acceptance or rejection is, therefore, still pending.

If the revised version is not submitted in time the manuscript will be withdrawn.
Should you need additional time to prepare your review, please let us know.

The revised manuscript should follow the guideline listed below:

1. Response to the reviewers' comments should be on point by point basis and you should write your each answer just below the relevant comment of the reviewer in a separate ms word file.

2. Also please indicate where changes have been made (with a different highlighted color in the text) in the revised manuscript.

Regards,
Prof. Dr. Nesrin Gökhan Kelekçi
FABAD Journal of Pharmaceutical Sciences
Editor

Reviewer comments:

Reviewer1

Corrections have been made on the manuscript.

- Statistical analysis has not been performed on *in vivo* model. The authors also should perform statistical analysis on *in vivo* model.

Reviewer2

Corrections have been made on the manuscript.

- Authors should take the attached revised MS into consideration while doing corrections.

- Ethical approval number should be provided for this study. Otherwise the MS is not acceptable.

- Authors should give information regarding the ethnopharmaceutical (traditional) preparation method of the plant. Which part of the plant, and how it has been prepared to be used for the treatment of malaria?

- Authors should give information regarding the voucher specimen of the plant, in which herbarium it is kept and what is its registration number?

- Discussion part should be expanded.

- Pls add family name of the plant to the key words section.

- Please check the language of the manuscript, it is better to get help from a native English speaker.

- Write *in vivo* and *in vitro* in italic throughout the text.

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2 attachments

A599-Reviewer 1.docx
130K

A599-reviewer 2.docx
126K

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wiwied ekasari <wiwied-e@ff.unair.ac.id> Thu, Dec 12, 2019 at 2:28 PM
To: FABAD Ankara <fabadankara@gmail.com>

Dear Prof. Dr. Nesrin Gökhan Kelekçi
FABAD Journal of Pharmaceutical Sciences
Editor

Thank you very much for your information.
Yes, I will revise my manuscript according to the reviewer's suggestion as soon as possible.

Best regard
Dr. Wiwied Ekasari

[Quoted text hidden]

- **Answer to reviewer(s)**

Reviewer 1

1. Corrections have been made on the manuscript.

   Answer : Thank you very much

2. Statistical analysis has not been performed on *in vivo* model. The authors also should perform statistical analysis on *in vivo* model.

   Answer :

   Statistical analysis

   Data are expressed as mean ± standard deviation (SD). IC50 values were calculated using Probit analysis. Statistical significance for heme polymerization inhibitory activity assay was determined by ANOVA (*One Way*) at significance level of $P < 0.05$

Reviewer 2

1. Corrections have been made on the manuscript.

   Answer : Thank you very much

2. Authors should take the attached revised MS into consideration while doing corrections.

   Answer : Yes, I did

3. Ethical approval number should be provided for this study. Otherwise the MS is not acceptable.

   Answer : Ethical approval number No : 2.KE.120.07.2018

4. Authors should give information regarding the ethnopharmaceutical (traditional) preparation method of the plant. Which part of the plant, and how it has been prepared to be used for the treatment of malaria?

   Answer :

   This plat in Indonesia has been used traditionally to treat various of diseases, especially the leaves of this plant are used to treat inflammation, analgesic as well as malaria infection. To treat malaria, the leaves are boiled and drink it when it become cooled (Sopi and Tallan, 2015) .

5. Authors should give information regarding the voucher specimen of the plant, in which herbarium it is kept and what is its registration number?

   Answer :

   H. annuus leaves were obtained in November 2016 from Oro-Oro Ombo Village, Batu, East Java and determined in Materia Medica Batu, Batu, East Java, Indonesia. specimen was deposited as the herbarium in Department of Pharmacognosy and Phytochemical, Faculty of Pharmacy, Universitas Airlangga, (Number : 04/WE/XI/2016)

6. Discussion part should be expanded.

   Answer :

   **** In Vivo* Antimalarial Activity of 80% Ethanol Extracts of *H. annuus* Leaves on Parasitaemia**

   In order to obtain the optimal therapeutic effect, the factors that are closely related to the therapeutic effect should be considered during the rational doses and drug interval regulation. The factors are including the resulted activity of the drug used. (Shargel, 2005)

The therapeutic effect of antimalarial drug depends on the availability of the drug in the blood that able to inhibit the growth of *Plasmodium* maximally. The various doses of antimalarial drug, including the repeated doses are usually applied during the development of antimalarial drug (Ndiaye et al., 2011). The effect of plant extract is less effective and the bioavailability of drugs in the blood is faster to disappear when it is applied as short administration (once a day). Twice a day administration can extend the act of extract in the blood (long acting), therefore repeated dose is better to obtain its optimum effectiveness.

Muti'ah et al. (2013) reported that inhibition percentage of 80% ethanol extract of *H. annuus* leaves administer 100 mg/kg once daily as a single dose (61.8%) increases to 82.05% in twice a day administration. Inhibition percentage of 10 mg/kg once daily administration increases from 57.9% to 76% in twice a day treatment as well.

Based on the discussion above, it can be concluded that 80 % ethanol extract of *H. annuus* leaves with twice daily administration (repeated dose) for 4 days treatment can inhibit the growth of *P. berghei* higher than once a day administration (single dose).

*** Heme Polymerization Inhibitory Activity Assay**

This *in vitro* antimalarial activity assay is performed by heme detoxification inhibition method. In the intraerythrocytic phase, the parasite will degrade hemoglobin into free heme and globin. Globin will then be converted into a small peptide to be used for enzyme synthesis. Free heme is toxic to parasites as it contains reactive oxygen species (ROS) which can lyse the parasitic membrane and disrupt the parasitic enzymatic activity. Thus, the parasite will convert the free heme into a non-toxic form, hemozoin (malaria pigment), with a special mechanism called heme detoxification mechanism (Kumar et al., 2007).

The mechanism of heme detoxification has been identified as: 1) Biocrystallization of heme spontaneously, 2) Heme degradation in food vacuole facilitated by hydrogen peroxide (H_2O_2), 3) Glutathione mediated heme degradation, 4) Heme oxygenation was found in *Plasmodium berghei* (rodent malaria) and *Plasmodium knowlesi* (simian malaria) but not in *Plasmodium falciparum* (human malaria). Gluthatione-dependent and enzymatic heme degradation occur in the outside of food vacuole of parasite. Among the above mechanisms, biocrystallization is the major mechanism occurs in the malaria parasite (Sherman, 1998; Ziegler *et al.*, 2002; Tekwani and Walker, 2005). This process is an important target for the development of antimalaria drug (Fidock *et al.*, 2004).

The use of hematin in this study as the main ingredient will react to β-hematin as well as hemozoin. Glacial acetic acid is used to create an acidic atmosphere which adapts to the condition of the parasitic food vacuole. Washing uses DMSO solution is done to remove residual hematin which is still mixed with β-hematin crystals (Tekwani and Walker, 2005).

7. Pls add family name of the plant to the key words section.

   Answer : Yes, I did

8. Please check the language of the manuscript, it is better to get help from a native English speaker.

   Answer : Yes, I did

9. Write *in vivo* and *in vitro* in italic throughout the text.

   Answer : Yes, I did

3. ARTIKEL DITERIMA DAN DITERBITKAN

wiwied ekasari <wiwied-e@ff.unair.ac.id>

Decision on your manuscript FABAD A-599

2 messages

FABAD Ankara <fabadankara@gmail.com> Thu, Apr 9, 2020 at 8:30 PM
To: wiwied-e@ff.unair.ac.id
Cc: Suna Atasayar <sunaatasayar@gmail.com>, Suna Atasayar <suna@hacettepe.edu.tr>

Dear Wiwied Ekasari,

I am pleased to inform you that your article entitled "Antimalarial Activity of Multiple Dose on *Plasmodium berghei* Infected Mice and Heme Detoxification Inhibitory Activity of *Helianthus annuus* L. Leaf Extract" (A-599) has been accepted for publication in FABAD Journal of Pharmaceutical Sciences.

We wish to thank you for submission of the manuscript to FABAD Journal of Pharmaceutical Sciences and look forward to a continued collaboration in the future.

Thank you very much for your kind interest.

Best regards,

Prof. Dr. Nesrin Gökhan Kelekçi

FABAD Journal of Pharmaceutical Sciences

Editor

Acceptance Letter A599.docx
82K

wiwied ekasari <wiwied-e@ff.unair.ac.id> Thu, Apr 9, 2020 at 9:25 PM
To: FABAD Ankara <fabadankara@gmail.com>

Dear Prof. Dr. Nesrin Gökhan Kelekçi

FABAD Journal of Pharmaceutical Sciences

Thank for your information.

I am very happy to hear this news and look forward to a continued collaboration in the future.

Best regard

Dr. Wiwied Ekasari, MSi. Apt

wiwied ekasari <wiwied-e@ff.unair.ac.id>

proof of your manuscript

2 messages

FABAD Ankara <fabadankara@gmail.com> Mon, May 4, 2020 at 3:01 PM
To: wiwied-e@ff.unair.ac.id

Dear Wiwied EKASARI,

You can find the attached proof of your accepted manuscript entitled "Antimalarial Activity of Multiple Dose on Plasmodium berghei Infected Mice and Heme Detoxification Inhibitory Activity of Helianthus annuus L. Leaf Extract (Code: A599)" and acceptance letter for FABAD Journal of Pharmaceutical Sciences. Please check the proof and make your corrections on pdf file. We will be greatfull if you could send us corrected proof in 5 days. Please make your correction on pdf file. It is very important not to change anything in the content. If you do, you should be aware that your review would need to go under second evaluation.
P.S. Please check the format of your manuscript including references, key word numbers, titles (Turkish and English), ORCID IDs according to author's instructions. Unfited manuscripts will not be published. Acceptance letter of your manuscript is also attached. Thank you very much for your kind interest.

Sincerely Yours,
Nesrin Gökhan Kelekçi

2 attachments

A-599.pdf
171K

A599.pdf
483K

wiwied ekasari <wiwied-e@ff.unair.ac.id> Wed, May 6, 2020 at 9:35 PM
To: FABAD Ankara <fabadankara@gmail.com>

Dear Prof. Dr. Nesrin Gökhan Kelekçi
FABAD Journal of Pharmaceutical Sciences

Thank you for your email and the acceptance letter of my manuscript . Here I send you my manuscript correction

I am very happy to hear that my manuscript will be published in FABAD Journal of Pharmaceutical Sciences, 45(2);2020.

We look forward to a continued collaboration in the future.

Best regard

Dr. Wiwied Ekasari, MSi. Apt

[Quoted text hidden]

A-599_rev_final.pdf
222K

FABAD-A599

2 messages

Suna Atasayar <sunaatasayar@gmail.com> Mon, Jun 29, 2020 at 7:05 PM
To: wiwied-e@ff.unair.ac.id

Dear author,

According to the new rules, the document of the ethical statement related to your work should be sent by email urgently. You can scan the document and send it to me as soon as possible. Otherwise, your article will not be able to be published.

Thank you,

Best regards,
On behalf of editorial team
Suna Sabuncuoğlu

--

Assoc. Prof. Dr. Suna SABUNCUOGLU, E. R. T.
Hacettepe University
Faculty of Pharmacy
Department of Toxicology
Ankara 06100 TURKEY
Tel: +90 312 309 29 58- 305 21 78
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Doç. Dr. Suna SABUNCUOĞLU, E. R. T.
Hacettepe Üniversitesi
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06100 Ankara
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wiwied ekasari <wiwied-e@ff.unair.ac.id> Thu, Jul 2, 2020 at 8:43 PM
To: Suna Atasayar <sunaatasayar@gmail.com>

Dear Mr. Suna Sabuncuoğlu
Thank you for your information.
Here I send you the ethical statement related to my work (attachment).

Best regard
Dr. Wiwied Ekasari

[Quoted text hidden]

ethical_No2.KE.120.07.2018.jpeg
421K