1. PROSES SUBMIT

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

7390385: Acknowledging Receipt

2 messages

Evidence-Based Complementary and Alternative Medicine <Reem.Salama@hindawi.com>
Thu, Jun 27, 2019 at 11:03 PM
To: wiwied-e@ff.unair.ac.id
Cc: reem.salama@hindawi.com, dwi.widya.pratiwi.2014@gmail.com, amandaelmira@gmail.com, suciati@ff.unair.ac.id, aty_ww@yahoo.com, arwatiheny@yahoo.com

Dear Dr. Ekasari,

The Research Article titled "Various Parts of Helianthus Annuus Plants as a New Source of Antimalarial Drugs," by Wiwied Ekasari, Dwi Widya Pratiwi, Zelmira Amanda, Suciati -, Aty Widyawaruyanti and Heny Arwati has been received and assigned the number 7390385.

The special issue for which the paper is being processed is
"Natural Products as Sources of Antimalarial Drugs"

All authors will receive a copy of all the correspondences regarding this manuscript.

Thank you for submitting your work to Evidence-Based Complementary and Alternative Medicine.

Best regards,

--
****
Reem Salama
Editorial Office
Hindawi
http://www.hindawi.com
****

2. PROSES REVIEW

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

7390385: Major Revision Required

3 messages

Philip F. Uzor <ecam@hindawi.com> Thu, Sep 19, 2019 at 10:05 AM
Reply-To: jericajona.lorenzo@hindawi.com
To: wiwied-e@ff.unair.ac.id
Cc: dwie.widyapratiwi@gmail.com, zelmira.amanda-2014@ff.unair.ac.id, suciati@ff.unair.ac.id, aty-w@ff.unair.ac.id, arwatiheny@yahoo.com

Dear Dr. Ekasari,

Following the review of Research Article titled "Various Parts of Helianthus Annuus Plants as a New Source of Antimalarial Drugs" by Wiwied Ekasari, Dwi Widya Pratiwi, Zelmira Amanda, Suciati -, Aty Widyawaruyanti and Heny Arwati, I recommend that it should be revised taking into account the changes requested by the reviewer(s). Since the requested changes are major, the revised manuscript will undergo a second round of review by the same reviewer(s). Please login to the Manuscript Tracking System to read the submitted review report(s) and submit the revised version of your manuscript no later than Thursday, October 17, 2019.

To submit the revised version of your manuscript, please access "Author Activities" in your account and upload the PDF file of your revised manuscript. Also, please submit your replies to the comments of the reviewer(s) as an additional PDF file.

Best regards,

Philip F. Uzor

---

wiwied ekasari <wiwied-e@ff.unair.ac.id> Mon, Sep 30, 2019 at 11:01 AM
To: Jericajonalorenzo <jericajona.lorenzo@hindawi.com>

Dear Mr. Philip F. Uzor,
Thank you for your email, yes I will revise my manuscript according to the reviewers' recommendations and submit the revised version of my manuscript no later than Thursday, October 17, 2019.

Best regards
Dr. Wiwied Ekasari

[Quoted text hidden]

▪ Review report(s)

Reviewer 1

Major comments

1. In Introduction: authors should include justification for testing H. annuus ethanolic extracts for inhibition of β-hematin formation in vitro. (ii) On line 52, please provide citations to "…..possessed by chloroquine and artemisinin."
2. In Materials and Methods, please add a sub-section "Statistical analysis".
3. In Results and Discussion:
   (i) Table 5 should be deleted as the parasitemias at D3 do not differ among all treatments and do not differ for each treatment from D1. It would if the be preferable if the parasitemia data from D1 to D7 be presented as a graph such as depicted in Figure 1, with panels A, B, etc. showing results from each treatment regimen. Each data point should also include SD bar so that readers can see for themselves the differences (if any). Thus, text, lines 180-193, will require revision to reflect the results of (new) Figure 1. An explanation should be included for inclusion of doxycycline as positive control (with pertinent citations). (ii) On line 204, sentence "Some references reported ….. of some enzymes." should read "Free heme is toxic to parasites as it causes lysis of parasite acid vacuolar membrane.", and cite the seminal paper "Chou, A. C., and C. D. Fitch. 1981. Mechanism of hemolysis induced by ferriprotoporphyrin IX. J. Clin. Investig. 68:672–677".

Minor comments.

1. Please define "CMC Na".
2. In the Tables, please adjust values in accordance with SD, e.g. in Table 2, "86.64 ± 1.72" should read "87 ± 2".
3. In Table 2 and (new) Table 5, IC50 should include "± SD"; in Table 4, ED50 should include "± SD".
4. In (new) Table 5, please define "K(-)".
5. Line 131, "Discussions" should read "Discussion".
6. Line 215, "Conclusions" should read "Conclusion".
7. In (new) Figure 1, y-axis should read "Percent parasitaemia"; x-axis should read "Day post-parasite inoculation"; "100mg" should read "100 mg' etc.; and there should be a succinct informative figure legend.
8. The revised manuscript should be proof-read by an English editing service for scientific manuscript.

Reviewer 2

1) Please provide the full abbreviation for the term CMC Na at first use.
2) In page 3 line 118, since authors already mentioned that a Basilico method, it is unnecessary to include the method in details. In general, the Materials and Methods section is too lengthy. Authors should consider removing unnecessary details.
3) In page 4 line 132, please include references for the first sentence.
4) Throughout the article authors uses a mix of two and three decimals for numerical data. Authors should present numerical data with uniformed decimal.
5) In page 4 line 152-156. These sentences are redundant and can be removed.
6) In Figure 1, please provide the standard error for each data point. Additionally, please include space between the number and unit.
7) Table 6 should come after the paragraph describing it at line 200.
8) In page 6 line 211, the paragraph should be merged into the conclusion section.
9) In general, the conclusion in underwhelming. Authors should consider rewriting the conclusion.

▪ Answers of the reviewer(s)

Reviewer 1

Major comments

1. In Introduction: authors should include justification for testing H. annuus ethanolic extracts for inhibition of β-hematin formation in vitro. (ii) On line 52, please provide citations to "…..possessed by chloroquine and artemisinin."

   Answer :

   Inhibition of heme detoxification is known as one of potential biochemical target which also possessed by chloroquine and artemisinin [6,7]. The highest antimalarial activity of *H. annuus* plant part as well as its mechanism to inhibit heme detoxification were expected to be obtained through this study as it can be a new source of antimalarial drug.

2. In Materials and Methods, please add a sub-section "Statistical analysis".

   Answer :

   Statistical analysis

   Data were analyzed using Windows SPSS software version 16 and expressed as Mean ± Standard Deviation (M ± SD). IC_{50} values are calculated using Probit analysis. Statistical significance was determined by Kruskall Wallis's non-parametric, Independent *t*-test, and ANOVA (*One Way*).

3. In Results and Discussion:

   (i) Table 5 should be deleted as the parasitemias at D3 do not differ among all treatments and do not differ for each treatment from D1. It would if the be preferable if the parasitemia data from D1 to D7 be presented as a graph such as depicted in Figure 1, with panels A, B, etc. showing results from each treatment regimen. Each data point should also include SD bar so that readers can see for themselves the differences (if any). Thus, text, lines 180-193, will require revision to reflect the results of (new) Figure 1. An explanation should be included for inclusion of doxycycline as positive control (with pertinent citations). (ii) On line 204, sentence "Some references reported ….. of some enzymes." should read "Free heme is toxic to parasites as it causes lysis of parasite acid vacuolar membrane.", and cite the seminal paper "Chou, A. C., and C. D. Fitch. 1981. Mechanism of hemolysis induced by ferriprotoporphyrin IX. J. Clin. Investig. 68:672–677".

   Answer :

   (i) Yes, I have revised according to the suggestions

Table 5**:** Mean percentage of parasitaemia on day 1 until day 7, inhibition, and mice survival time of 96% ethanol *H. annuus* root extract compared with control

Sample	Dose (mg/kg)	Mean % parasitaemia							Mean % inhibition (D_1-D_3)	*MST*
		1	2	3	4	5	6	7		
96% ethanol extract of *H. annuus* root	100	0.00	0.00	1.06 ± 1.14	8.51 ± 9.33	17.97 ± 13.36	28.64 ± 14.44	36.50 ± 13.19	70.18 ± 32.14	7.4 ± 0.50
	200	0.00	0.00	1.01 ± 0.90	9.85 ± 5.27	20.12 ± 8.01	30.01 ± 10.61	36.92 ± 13.01	71.41 ± 25.34	9.8 ± 0.31
	400	0.00	0.00	0.74 ± 0.69	5.94 ± 3.98	20.05 ± 5.02	35.24 ± 4.33	42.10 ± 8.60	79.15 ± 19.61	9.6 ± 0.30
	800	0.00	0.00	1.33 ± 1.19	5.75 ± 3.90	17.71 ± 8.39	27.19 ± 8.30	29.84 ± 8.59	62.49 ± 33.52	9.0 ± 0.35
Doxycycline	13	0.00	0.00	0.18 ± 0.25	0.81 ± 0.44	1.19 ± 0.80	1.98 ± 0.92	3.04 ± 1.11	94.80 ± 7.12	14.0 ± 0.00
Na CMC	-	0.00	0.23 ± 0.32	3.55 ± 1.71	18.40 ± 12.09	25.99 ± 16.96	42.23 ± 23.42	47.30 ± 30.70	-	7.2 ± 0.45

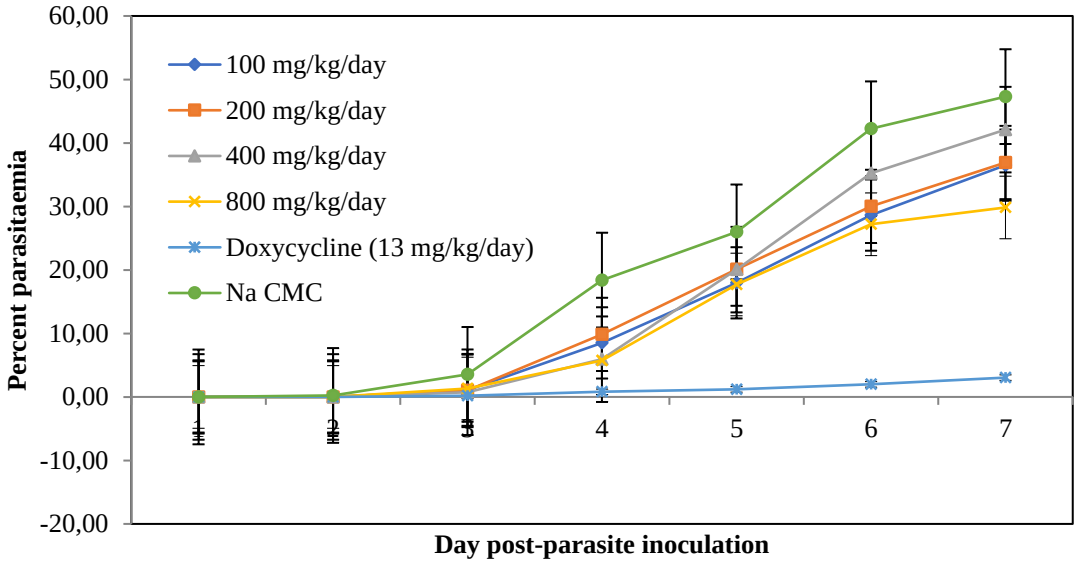

Figure 1 shows that 96 hours or the fourth day after parasite inoculation, there is an increase in parasitic growth in the negative dose and control group, whereas, in doxycycline the parasite growth is relatively stable, which is under 3%. This is thought to be related to the half-life of doxycycline which ranges from 12 to 22 hours [10,20,21] which allows doxycycline to last longer in the body and inhibit the growth of parasites. It is in contrast to extracts or traditional medicines that tend to have a short half-life, such as artemisinin and its derivatives [22,23]. Based on the antimalarial test results of *H. annuus* root in vivo, it can be concluded that the 96% ethanol of *H.annuus* root extract has more potential activities as curative antimalarial than prophylactic.

(ii) Yes, I have revised according to the suggestions
Free heme is toxic to parasites as it causes lysis of parasite acid vacuolar membrane [24]

Minor comments.

1. Please define "CMC Na".
   Answer :
   sodium carboxy methyl cellulose (Na CMC)

2. In the Tables, please adjust values in accordance with SD, e.g. in Table 2, "86.64 ± 1.72" should read "87 ± 2".
   Answer :
   For numeric data, yes we have changed it to be uniform using two decimals. We chose to use two decimals places to display numerical data because for *in vitro* antimalarial activity testing and inhibition of heme detoxification, the dose used was also up to two decimals places (0.01 µg / mL).

3. In Table 2 and (new) Table 5, IC50 should include "± SD"; in Table 4, ED50 should include "± SD".
   Answer :

Table 2: IC_{50} values of 96% ethanol extract of various parts of *H. annuus* plants against *P. falciparum* strain 3D7

***H. annuus* plants part**	**% Inhibition at each concentration (µg/mL)**					**IC_{50} (µg/mL)**
	100	10	1	0,1	0,01	
Root	86.64 ± 1.72	73.28 ± 6.87	31.98 ± 3.72	22.27 ± 0.00	7.29 ± 7.44	~~2.033~~ 2.31 ± 1.40
Stems	64.36 ± 4.55	56.44 ± 1.05	30.69 ± 7.70	18.81 ± 4.90	0	~~9.518~~ 10.23 ± 5.02
Seeds	84.36 ± 1.03	22.18 ± 6.94	14.18 ± 3.86	6.18 ± 10.29	0	~~19.298~~ 19.34 ± 5.51
Flowers	85.66 ± 8.69	48.36 ± 2.61	31.97 ± 2.90	19.26 ± 8.69	0	~~4.723~~ 4.78 ± 0.00
Leaf	96.32 ± 1.82	47.06 ± 4.68	24.26 ± 11.70	16.54 ± 6.24	6.98 ± 1.04	~~4.009~~ 4.27 ± 2.19

Table 4: Mean percentage of parasitaemia, growth, and inhibition against *P. berghei* of 96% ethanol *H. annuus* root extract compared with control

Sample	Dose (mg/kg)	Mean % parasitaemia		Mean % growth	Mean % inhibition	ED_{50} (mg/kg)
		D_0	D_4			
96% ethanol extract of *H. annuus* root	1	1.11 ± 0.14	26.17 ± 1.39	6.27 ± 0.36	35.83 ± 4.69	10.44 ±
	10	0.99 ± 0.23	21.20 ± 0.86	5.05 ± 0.17	48.26 ± 2.77	
	100	0.95 ± 0.13	15.42 ± 1.74	3.62 ± 0.42	62.97 ± 5.27	
	250	1.15 ± 0.39	11.95 ± 1.84	2.70 ± 0.42	72.33 ± 5.30	
Na CMC	-	1.24 ± 0.30	40.29 ± 6.06	9.76 ± 1.48	-	

4. In (new) Table 5, please define "K(-)".
   Answer

Table 5: Mean percentage of parasitaemia on day 1 until day 7, inhibition, and mice survival time of 96% ethanol *H. annuus* root extract compared with control

Sample	Dose (mg/kg)	Mean % parasitaemia							Mean % inhibition (D_1-D_3)	*MST*
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5. Line 131, "Discussions" should read "Discussion".
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7. In (new) Figure 1, y-axis should read "Percent parasitaemia"; x-axis should read "Day post-parasite inoculation"; "100mg" should read "100 mg' etc.; and there should be a succinct informative figure legend.
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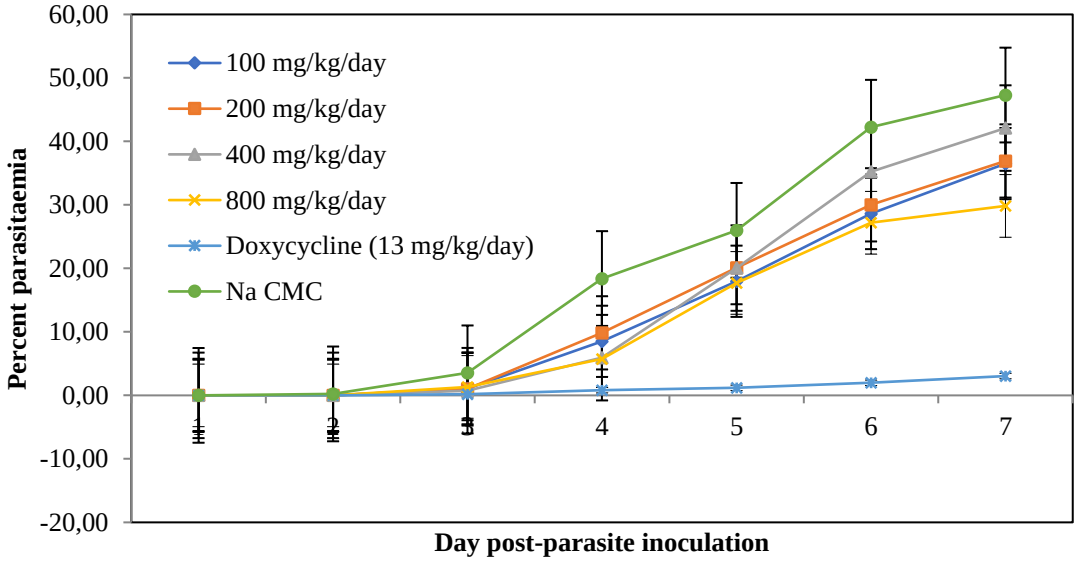

Figure 1: Percentage of parasite growth during seven days after inoculated by parasites

8. The revised manuscript should be proof-read by an English editing service for scientific manuscript.
   Answer :
   Yes, the revised manuscript have been proof-read by an English editing service for scientific manuscripts.

Reviewer 2

1. Please provide the full abbreviation for the term CMC Na at first use.
   Answer : sodium carboxy methyl cellulose (Na CMC)

2. In page 3 line 118, since authors already mentioned that a Basilico method, it is unnecessary to include the method in details. In general, the Materials and Methods section is too lengthy. Authors should consider removing unnecessary details.
   Answer :
   Inhibition of heme detoxification was assessed using Basilico method [11] which has been modified. The extract and positive control (chloroquine diphosphate) were diluted in dimethyl sulfoxide (DMSO) with a range of concentration at 2-0.01 mg/mL. The amount of hematin present in each sample was calculated using a standard curve of hematin dissolved in 0.2 M NaOH

3. In page 4 line 132, please include references for the first sentence.
   Answer : Yes, I have included references according to the suggestions

4. Throughout the article authors uses a mix of two and three decimals for numerical data. Authors should present numerical data with uniformed decimal.
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   For numeric data, yes we have changed it to be uniform using two decimals. We chose to use two decimals places to display numerical data because for *in vitro* antimalarial activity testing and inhibition of heme detoxification, the dose used was also up to two decimals places (0.01 µg / mL).

5. In page 4 line 152-156. These sentences are redundant and can be removed.
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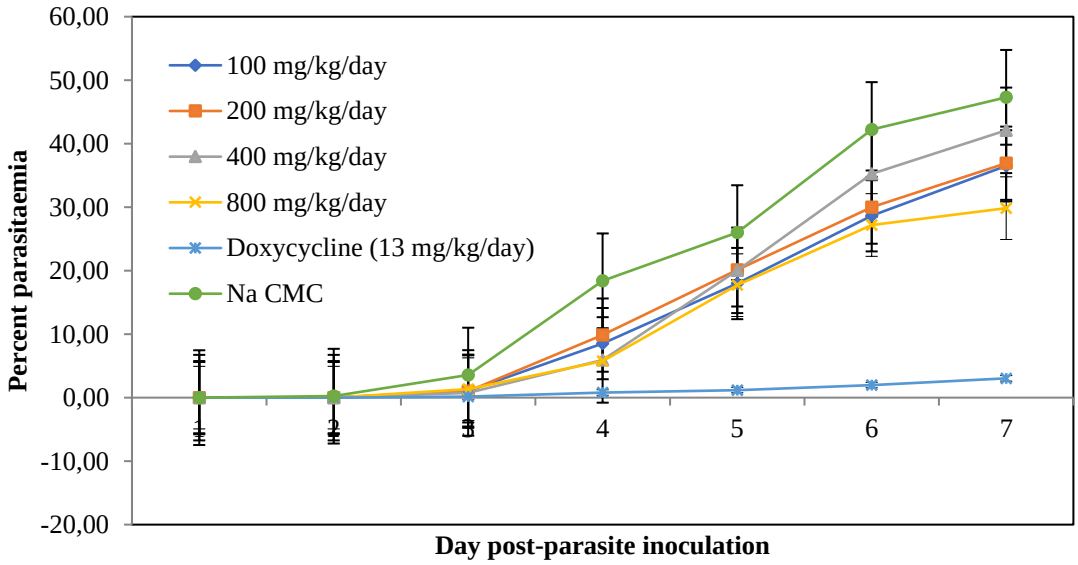

Figure 1**:** Percentage of parasite growth during seven days after inoculated by parasites

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   Answer
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8. In page 6 line 211, the paragraph should be merged into the conclusion section.
   Answer
   Yes, I have revised according to the suggestions

9. In general, the conclusion in underwhelming. Authors should consider rewriting the conclusion.
   Answer
   Conclusion
   Based on the results, it showed that the root from *H. annuus* plants has the highest antimalarial activity among the other plant parts, in in vitro, in vivo, as well as heme detoxification inhibition assay.

7390385: Revised Version Received

2 messages

Evidence-Based Complementary and Alternative Medicine <jericajona.lorenzo@hindawi.com> Wed, Oct 16, 2019 at 10:00 PM
To: wiwied-e@ff.unair.ac.id
Cc: jericajona.lorenzo@hindawi.com, dwie.widyapratiwi@gmail.com, zelmira.amanda-2014@ff.unair.ac.id, suciati@ff.unair.ac.id, aty-w@ff.unair.ac.id, arwatiheny@yahoo.com

Dear Dr. Ekasari,

The revised version of Research Article 7390385 titled "Various Parts of Helianthus Annuus Plants as a New Source of Antimalarial Drugs" by Wiwied Ekasari, Dwi Widya Pratiwi, Zelmira Amanda, Suciati -, Aty Widyawaruyanti and Heny Arwati has been received. The editor assigned to handle the review process of your manuscript will inform you as soon as a decision is reached.

Thank you for submitting your work to Evidence-Based Complementary and Alternative Medicine.

Best regards,

--
****
Jerica Lorenzo
Editorial Office
Hindawi
http://www.hindawi.com
****

wiwied ekasari <wiwied-e@ff.unair.ac.id> Thu, Oct 17, 2019 at 8:05 PM To: Evidence-Based Complementary and Alternative Medicine <jericajona.lorenzo@hindawi.com>

Dear Mr. Lorenzo

Thank you for your information.

Best regard
Wiwied Ekasari
[Quoted text hidden]

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

7390385: Minor Revision Required

3 messages

Philip F.Uzor <ecam@hindawi.com> Thu, Oct 24, 2019 at 5:10 AM
Reply-To: jericajona.lorenzo@hindawi.com
To: wiwied-e@ff.unair.ac.id
Cc: dwie.widyapratiwi@gmail.com, zelmira.amanda-2014@ff.unair.ac.id, suciati@ff.unair.ac.id, aty-w@ff.unair.ac.id, arwatiheny@yahoo.com

Dear Dr. Ekasari,

Following the review of your Research Article titled "Various Parts of Helianthus Annuus Plants as a New Source of Antimalarial Drugs," by Wiwied Ekasari, Dwi Widya Pratiwi, Zelmira Amanda, Suciati -, Aty Widyawaruyanti and Heny Arwati, I recommend that it should be revised taking into account the changes requested by the reviewer(s). Please login to the Manuscript Tracking System to read the submitted review report(s) and submit the revised version of your manuscript not later than Wednesday, November 06, 2019.

To submit your revised manuscript, please access "Current Manuscripts" in your account and upload the PDF file of your revised manuscript. You are also asked to submit your replies to the reviewer(s) comments as an additional PDF file.

Best regards,

Philip F. Uzor

---

wiwied ekasari <wiwied-e@ff.unair.ac.id> Tue, Nov 5, 2019 at 9:50 PM
To: Jericajonalorenzo <jericajona.lorenzo@hindawi.com>

Dear Mr. Philip F. Uzor,

Thank you for your email, for your information I have submitted my revised manuscript. I hope that this revised manuscript can be accepted for publication in this journal.

Best regard

Dr. Wiwied Ekasari, MSi, Apt
Department of Pharmacognosy and Phytochemistry,
Faculty of Pharmacy, Universitas Airlangga,
Surabaya, Indonesia 60115

[Quoted text hidden]

Dear Reviewers,
Thank you for all the suggestions and revisions given for our manuscript with the title **Various Parts of *Helianthus annuus* Plants as New Sources of Antimalarial Drugs.**

We have revised the manuscript in accordance with all the reviewers' requests, because it greatly improved the quality of the contents of our manuscript.

For numeric data, yes we have changed it to be uniform using two decimals. We chose to use two decimals places to display numerical data because for *in vitro* antimalarial activity testing and inhibition of heme detoxification, the dose used was also up to two decimals places (0.01 µg / mL).

We also inform you that the results of the revised manuscript have been proof-read by an English editing service for scientific manuscripts.
We sincerely hope that this revised manuscript can be accepted for publication in this journal.

Best regard

Dr. Wiwied Ekasari, MSi., Apt
Department of Pharmacognosy and Phytochemistry
Faculty of Pharmacy, Universitas Airlangga
Surabaya, Indonesia 60115

3. ARTIKEL DITERIMA UNTUK PUBLIKASI

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

7390385: Your manuscript has been accepted

3 messages

Philip F. Uzor <ecam@hindawi.com> Mon, Nov 11, 2019 at 8:38 AM
Reply-To: jericajona.lorenzo@hindawi.com
To: wiwied-e@ff.unair.ac.id
Cc: dwie.widyapratiwi@gmail.com, zelmira.amanda-2014@ff.unair.ac.id, suciati@ff.unair.ac.id, aty-w@ff.unair.ac.id, arwatiheny@yahoo.com

Dear Dr. Ekasari,

The review process of Research Article 7390385 titled "Various Parts of Helianthus Annuus Plants as a New Source of Antimalarial Drugs" by Wiwied Ekasari, Dwi Widya Pratiwi, Zelmira Amanda, Suciati -, Aty Widyawaruyanti and Heny Arwati submitted to Evidence-Based Complementary and Alternative Medicine has been completed. I am pleased to inform you that your manuscript has now been accepted for publication in the journal.

The special issue for which the paper is being processed is
"Natural Products as Sources of Antimalarial Drugs"

The publication process of your manuscript will be initiated upon the receipt of electronic files. Please log in to the Manuscript Tracking System at the link below using your username and password, and upload the electronic files of your final accepted version within the next 2-3 days.

http://mts.hindawi.com/author/7390385/upload.files/

The electronic files should include the following:

1- Source file of the final accepted manuscript (Word or TeX/LaTeX).
2- PDF file of the final accepted manuscript.
3- Editable figure files (each figure in a separate EPS/PostScript/Word file) if any, taking into consideration that TIFF, JPG, JPEG, BMP formats are not editable.

If you have deposited your manuscript on a preprint server (e.g. arXiv, bioRxiv, chemRxiv), now would be a good time to update it with the accepted version. If you have not deposited your manuscript on a preprint server, you are free to do so.

Thank you again for submitting your manuscript to Evidence-Based Complementary and Alternative Medicine.

Best regards,

Philip F. Uzor

wiwied ekasari <wiwied-e@ff.unair.ac.id> Mon, Nov 11, 2019 at 9:30 PM
To: Jericajonalorenzo <jericajona.lorenzo@hindawi.com>

Dear Mr. Philip F.Uzor

Thank you for your information. We are very happy to hear the news that our manuscript can be published in your journal . But sorry, I made mistake while inserting electronic files of my final accepted version. There should be 3 files that I will enter , but I just entered one files (Source file of the final accepted manuscript in Word), the system is closed, and I cannot enter other files (PDF file of the final accepted and Editable Figure Files). Can you help me to overcome this problem? I really need your help.

Best regards,

Wiwied Ekasari

[Quoted text hidden]

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

7390385: Galley Proof Corrections

1 message

Evidence-Based Complementary and Alternative Medicine Sun, Nov 24, 2019 at 8:45 PM
<production.b@hindawi.com>
To: wiwied-e@ff.unair.ac.id
Cc: aty-w@ff.unair.ac.id, zelmira.amanda-2014@ff.unair.ac.id, dwie.widyapratiwi@gmail.com, arwatiheny@yahoo.com, suciati@ff.unair.ac.id

Dear Dr. Ekasari,

This is to confirm the receipt of the first galley proof corrections of Research Article 7390385 titled "Various Parts of Helianthus Annuus Plants as a New Source of Antimalarial Drugs,".

Thank you for your cooperation.

Best regards,

--
****
Hindawi Production Team
Hindawi
https://www.hindawi.com
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4. ARTIKEL DITERBITKAN

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

7390385: Your article has been published

2 messages

Jerica Lorenzo <jericajona.lorenzo@hindawi.com> Wed, Nov 27, 2019 at 1:16 PM
To: wiwied-e@ff.unair.ac.id

Dear Dr. Ekasari,

I am pleased to let you know that your article has been published in its final form in "Evidence-Based Complementary and Alternative Medicine."

Wiwied Ekasari, "Various Parts of Helianthus annuus Plants as New Sources of Antimalarial Drugs," Evidence-Based Complementary and Alternative Medicine, vol. 2019, Article ID 7390385, 7 pages, 2019. https://doi.org/10.1155/2019/ 7390385.

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https://www.hindawi.com/ journals/ecam/2019/7390385/reprint/.

Best regards,

Jerica Lorenzo
Evidence-Based Complementary and Alternative Medicine
Hindawi
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wiwied ekasari <wiwied-e@ff.unair.ac.id> Fri, Nov 29, 2019 at 10:00 AM
To: Jerica Lorenzo <jericajona.lorenzo@hindawi.com>

Dear Mr. Jerica Lorenzo

Thank you for the good news from you.

Best Regard
Dr. Wiwied Ekasari

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