1. PROSES SUBMIT

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

Confirmation of your submission to BMC Complementary Medicine and Therapies - BCAM-D-20-00299

1 message

BMC Complementary & Alternative Medicine - Editorial Office <em@editorialmanager.com>
Mon, Feb 24, 2020 at 1:40 PM

Reply-To: BMC Complementary & Alternative Medicine - Editorial Office <jeanelle.depadua@springernature.com>
To: Wiwied - Ekasari <wiwied-e@ff.unair.ac.id>

BCAM-D-20-00299
Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification Wiwied - Ekasari, Ph.D; Dewi Resty Basuki, Master Degree; Heny - Arwati, Doctor Degree; Tutik Sri Wahyuni, Doctor Degree

BMC Complementary Medicine and Therapies

Dear Dr Ekasari,

Thank you for submitting your manuscript 'Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification' to BMC Complementary Medicine and Therapies.

The submission id is: BCAM-D-20-00299

Please refer to this number in any future correspondence.

During the review process, you can keep track of the status of your manuscript by accessing the following website:

https://www.editorialmanager.com/bcam/

If you have forgotten your password, please use the 'Send Login Details' link on the login page at https://www.editorialmanager.com/bcam/. For security reasons, your password will be reset.

Best wishes,

Editorial Office
BMC Complementary Medicine and Therapies
https://bmccomplementalternmed.biomedcentral.com/

BCAM-D-20-00299 - Journal requirements for your submission

2 messages

BMC Complementary & Alternative Medicine - Editorial Office Thu, Feb 27, 2020 at 9:24 AM
<em@editorialmanager.com>
Reply-To: BMC Complementary & Alternative Medicine - Editorial Office <jeanelle.depadua@springernature.com>
To: Wiwied - Ekasari <wiwied-e@ff.unair.ac.id>

BCAM-D-20-00299
Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification Wiwied - Ekasari, Ph.D; Dewi Resty Basuki, Master Degree; Heny - Arwati, Doctor Degree; Tutik Sri Wahyuni, Doctor Degree

BMC Complementary Medicine and Therapies

Dear Dr Ekasari,

Your submission entitled "Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification" has been received.

Before we can further process it you are kindly requested to make the following corrections within 4 working days to meet the journal's requirements (please also refer to the Submission Guidelines available on the journal website):

Any questions relating to the requested formatting changes should be sent to, Ms. Princess Quilatan (princess.quilatan@biomedcentral.com).

FORMATTING CHANGES:

Points to request:

1. ARRIVE guidelines

- In accordance with BioMed Central editorial policies (http://www.biomedcentral.com/submissions/editorial-policies#standards+of+reporting), could you please ensure your manuscript reporting adheres to the ARRIVE guidelines (http://www.nc3rs.org.uk/page.asp?id=1357) for the reporting of animal experiments. This is so your methodology can be fully evaluated and utilised. Can you please include a completed ARRIVE checklist as an additional file when submitting your revised manuscript. Please complete the checklist in full by inserting the page number/paragraph and section of your manuscript which reports the information that meets the criteria of the checklist. For example, “Methods, paragraph 2”. If a criterion is not applicable for your particular manuscript/study, we can accept “N/A”.

- Please note that checklists completed incorrectly will be returned for revision as we cannot progress your manuscript to peer review until the checklist has been completed.

2. Declarations

- Please add the heading "Declarations" before you list the Declarations subheadings. In your manuscript, this will be directly after the Abbreviations section.

3. Ethics approval and consent to participate

- Please include the full name of the ethics committee (and the institute to which it belongs to) that approved the study and the committee’s reference number if appropriate in the "Ethics Approval and Consent to Participate" subsection of the Declarations.

4. Funding

- Please state clearly the role the funder(s) had in your study in the "funding" section of the declarations.

5. Please rename Conflicting Interest to Competing Interests.

6. Methods of Euthanasia

- Please state the procedure/process of euthanasia used in the mice in the “Methods” section.

Further information about our editorial policies can be found at the following links:

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When you have completed your revisions and are ready to submit your manuscript, please log onto Editorial Manager as an author. The URL is https://www.editorialmanager.com/bcam/.
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Please go to the menu item 'Submissions Sent Back to Author', and click on 'Edit Submission'. If no changes are to be made to the metadata, please go immediately to the last submission step 'attach files', and replace the necessary files. Following this, please:

1. Build the PDF,
2. Click 'View submission' to ensure all the correct changes have been incorporated
3. Click 'approve submission' to ensure the submission of your manuscript is fully complete.

Thank you for submitting your work to this journal.

With kind regards,

Editorial Office
BMC Complementary Medicine and Therapies
https://bmccomplementalternmed.biomedcentral.com/

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wiwied ekasari <wiwied-e@ff.unair.ac.id> **Fri,** Feb 28, 2020 at 9:33 AM To: BMC Complementary & Alternative Medicine - Editorial Office <jeanelle.depadua@springernature.com>

Dear Editor,

Thank you very much for your email.
Yes , I will revise my manuscript according to your suggestion.

Best regard,
Dr. Wiwied Ekasari, Apt

[Quoted text hidden]

Your submission to BMC Complementary Medicine and Therapies - BCAM-D-20-00299

2 messages

BMC Complementary & Alternative Medicine - Editorial Office <em@editorialmanager.com> Tue, Mar 10, 2020 at 12:31 AM

Reply-To: BMC Complementary & Alternative Medicine - Editorial Office <jeanelle.depadua@springernature.com>
To: Wiwied - Ekasari <wiwied-e@ff.unair.ac.id>

BCAM-D-20-00299
Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification Wiwied - Ekasari, Ph.D; Dewi Resty Basuki, Master Degree; Heny - Arwati, Doctor Degree; Tutik Sri Wahyuni, Doctor Degree

BMC Complementary Medicine and Therapies

Dear Dr Ekasari,

Thank you for submitting your manuscript, "Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification" (BCAM-D-20-00299), to BMC Complementary Medicine and Therapies.

Before it can be sent out for review, please carry out the corrections, below.

Please submit your revised manuscript by accessing the following site:

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If you have forgotten your password, please use the 'Send Login Details' link on the login page at https://www.editorialmanager.com/bcam/. For security reasons, your password will be reset.

Please note, if your manuscript is accepted you will not be able to make any changes to the authors, or order of authors, of your manuscript once the editor has accepted your manuscript for publication. If you wish to make any changes to authorship before you resubmit your revisions, please reply to this email and ask for a 'Request for change in authorship' form which should be completed by all authors (including those to be removed) and returned to this email address. Please ensure that any changes in authorship fulfil the criteria for authorship as outlined in BioMed Central's editorial policies (http://www.biomedcentral.com/about/editorialpolicies#authorship).

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By resubmitting your manuscript you confirm that all author details on the revised version are correct, that all authors have agreed to authorship and order of authorship for this manuscript and that all authors have the appropriate permissions and rights to the reported data.

Please be aware that we may investigate, or ask your institute to investigate, any unauthorised attempts to change authorship or discrepancies in authorship between the submitted and revised versions of your manuscript.

We look forward to receiving your revised manuscript before 23 Mar 2020.

Best wishes,

Esther Fagelson
BMC Complementary Medicine and Therapies
https://bmccomplementalternmed.biomedcentral.com/

Editor's comments:

1. Please provide a timeline of your experiment

2. Please clarify your euthanasia/sacrifice methods, including whether animals were anaesthetised and/or unconscious, injection dosages if applicable, methods used and rationale etc.

Please try to be as detailed as possible.

3. We note your manuscript has a high degree of overlap with this pre-print:

https://www.researchsquare.com/article/rs-12642/v1

please clarify if your article is still undergoing peer review in this journal.

Editorial Policies

Please read the following information and revise your manuscript as necessary. If your manuscript does not adhere to our editorial requirements this will cause a delay whilst the issue is addressed. Failure to adhere to our policies may result in rejection of your manuscript.

In accordance with BioMed Central editorial policies and formatting guidelines, all submissions to BMC Complementary Medicine and Therapies must have a Declarations section which includes the mandatory sub-sections listed below. Please refer to the journal's Submission Guidelines web page for information regarding the criteria for each sub-section (https://bmccomplementalternmed.biomedcentral.com/).

Where a mandatory section is not relevant to your study design or article type, for example, if your manuscript does not contain any individual persons data, please write "Not applicable" in these sections.

For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must state that data will not be shared, and provide reasons for this in the manuscript text. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page - http://www.biomedcentral.com/ submissions/editorial-policies#availability+of+data+and+materials.

Declarations
- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements
- Authors' Information

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

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wiwied ekasari <wiwied-e@ff.unair.ac.id> **Thu,** Mar 12, 2020 at 4:12 PM To: BMC Complementary & Alternative Medicine - Editorial Office <jeanelle.depadua@springernature.com>

Dear Mr. Esther Fagelson
BMC Complementary Medicine and Therapies .

Thank you very much for your information.

Best Regard
Dr. Wiwied Ekasari
[Quoted text hidden]

Your submission to BMC Complementary Medicine and Therapies - BCAM-D-20-00299R1

2 messages

BMC Complementary & Alternative Medicine - Editorial Office <em@editorialmanager.com> Fri, Mar 27, 2020 at 1:59 AM

Reply-To: BMC Complementary & Alternative Medicine - Editorial Office <jeanelle.depadua@springernature.com>
To: Wiwied - Ekasari <wiwied-e@ff.unair.ac.id>

BCAM-D-20-00299R1
Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification Wiwied - Ekasari, Ph.D; Dewi Resty Basuki, Master Degree; Heny - Arwati, Doctor Degree; Tutik Sri Wahyuni, Doctor Degree

BMC Complementary Medicine and Therapies

Dear Dr Ekasari,

Thank you for submitting your manuscript, "Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification" (BCAM-D-20-00299R1), to BMC Complementary Medicine and Therapies.

Before it can be sent out for review, please carry out the corrections, below.

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Please note, if your manuscript is accepted you will not be able to make any changes to the authors, or order of authors, of your manuscript once the editor has accepted your manuscript for publication. If you wish to make any changes to authorship before you resubmit your revisions, please reply to this email and ask for a 'Request for change in authorship' form which should be completed by all authors (including those to be removed) and returned to this email address. Please ensure that any changes in authorship fulfil the criteria for authorship as outlined in BioMed Central's editorial policies (http://www.biomedcentral.com/about/editorialpolicies#authorship).

Once you have completed and returned the form, your request will be considered and you will be advised whether the requested changes will be allowed.
By resubmitting your manuscript you confirm that all author details on the revised version are correct, that all authors have agreed to authorship and order of authorship for this manuscript and that all authors have the appropriate permissions and rights to the reported data.

Please be aware that we may investigate, or ask your institute to investigate, any unauthorised attempts to change authorship or discrepancies in authorship between the submitted and revised versions of your manuscript.

We look forward to receiving your revised manuscript before 02 Apr 2020.

Best wishes,

Kate Gaines
On behalf of,
Esther Fagelson
BMC Complementary Medicine and Therapies
https://bmccomplementalternmed.biomedcentral.com/

Editor's comments:

Thank you for performing the requested revisions.

However, we request further clarification. Please provide a more specific timeline of your experiments, including details such as the date your in vitro experiment was initiated and completed, and when the in vivo experiment was initiated and completed.

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/ authorandreviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/ getpublished/writing-resources). These cover common mistakes that occur when writing in English.

Editorial Policies

Please read the following information and revise your manuscript as necessary. If your manuscript does not adhere to our editorial requirements this will cause a delay whilst the issue is addressed. Failure to adhere to our policies may result in rejection of your manuscript.

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Where a mandatory section is not relevant to your study design or article type, for example, if your manuscript does not contain any individual persons data, please write "Not applicable" in these sections.

For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must state that data will not be shared, and provide reasons for this in the manuscript text. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page - http://www.biomedcentral.com/ submissions/editorial-policies#availability+of+data+and+materials.

Declarations
- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements
- Authors' Information

As a result of the significant disruption that is being caused by the COVID-19 pandemic we are very aware that many researchers will have difficulty in meeting the timelines associated with our peer review process during normal times. Please do let us know if you need additional time. Our systems will continue to remind you of the original timelines but we intend to be highly flexible at this time.

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wiwied ekasari <wiwied-e@ff.unair.ac.id> **Wed,** Apr 1, 2020 at 12:31 PM To: BMC Complementary & Alternative Medicine - Editorial Office <jeanelle.depadua@springernature.com>

Dear Editor
BMC Complementary Medicine and Therapies

Thank you for your email. I inform you that I have sent the manuscript revision.

Best regard
Dr. Wiwied Ekasari
[Quoted text hidden]

2. PROSES REVIEW

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

Your submission to BMC Complementary Medicine and Therapies - BCAM-D-20-00299R2

2 messages

BMC Complementary & Alternative Medicine - Editorial Office Thu, Sep 24, 2020 at 10:18 PM
<em@editorialmanager.com>
Reply-To: BMC Complementary & Alternative Medicine - Editorial Office <eloisa.hadenolasco@springernature.com>
To: Wiwied - Ekasari <wiwied-e@ff.unair.ac.id>

BCAM-D-20-00299R2
Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification Wiwied - Ekasari, Ph.D; Dewi Resty Basuki, Master Degree; Heny - Arwati, Doctor Degree; Tutik Sri Wahyuni, Doctor Degree

BMC Complementary Medicine and Therapies

Dear Dr Ekasari,

Your manuscript "Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification" (BCAM-D-20-00299R2) has been assessed by our reviewers. They have raised a number of points which we believe would improve the manuscript and may allow a revised version to be published in BMC Complementary Medicine and Therapies.

Their reports, together with any other comments, are below. Please also take a moment to check our website at https://www.editorialmanager.com/bcam/ for any additional comments that were saved as attachments.
If you are able to fully address these points, we would encourage you to submit a revised manuscript to BMC Complementary Medicine and Therapies.

Once you have made the necessary corrections, please submit online at:

https://www.editorialmanager.com/bcam/

If you have forgotten your password, please use the 'Send Login Details' link on the login page at https://www.editorialmanager.com/bcam/. For security reasons, your password will be reset.

A point-by-point response letter must accompany your revised manuscript. This letter must provide a detailed response to each reviewer/editorial point raised, describing exactly what amendments have been made to the manuscript text and where these can be viewed (e.g. Methods section, line 12, page 5). Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes. If you disagree with any comments raised, please provide a detailed rebuttal to help explain and justify your decision.

Please also ensure that your revised manuscript conforms to the journal style, which can be found at the Submission Guidelines on the journal homepage.

A decision will be made once we have received your revised manuscript, which we expect by 24 Oct 2020.

Please note, if your manuscript is accepted you will not be able to make any changes to the authors, or order of authors, of your manuscript once the editor has accepted your manuscript for publication. If you wish to make any changes to authorship before you resubmit your revisions, please reply to this email and ask for a 'Request for change in authorship' form which should be completed by all authors (including those to be removed) and returned to this email address. Please ensure that any changes in authorship fulfil the criteria for authorship as outlined in BioMed Central's editorial policies (http://www.biomedcentral.com/about/editorialpolicies#authorship).

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By resubmitting your manuscript you confirm that all author details on the revised version are correct, that all authors have agreed to authorship and order of authorship for this manuscript and that all authors have the appropriate permissions and rights to the reported data.

Please be aware that we may investigate, or ask your institute to investigate, any unauthorised attempts to change authorship or discrepancies in authorship between the submitted and revised versions of your manuscript.

I look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

Anne Menard
BMC Complementary Medicine and Therapies
https://bmccomplementalternmed.biomedcentral.com/

Editor Comments:
1. A point-by-point response letter must accompany your revised manuscript. This letter should provide a detailed response to each reviewer/editorial point raised, describing exactly what amendments have been made to the manuscript text and where these can be viewed (e.g. Methods section, page 5, line 12).

2. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.

We operate a transparent peer review process for this journal where reviewer reports are published with the article but the reviewers are not named (unless they opt in to include their name).

Reviewer reports:

Reviewer 1: The manuscript describes the beneficial effect of the extract from Cassia spectabilis DC Leaf extract against malaria, a life -threatening tropical disease. The findings are worth publishing, though there is a need for the manuscript to be proofread for correction of English language, in order to ease comprehension of the work presented. Other questions remarks/suggestions arising from the manuscript are as follows:

Title: lines 1-2
1) Authors may consider "Antimalarial Activity of …", instead of "Antimalaria Activity of …"

Lines 52-92
2) Authors may extend the "background" section to include the importance of heme detoxification.

3) There is a need to reformulate several sections (e.g., Lines 75, 96, 110, 140-141, 152, 182-183).

Plant material
4) The parasites used in this study, including P. falciparum and P. berghei, are also biological materials, may be properly described/presented in the section Methods. Moreover, authors should clearly indicate the source of these biological materials.

Isolation, lines 117-128
5) A flowchart may be included in the manuscript to better illustrate the protocol used for preparation of the plant active fractions.

Lines 130-148
6) Authors may revise this section so as to show/indicate when the parasites were added into cultures. The estimated parasite density used (number of parasite per well or mL) and the final DMSO concentration in the cultures may also be provided.
It is not clear how many times the in vitro experiment was conducted, and this may be also indicated by the authors.

Line 151
7) How was infection process carried out? Authors may bring more information on this, for better understanding of the protocol.
Lines 154-199

8) What happened to the animals after completion of the suppressive effect of ethanolic extract of C. spectabilis DC leaf combined with artesunate. Were they euthanized?

Lines 202 - 203
9) Authors wrote "…. classification according to Gessler et al., where extract with IC50 less than 10 µg/mL was considered very good…". In line with this, one may wonder why the Fractions C5-C8 and C9 were not carried further in the fractionation process.

Lines 206 - 214
10) The IC50 values for the methanol and hexane extracts, fractions C1, C2 & C5, as well as sub-fraction SFC.8.4 should be cross-checked.

11) Authors may explain why the effect of C. spectabilis on parasitic stage development, as well as subsequent experiments, were not carried out on the selected sub-fraction C.8.3 or isolate C8.3.2, that were relatively pure active fractions?

Lines 250 - 253

12) Footnotes explaining how %parasitemia, %growth and % inhibition were generated may be included.

Lines 257 - 258

13) It is important to carry out statistical analyses of results and present significant differences within the manuscript. For example, the statement "After 24 hours, the incubation period of the parasite was inhibited 100% compared to the control (Fig. 2)", may be justified by indicating a P value.

Lines 301-307:

14) This paragraph may be reformulated to ease understanding.

Reviewer 2: Antimalaria Activity of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification

This manuscript is too full of words at the lack of precision expected of a scientific work.

1. Many statements are qualitative and do not give an idea of how good is good in "Cassia spectabilis DC leaf has shown a good antimalarial activity".
2. The construction of sentences is very poor. E.g. " In vitro antimalarial activity testing using P. falciparum which was done with bioassay guide isolation in order to obtain the active compound"
3. " In vivo testing towards infected P. berghei mice"- should be "In vivo testing using
4. Binomial names of all organisms must be italicized: e,g, P. berghei, C. spectabilis. Likewise In vivo, In vitro must be italicized.
5. "The results showed that active antimalarial isolate obtained from C. spectabilis DC leaf had a structural pattern that was identical to (-)-7-hydroxyspectaline"- I believe that "isolate" could better be stated as "molecule" provided that the authors are sure of the purity of the molecule. There is need to present the spectra of standard (-)-7-hydroxyspectaline and the molecule which has been isolated by the authors. Unfortunately there is not a single chromatogram in the manuscript that has the aim of extraction and isolation of metabolites.
6. Sentences like "Prophylactic test on infected P. berghei mice obtained the highest dose of inhibition percentage of90% ethanol extract of C. spectabilis DC leaf was 68.61% while positive (doxycycline)control at 100 mg kg -1 was 73.54%"- need to be simplified.- infected P. berghei mice must be "P. berghei infected mice. "the highest dose of inhibition percentage" is meaningless.
7. This is a bad sentence: Previous study related to this plant with in vivo shows that this plant is quite potential to be continued (1)
8. " New antimalarial active compounds have also been obtained from plant in the same genus,namely Cassiarin A alkaloid compound from C. siamea plant (2, 3)" is another bad sentence- it should be "another plant C. siamea from the same genus as C. spectabilis. Further it is not clear if both (-)-7-hydroxyspectaline and Cassiarin A are shared by both the plants.
9. A common mistake through- out the manuscript is reflected by sentences like "For this reason, an in vitro research for antimalarial active compound from C. spectabilis DC plant with bioassay guide isolation is conducted." In vitro can never be antimalarial since malaria is the name of a disease seen in animals but can which cannot be mimicked in vitro. So all in vitro studies must be called as "anti - plasmodial"
10. "Furthermore, antimalarial drug development and discovery is expected to provide new drugs with potential and safe drug mechanisms for humans"- what is implied by potential and safe drug mechanisms"?
11. "Research related to the biochemical process of malaria parasites plays an important role in the development of new antimalarial drugs."- "biochemical process of malaria parasites" must be "biochemical process unique to malaria parasites".
12. "It will also test the effect of C. spectabilis DC leaf ethanol extract on biochemical activity in the malaria parasite food vacuole including determining the potential for extracts in the detoxification of malaria parasite heme and antimalarial activity of the parasite in each life cycle"- who is It? "on biochemical activity in the malaria parasite food vacuole" is very vague. All that the authors have done is to study heme detoxification process. "Each life cycle" is meaningless.
13. " is amounting to 150 mg kg-1 by giving three times a day orally (1).- is it 150 mg kg-1 each time amounting to 450 mg/day?
14. "Based on the foregoing, a combination of ethanol extract of C. spectabilis DC leaf extract will also be tested with artesunate which is one of the artemisinin derivatives to determine the inhibition of growth in P. berghei mice with in vivo."- "will also be tested " must be "has been tested". It is not clear why leaf extract has been tested only in combination with artesunate but not alone in mouse model of malaria. "which is one of the artemisinin derivatives" must be removed since it is known to all that it is a derivative.
15. "It is hoped that after this study, an appropriate combination model between artesunate and 90% leaf ethanol

extract will obtain C. spectabilis DC that produces the greatest therapeutic effect" is a poorly constructed sentence. "combination model" must be replaced with "combination", between should be "of", "will obtain" must be "will be obtained". Further given enough Artesunate there can be no advantage of supplementation with leaf extract. The authors must find out if the leaf extract is capable of enhancing the oral bioavailability or pharmacokinetics of Artesunate and if the plant extract is capable of delaying the advent of Artesunate resistance.

16. "The mice were sacrificed by cervical dislocation after anesthetized by intraperitoneal injection of 100mg/kg BB ketamine (9) .The death animals were buried." Are bad sentences- "anesthetized" must be "anesthesia", 100mg must be 100 mg, "death" must be "dead".

17. "The extract was made by macerating dried C. spectabilis DC leaf powder using 90% ethanol as many as three times"- there is no use of saying "as many as", it must be told how many grams of leaf powder was extracted with how much volume of solvent each time.

18. "The extract was practiced in liquid-liquid with ethyl acetate and 3% tartaric acid." Is a wrong sentence and raises many questions: practiced is meaningless; it ought to be "the extract was subjected to liquid -liquid partition using ethyl acetate and 3% tartaric acid".

It may be better to state procedure exactly as practiced. Was the dried extract first dissolved in 3% Tartaric acid? What was the reason for use of Tartaric acid must be stated.

19. "The aqueous layer was adjusted at pH 9 with saturated NaHCO3 and extracted with chloroform." State what was done to the organic layer. "adjusted at pH 9" must be "adjusted to pH 9"

20 "The chloroform fraction was then separated using column chromatography (chloroform-ethyl acetate-methanol) produced nine fractions."- is a very poor description of the method. Chloroform fraction (weight??) which column was used, what was the resin?? "produced nine fractions."-must be "to obtain nine fractions". Give exact description of chloroform-ethyl acetate-methanol, steps, ratios, size of column, volume per fraction etc

21. "In vitro antimalarial activity test: Stock sample solutions were prepared in DMSO and diluted to the required concentration with complete media (RPMI 1640 plus 10% human plasma, 25 mM of HEPES, and 25 mM of NaHCO3) until the final concentrations of the sample on the well culture plate were 10, 1, 0.1, 0.01, and 0.001 µg mL-1. The test was carried out in duplicate. The plates were incubated in CO2 condition at 37ºC in a wax tube."

(a) This is not antimalaria test but a test for antiplasmodial activity.

(b) Since dilutions have been made on stocks in DMSO, it is important to mention what the concentration of sample was in DMSO and what was the method by which 10, 1, 0.1, 0.01, and 0.001 µg mL-1.concentrations were obtained in the wells. What was the concentration of DMSO in each well must also be stated.

(c) CO2 condition in a wax tube- these are vague and unclear.

22. "For test stage-specific antimalarial activity in vitro, incubation is performed at 6, 12, 24, and 48 hours"- antimalarial is wrong again, the incubation details are inadequate to the extent that what is incubated is also not clear.

23. "After the incubation, the contents of the well were harvested and the red cells were transferred to clean microscopic slides to form a series of thick films. The film was stained for 10 minutes in a 10% Giemsa solution (pH 7.3). Each 50% of inhibitory concentration (IC50) was calculated based on the inhibition percentage towards P. falciparum using probit analysis."-

(a) Since smears made were thick, what were the number of cells per field?

(b) Counting 1000 cells is not enough to make a good judgment of % parasitemia. At least 3000 cells must be counted. How IC50 was determined must be described.

24. A, B, C, D, E, and F should be A-F

25. Testing of inhibition of heme polymerization using the Basilico method(13) has been modified.- Essential elements of Basilico method must be stated in brief and the modifications made must be mentioned in detail.

26. Making a standard hematin curve started from making a 1 mM hematin solution in 0.2 M NaOH.- is a poorly constructed sentence. What is meant by hematin curve? What is the difference between hematin and beta hematin?

27. Table 2. The percentage inhibition of chloroform fractions of C. spectabillis DC leaf against P.falciparum 3D7strain: there is no meaning of percentage inhibition of chloroform fractions. Are you inhibiting the fractions???

28. All tables showing % parasitemia must be replaced with graphs showing the same data.

29. Table 2: has 12.44 ± 17.59. What does it mean? Was standard deviation more than the mean? What is the reliability of data that has standard deviation greater than the mean?

30. Isolation from chloroform extract obtained nine fractions- is a poorly constructed sentence. Give details of what exactly was done.

31. The spectral chracteristics given must be replaced with the NMR spectra obtained and commented upon.

32. Table 5 has Ring, Trophozoite and Sporozoite. This is quite strange because it is not clear from where did the authors get the Sporozoites. The table mentions DMSO. Does it mean that authors have tested DMSO against the parasite?

33. leaf was shown in Table 6 must be " is shown in table 6".

34. Table 6: 100 mg adult human dose: why was human dose given to a mouse?

35. Table 8 has "level of hematin (mm)"- what is mm?

36. There is need to have structure for 7-hydroxycassine.

37. Discussion needs significant qualitative improvement with decrease in number of words used. The data used to suggest that combination of Artesunate with leaf extract will reduce requirement for Artesunate is not strong enough. In fact there is enough evidence to suggest that the use of whole leaf of A annua is more potent and promising than the same amount of Artemisinin coming as pure Artemisinin. (Dried whole-plant Artemisia annua slows evolution of malaria drug resistance and overcomes resistance to artemisinin

Mostafa A. Elfawala, Melissa J. Towlerb, Nicholas G. Reichc, Pamela J. Weathersb, and Stephen M. Richa, PNAS 2014). So instead of combining C. spectabillis with artesunate/artemisinin why cant people chew the leaves of A annua itself?
38. List of abbreviations has ELISA and HRFABMS : but there seems to be neither data nor mention of these in the text.

****

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/ authorandreviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/ getpublished/writing-resources). These cover common mistakes that occur when writing in English.

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- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements
- Authors' Information

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wiwied ekasari <wiwied-e@ff.unair.ac.id> **Fri,** Sep 25, 2020 at 12:43 PM To: BMC Complementary & Alternative Medicine - Editorial Office <eloisa.hadenolasco@springernature.com>

Dear Editor
BMC Complementary Medicine and Therapies.

Thank you very much for your email.
Yes, I will revise my manuscript according to the suggestions of the reviewers.

Best regards
Dr. Wiwied Ekasari, MSi., Apt

[Quoted text hidden]

- **ANSWER TO REVIEWERS**

REVIEWER 1:

The manuscript describes the beneficial effect of the extract from *Cassia spectabilis* DC leaf extract against malaria, a life-threatening tropical disease. The findings are worth publishing, though there is a need for the manuscript to be proofread for correction of English language, in order to ease comprehension of the work presented. Other questions remarks/suggestions arising from the manuscript are as follows:

1) Title, lines 1–2: Authors may consider "Antimalarial Activity of …", instead of "Antimalaria Activity of …"

   ANSWER:

   The title has been changed to "Antiplasmodial Activity of Ethanolic Extract of *Cassia spectabilis* DC Leaf and Its Inhibition Effect in Heme Detoxification" [line 1–2].

2) Lines 52–92: Authors may extend the "background" section to include the importance of heme detoxification.

   ANSWER:

   The background on the important of inhibition of heme detoxification has been added [lines 80–94].

   "Furthermore, antimalarial drug development and discovery is expected to provide new drugs which is not only have antiplasmodial activity *in vitro* and *in vivo*, but also has a safety mechanism to be applied to human. Research related to the biochemical process of malaria parasites plays an important role in the development of new antimalarial drugs. Malaria parasites consume hemoglobin from erythrocytes during their life cycle, however, parasites are unable to digest iron-containing heme molecule. Heme is toxic due to the reactivity of iron. Therefore, parasite has developed the mechanism to detoxify it by polymerization of heme to form hemozoin or malaria pigmen (6,7). The structure of hemozoin through X-ray diffraction and IR spectroscopy has been found to be similar to β-hematin (8) β-hematin is synthetic hemozoin which chemically (8), spectroscopically (9) and crystalographically (10) similar to hemozoin which consists of Ferriprotoporphyrin units linked into a polymer by propionate oxygen-iron bonds (8, 11). The inhibition of heme detoxification has been the target of antimalarial drugs, such as chloroquine and artemisinin (12, 13), since inhibit the heme detoxification can kill the parasites."

3) There is a need to reformulate several sections (e.g., Lines 75, 96, 110, 140-141, 152, 182-183).

   ANSWER:

   - Line 75 has been reformulated [lines 98–101].

     "Currently, the effect of ethanol extract of *C. spectabilis* DC leaf on biochemical activity such as potential inhibition of heme detoxification in the food vacuole of malaria parasite and stage-specific activity against asexual stage of parasite has been tested."
   - Line 96 has been reformulated [lines 124–129].

     "*C. spectabilis* DC leaf was obtained from Purwodadi Botanical Garden-Indonesian Institute of Sciences [Lembaga Ilmu Pengetahuan Indonesia, LIPI], Pasuruan District, East Java Province, Indonesia, and the determination of specimen was performed at the above institution. The specimen was then deposited as herbarium in the Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Universitas Airlangga with registration number of 02/W/XI/2016."
   - Line 110 has been reformulated [lines 153–156].

"At the end of the tests, all animals were followed the euthanasia procedure. The mice were sacrificed by cervical dislocation after anesthesia by intraperitoneal injection of 100 mg/kg bodyweight ketamine (19). The dead animals were then buried."

- Line 140–141 has been formulated [lines 219–221].
  "The 50% inhibitory concentration (IC_{50}) value was determined using probit analysis based on the relation of log concentration of test compound and % inhibition of parasites growth."
- Line 152 has been formulated [lines 233–238].
  "Each mouse in each group was infected with $1x10^6$ infected erythrocytes. Thin blood films from each mouse were made at 72 hours post infection. Determination of parasitemia, percentage of the parasites' growth, percentage inhibition of parasites' growth, and effective dose 50 (ED_{50}) were based on Ekasari et al (20)."
- Lines 182–183 has been formulated [lines 273–279].
  "The inhibition of heme polymerization test was performed based on the Basilico method (23) with slight modification in the concentration of hematin solution and the sample used. The Basilico method is an *in vitro* spectrophotometric microassay of heme polymerization. A 96-well U-bottomed microplates was used in this assay. The relative amounts of polymerized and unpolymerized hematin were determined using an ELISA reader. The final concentration of the extract samples ranged from 2 to 0.01 mg/ml."

4) Plant material: The parasites used in this study, including *P. falciparum* and *P. berghei*, are also biological materials, may be properly described/presented in the section Methods. Moreover, authors should clearly indicate the source of these biological materials.

ANSWER:

Following the reviewer suggestion, we have explained the information of *P. falciparum* and *P. berghei* as well as their sources in the method section of revised manuscript [lines 132–141].

"**Parasite and culture preparation**

Plasmodium falciparum 3D7 strain was obtained from Faculty of Pharmacy, Universitas Airlangga, Surabaya. The parasite was cultured in complete RPMI 1640 medium supplemented with 5.96 g HEPES, 0.05 g hypoxanthine, 2.1 g $NaHCO_3$, 50 µg/ml gentamycin and completed with 10% human O+ serum under anaerobe condition and incubated in a 37 ^oC incubator (18). Parasitemia was observed daily prior to antimalarial assay. *Plasmodium berghei* ANKA strain was originally obtained from Eijkman Institute for Molecular Biology, Jakarta, and maintained at Faculty of Pharmacy, Universitas Airlangga. The *P. berghei* ANKA was infected into male BALB/c mice and observed the parasitemia level."

5) Isolation, lines 117–128: A flowchart may be included in the manuscript to better illustrate the protocol used for preparation of the plant active fractions

ANSWER:

We have added the suggested content to the manuscript on the "Isolation of compound from *C. spectabilis* DC leaf" sub-section [lines 195–196].

"The procedures employed for the preparation of the plant active compounds are illustrated in Figure 1."

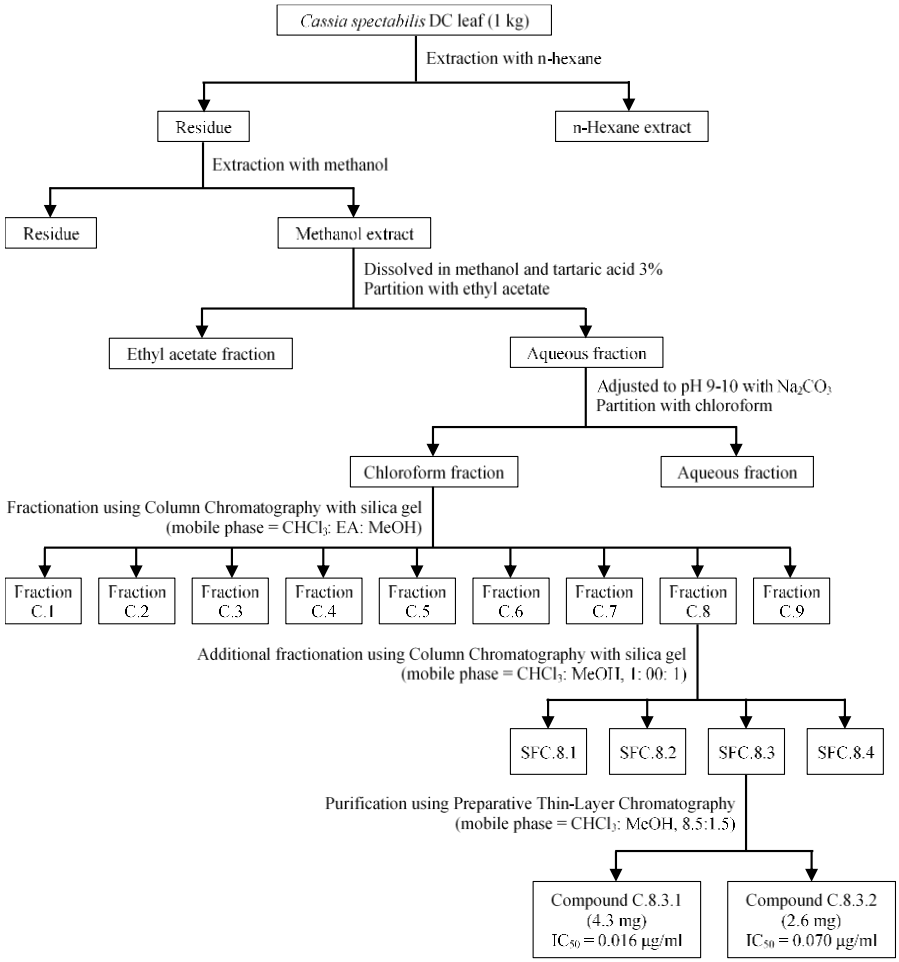

Figure 1. Flowchart of isolation steps of antiplasmodial alkaloid from *C. spectabilis* DC leaf

6) Lines 130–148: Authors may revise this section so as to show/indicate when the parasites were added into cultures. The estimated parasite density used (number of parasites per well or mL) and the final DMSO concentration in the cultures may also be provided.
It is not clear how many times the in vitro experiment was conducted, and this may be also indicated by the authors.

ANSWER:

The sentence has been revised [lines 201–209].

"The extract was dissolved in DMSO (the final DMSO concentration in a well culture plate not more than 0.5%) and diluted with complete RPMI medium containing RPMI 1640, 10% human plasma, 25 mM HEPES, and 25 mM $NaHCO_3$ to make the final concentrations of 10, 1, 0.1, 0.01, and 0.001 µg/ml. Stock of parasite cultures were further diluted with uninfected type O+ human erythrocytes and culture medium to make initial parasitemia of 1% and a hematocrit of 2%. This final parasite culture was immediately used for antiplasmodial assay. The test was carried out in duplicate."

7) Line 151: How was infection process carried out? Authors may bring more information on this, for better understanding of the protocol.

ANSWER:

We have explained in the method section the process of infection was done by intraperitoneal injection [lines 245–251].

8) Lines 154–199: What happened to the animals after completion of the suppressive effect of ethanolic extract of *C. spectabilis* DC leaf combined with artesunate. Were they euthanized?

ANSWER:

We have explained in the manuscript in the method section of experimental animal which mentioned that the end of the tested period [lines 152–156].

"At the end of the tests, all animals were followed the euthanasia procedure. The mice were sacrificed by cervical dislocation after anesthesia by intraperitoneal injection of 100 mg/kg bodyweight ketamine (19). The dead animals were then buried."

9) Lines 202–203: Authors wrote "…. classification according to Gessler et al., where extract with IC_{50} less than 10 µg/mL was considered very good…". In line with this, one may wonder why the Fractions C.5-C.8 and C.9 were not carried further in the fractionation process.

ANSWER:

The result was demonstrated that fraction C.5-C.8 possessed IC_{50} value less than 10 µg/ml which indicated a strong activity. This current study, fraction C.8 was chosen for further isolation due to the highest activity.

10) Lines 206–214: The IC_{50} values for the methanol and hexane extracts, fractions C.1, C.2 & C.5, as well as sub-fraction SFC.8.4 should be cross-checked.

ANSWER:

- Table 1: IC_{50} value of hexane extract was ND (not detected).
- Table 1: IC_{50} value of methanolic extract was 1.10 µg/ml.
- Table 2: IC_{50} value of C.1 fraction was >10 µg/ml.
- Table 2: IC_{50} value of C.2 fraction was ND (not detected).
- Table 2: IC_{50} value of C.5 fraction was 1-0.1 µg/ml.

11) Authors may explain why the effect of *C. spectabilis* on parasitic stage development, as well as subsequent experiments, were not carried out on the selected sub-fraction C.8.3 or isolate C8.3.2, that were relatively pure active fractions?

ANSWER:

Sub-fraction C.8.3 or compound C.8.3.2 from *C. spectabilis* were tested on tropozoites, mainly ring form. At each concentration of all isolates there was significant reduction in the number of parasitized cells. The measurement on this study was reduction in number of parasitized cell in the test cultures compared to control at 24-30 hours incubation. The result of inhibitory percentage from sub-fraction C.8.3 and compound C.8.3.1 showing highest than other sub-fraction and fraction. The percentage inhibitions are higher with increasing concentrations.

12) Lines 250–253: Footnotes explaining how % parasitemia, % growth and % inhibition were generated may be included.

ANSWER:

We have added in the revised manuscript the footnotes of table 5 which explained information of % parasitemia, % growth and % inhibition [lines 385–390].

"% parasitemia was obtained from total number of parasites divide to ring, trophozoite and schizont.
% growth was obtained from % parasitemia at incubation time minus % parasitemia at 0 hour.
% inhibition was calculated according to the following formula: % inhibition = ((parasitemia in negative group – parasitemia in treatment group) / parasitemia in negative control) x 100."

13) Lines 257–258: It is important to carry out statistical analyses of results and present significant differences within the manuscript. For example, the statement "After 24 hours, the incubation period of the parasite was inhibited 100% compared to the control (Fig. 2)", may be justified by indicating a P value.

ANSWER:

As suggested by the reviewer, we have changed this sentence in the manuscript [lines 398–402].

"At 12-24 hours of incubation period, parasite growth decreased but not significantly compared to negative control. Whereas at 48 hours of incubation, parasite growth decreased significantly ($p = 0.005$) compared to negative control, with an inhibition percentage of 100% (Figure 4)."

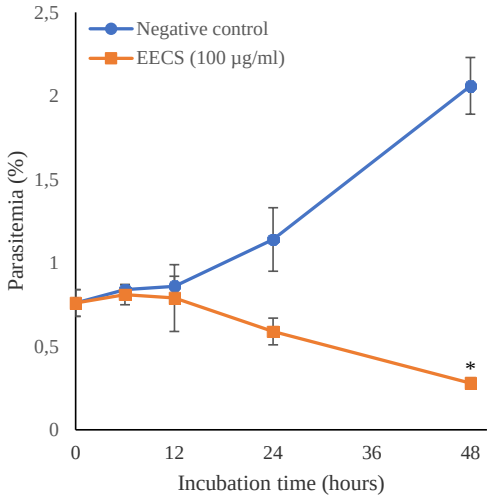

Figure 4. Percentage of parasitemia of 90% ethanolic extract *C. spectabilis* DC leaf and control at each incubation time against *P. falciparum* 3D7 *in vitro*. EECS = 90% ethanolic extract of *C. spectabilis* DC leaf. *$p < 0.05$.

14) Lines 301–307: This paragraph may be reformulated to ease understanding.

ANSWER:

Following your suggestion, we have reformulated the paragraph 1 in discussion section in the revised manuscript with red mark [lines 473–475].

"Anti-malarial activities of *C. spectabilis* DC leaf was conducted to extract, fraction and pure isolate. The active compounds were identified by TLC-densitometry, UV-Vis spectrophotometry, FTIR spectroscopy, and NMR."

Reviewer 2:

Antimalaria Activity of *Cassia spectabilis* DC Leaf and Its Inhibition Effect in Heme Detoxification

This manuscript is too full of words at the lack of precision expected of a scientific work.

1. Many statements are qualitative and do not give an idea of how good is good in "*Cassia spectabilis* DC leaf has shown a good antimalarial activity".

   ANSWER:

   The sentences have been revised [lines 24–27] and tried to explain how good the extract antiplasmodial phytomedicine with *in vitro* and *in vivo* tests and also the inhibition test against heme detoxification.

2. The construction of sentences is very poor. E.g. "*In vitro* antimalarial activity testing using *P. falciparum* which was done with bioassay guide isolation in order to obtain the active compound".

   ANSWER:

   The sentences have been reconstructed [lines 28–31].

"The extract was fractionated, sub-fractionated and isolated to obtain the purified compound. *In vitro* antiplasmodial activity test against *Plasmodium falciparum* to find out the active compound."

3. "*In vivo* testing towards infected *P. berghei* mice"– should be "*In vivo* testing using *P. berghei* infected mice".

   ANSWER:

   The sentence has been revised [lines 31–32].

   "*In vivo* test against *P. berghei* ANKA-infected mice…"

4. Binomial names of all organisms must be italicized: e.g. *P. berghei*, *C. spectabilis*. Likewise, *In vivo*, *In vitro* must be italicized.

   ANSWER:

   The Latin name such as *C. spectabilis*, *P. berghei*, *P. falciparum*, *in vivo* and *in vitro* have been italicized.

5. "The results showed that active antimalarial isolate obtained from *C. spectabilis* DC leaf had a structural pattern that was identical to (-)-7-hydroxyspectaline"– I believe that "isolate" could better be stated as "molecule" provided that the authors are sure of the purity of the molecule. There is need to present the spectra of standard (-)-7-hydroxyspectaline and the molecule which has been isolated by the authors. Unfortunately, there is not a single chromatogram in the manuscript that has the aim of extraction and isolation of metabolites.

   ANSWER:

   We have changed this sentence on the manuscript: "The results showed that active antimalarial compound isolated from *C. spectabilis* DC leaf had a structural pattern that was identical to (–)-7-hydroxycassine" [lines 37–39]. And we have added the suggested content to the manuscript on the "Results" section [lines 347–350].

   "Identification using TLC-densitometry showed that compound C.8.3.1 was in the range of λ 200-300 nm, with a value of R_F = 0.65. Identification using FTIR spectroscopy showed an absorption peak at 472.53 cm^{-1}; 657.68 cm^{-1}; 786.9 cm^{-1}; 864.05 cm^{-1}; 1101.28 cm^{-1}; 1382.87 cm^{-1} (Figure 3)."

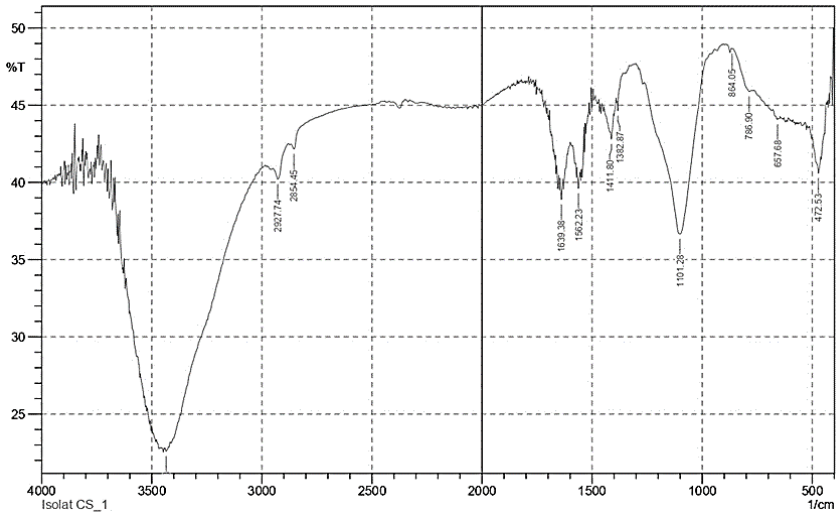

Figure 3. Fourier transform infra-red spectra of compound C.8.3.1 from *C. spectabilis* DC leaf

6. Sentences like "Prophylactic test on infected *P. berghei* mice obtained the highest dose of inhibition percentage of 90% ethanol extract of *C. spectabilis* DC leaf was 68.61% while positive (doxycycline) control at 100 mg kg^{-1} was 73.54%"– need to be simplified. "infected *P. berghei* mice" must be "*P. berghei* infected mice". "the highest dose of inhibition percentage" is meaningless.

ANSWER:

The sentence has been simplified as follows [lines 39–43]:

"Prophylactic test of 90% ethanolic extract of *C. spectabilis* DC leaf alone against *P. berghei* ANKA-*infected* mice obtained the highest percentage inhibition was 68.61%, while positive control (doxycycline 100 mg/kg) was 73.54%."

7. This is a bad sentence: "Previous study related to this plant with in vivo shows that this plant is quite potential to be continued (1)".

   ANSWER:

   This sentence has been revised [lines 60–62].

   "Previous study related to this plant using *in vivo* test showed that this plant was a potential antimalarial phytomedicine (1)."

8. "New antimalarial active compounds have also been obtained from plant in the same genus,namely Cassiarin A alkaloid compound from *C. siamea* plant (2,3)" is another bad sentence– it should be "another plant *C. siamea* from the same genus as *C. spectabilis*". Further it is not clear if both (-)-7-hydroxyspectaline and Cassiarin A are shared by both the plants.????

   ANSWER:

   The sentences have been revised [lines 62–68].

   "New antimalarial active compounds have also been obtained from different plant, *Cassia siamea* from the same genus of *C. spectabilis* that identified as Cassiarin A alkaloid compound (2, 3). Based on these results, an *in vitro* test on antiplasmodial activity to find out the active compound isolated from *C. spectabilis* DC has been conducted."

9. A common mistake throughout the manuscript is reflected by sentences like "For this reason, an *in vitro* research for antimalarial active compound from *C. spectabilis* DC plant with bioassay guide isolation is conducted". *In vitro* can never be antimalarial since malaria is the name of a disease seen in animals but can which cannot be mimicked *in vitro*. So, all *in vitro* studies must be called as "anti - plasmodial"

   ANSWER:

   All antimalarial term relates to the finding on this research has been changed to antiplasmodial.

10. "Furthermore, antimalarial drug development and discovery is expected to provide new drugs with potential and safe drug mechanisms for humans"– what is implied by "potential and safe drug mechanisms"?

    ANSWER:

    The sentence has been revised [lines 80–83].

    "Furthermore, antimalarial drug development and discovery is expected to provide new drugs which is not only have antiplasmodial activity *in vitro* and *in vivo*, but also has a safety mechanism to be applied to human."

11. "Research related to the biochemical process of malaria parasites plays an important role in the development of new antimalarial drugs"– "biochemical process of malaria parasites" must be "biochemical process unique to malaria parasites".

    ANSWER:

    The sentence has been revised [lines 83–84].

"Research related to the biochemical process that unique to malaria parasites plays an important role in the development of new antimalarial drugs."

12. "It will also test the effect of *C. spectabilis* DC leaf ethanol extract on biochemical activity in the malaria parasite food vacuole including determining the potential for extracts in the detoxification of malaria parasite heme and antimalarial activity of the parasite in each life cycle"– who is "It"? "on biochemical activity in the malaria parasite food vacuole" is very vague. All that the authors have done is to study heme detoxification process. "Each life cycle" is meaningless.

    ANSWER:

    The sentence has been revised [lines 98–101].

    "Currently, the effect of ethanol extract of *C. spectabilis* DC leaf on biochemical activity such as potential inhibition of heme detoxification in the food vacuole of malaria parasite and stage-specific activity against asexual stage of parasite has been tested."

13. "is amounting to 150 mg kg^{-1} by giving three times a day orally (1)"– is it 150 mg kg^{-1} each time amounting to 450 mg/day?

    ANSWER:

    Yes, the amount of extract that given at a dose of 150 mg/kg three times a day means that 450 mg/day in total.

14. "Based on the foregoing, a combination of ethanol extract of *C. spectabilis* DC leaf extract will also be tested with artesunate which is one of the artemisinin derivatives to determine the inhibition of growth *in P. berghei* mice with in vivo"– "will also be tested" must be "has been tested". It is not clear why leaf extract has been tested only in combination with artesunate but not alone in mouse model of malaria. "which is one of the artemisinin derivatives" must be removed since it is known to all that it is a derivative.

    ANSWER:

    The sentence has been revised [lines 110–115].

    "Based on this result, both ethanolic extract of *C. spectabilis* DC leaf alone and in combination with artesunate has been tested to determine the inhibition of growth of parasites in *P. berghei* ANKA-infected mice *in vivo*, since the ACT is more effective in reducing parasitemia (17)."

15. "It is hoped that after this study, an appropriate combination model between artesunate and 90% leaf ethanol extract will obtain *C. spectabilis* DC that produces the greatest therapeutic effect"– is a poorly constructed sentence. "combination model" must be replaced with "combination", "between" should be "of", "will obtain" must be "will be obtained".

    ANSWER:

    The sentence has been revised [lines 117–119].

    "A therapeutic effect of an appropriate combination of artesunate and 90% ethanolic extract of *C. spectabilis* DC leaf is reported herein."

16. "The mice were sacrificed by cervical dislocation after anesthetized by intraperitoneal injection of 100mg/kg BB ketamine (9). The death animals were buried"– are bad sentences. "anesthetized" must be "anesthesia", "100mg" must be "100 mg", "death" must be "dead".

    ANSWER:

The sentence has been revised [152–156].
"At the end of the tests, all animals were followed the euthanasia procedure. The mice were sacrificed by cervical dislocation after anesthesia by intraperitoneal injection of 100 mg/kg bodyweight ketamine (19). The dead animals were then buried."

17. "The extract was made by macerating dried *C. spectabilis* DC leaf powder using 90% ethanol as many as three times"– there is no use of saying "as many as", it must be told how many grams of leaf powder was extracted with how much volume of solvent each time.
ANSWER:
The sentence has been revised [lines 159–161].
"The extract was made by three times macerating dried *C. spectabilis* DC leaf powder using 90% ethanol. The macerated extract was then evaporated using a rotavapor."

18. "The extract was practiced in liquid-liquid with ethyl acetate and 3% tartaric acid"– is a wrong sentence and raises many questions. "practiced" is meaningless; it ought to be "the extract was subjected to liquid-liquid partition using ethyl acetate and 3% tartaric acid".
It may be better to state procedure exactly as practiced. Was the dried extract first dissolved in 3% Tartaric acid? What was the reason for use of Tartaric acid must be stated?
ANSWER:
The sentence has been revised [lines 164–170].
"A thousand grams of dried powder of *C. spectabilis* DC leaf was macerated with n-hexane, then the pulp powder was extracted again with methanol. The extract was subjected to liquid-liquid partition using ethyl acetate and 3% tartaric acid. The isolation proceess was done by adding 3% tartaric acid until the atmosphere becomes acidic to turn the alkaloids in alkaline form into alkaloids salts. This alkaloid salt was partitioned using ethyl acetate, and the alkaloids were present in the aqueous acidic layer at the bottom."

19. "The aqueous layer was adjusted at pH 9 with saturated $NaHCO_3$ and extracted with chloroform."– State what was done to the organic layer. "adjusted at pH 9" must be "adjusted to pH 9".
ANSWER:
The sentence has been revised [lines 171–174].
"The alkaloid was the isolated from their salt form in aqueous layer, by adding $NaCO_3$ to increase the pH to 9-10, and the alkaloids returned to alkaline form. Furthermore, the aqueous layer with pH 9-10 was then extracted liquid-liquid using chloroform. The fractions so called chloroform fraction."

20. "The chloroform fraction was then separated using column chromatography (chloroform-ethyl acetate-methanol) produced nine fractions"– is a very poor description of the method. Chloroform fraction (weight??) which column was used, what was the resin?? "produced nine fractions" must be "to obtain nine fractions". Give exact description of chloroform-ethyl acetate-methanol, steps, ratios, size of column, volume per fraction etc.
ANSWER:
The sentence has been revised [lines 176–184].
"The isolate pure alkaloid compound from other compounds, the chloroform fraction, was further fractionationed by column chromatography using stationary phase of silica gel 60 with a series of gradient mobile phases was started using 100% chlorofom, chloroform:ethyl acetate ($CHCl_3$: EtOAc;

2:1), chloroform:ethyl acetate:methanol ($CHCl_3$: EtOAc: MeOH; 2:1:2), and finally 100% methanol. The selection of the mobile phase was based on the results of the orientation by TLC, which gave good separation results. The solvent used for each gradient was 200 ml and the collected fractions were combined based on similarity of the TLC profile. Nine fractions (C.1–C.9) were obtained."

21. "*In vitro* antimalarial activity test: Stock sample solutions were prepared in DMSO and diluted to the required concentration with complete media (RPMI 1640 plus 10% human plasma, 25 mM of HEPES, and 25 mM of $NaHCO_3$) until the final concentrations of the sample on the well culture plate were 10, 1, 0.1, 0.01, and 0.001 µg mL-1. The test was carried out in duplicate. The plates were incubated in CO_2 condition at 37ºC in a wax tube."

    ANSWER:

    The sentences have been revised [lines 201–221].

    "The extract was dissolved in DMSO (the final DMSO concentration in a well culture plate not more than 0.5%) and diluted with complete RPMI medium containing RPMI 1640, 10% human plasma, 25 mM HEPES, and 25 mM $NaHCO_3$ to make the final concentrations of 10, 1, 0.1, 0.01, and 0.001 µg/ml. Stock of parasite cultures were further diluted with uninfected type O+ human erythrocytes and culture medium to make initial parasitemia of 1% and a hematocrit of 2%. This final parasite culture was immediately used for antiplasmodial assay. The test was carried out in duplicate. The plates containing parasite cultures and extracts were then incubated in a 37 ºC incubator in a candle jar for 48 hours. Observation of stage-specific antiplasmodial activity *in vitro* test was performed by sampling the blood films from each well at 6, 12, 24, and 48 hours. At the end of test thin films were prepared from each well and stained with 10% Giemsa solution prior to counting parasitemia (20). The 50% inhibitory concentration (IC_{50}) value was determined using probit analysis based on the relation of log concentration of test compound and % inhibition of parasites growth."

    (a) This is not antimalaria test but a test for antiplasmodial activity.

    ANSWER:

    The term of antimalarial in this study has been changed to antiplasmodial.

    (b) Since dilutions have been made on stocks in DMSO, it is important to mention what the concentration of sample was in DMSO and what was the method by which 10, 1, 0.1, 0.01, and 0.001 µg mL^{-1} concentrations were obtained in the wells. What was the concentration of DMSO in each well must also be stated?

    ANSWER:

    Yes, the concentration of DMSO in each well has been stated to "not more than 0.5%" [lines 201–202].

    (c) "CO_2 condition in a wax tube"– these are vague and unclear.

    ANSWER:

    The sentence has been revised because there was a mistyped. Actually, the test was not performed in a CO_2 incubator, not in a wax tube but in a candle jar [lines 209–211].

22. "For test stage-specific antimalarial activity in vitro, incubation is performed at 6, 12, 24, and 48 hours"– antimalarial is wrong again, the incubation details are inadequate to the extent that what is incubated is also not clear.

    ANSWER:

    The sentences have been revised [lines 211-213].

"Observation of stage-specific antiplasmodial activity in this *in vitro* test was performed by sampling the blood films from each well at 6, 12, 24, and 48 hours."

23. "After the incubation, the contents of the well were harvested and the red cells were transferred to clean microscopic slides to form a series of thick films. The film was stained for 10 minutes in a 10% Giemsa solution (pH 7.3). Each 50% of inhibitory concentration (IC_{50}) was calculated based on the inhibition percentage towards *P. falciparum* using probit analysis."
    (a) Since smears made were thick, what were the number of cells per field?

    ANSWER:

    There was a mistyped on this sentence. It is thin films not thick smears. The sentence has been revised as follows [lines 216–217]:

    "At the end of test thin films were prepared from each well and stained with 10% Giemsa solution prior to counting parasitemia (20)."

    (b) Counting 1000 cells is not enough to make a good judgment of % parasitemia. At least 3000 cells must be counted. How IC_{50} was determined must be described.

    ANSWER:

    The method to determine the parasitemia by counting the infected erythrocytes within 1,000 erythrocytes are the routine activity in our lab to justify the parasitemia post *in vitro* or *in vivo* tests, and the results so far have represented the inhibition of the extract against the parasites' growth (20). "The 50% inhibitory concentration (IC_{50}) value was determined using probit analysis based on the relation of log concentration of test compound and % inhibition of parasites growth." [lines 219–221]

24. "A, B, C, D, E, and F" should be "A-F".

    ANSWER:

    The sentence has been revised to A-F [lines 251–252].

    "The infected animals were randomly divided into six groups those were Group A-F."

25. "Testing of inhibition of heme polymerization using the Basilico method (13) has been modified"– Essential elements of Basilico method must be stated in brief and the modifications made must be mentioned in detail. (lines 182-183)

    ANSWER:

    The Basilico method has been explain briefly [lines 281–294].

    "A 100 µl of 1 mM hematin solution was mixed with 0.2 M NaOH and 50 µl of the test extract. A 50 µl of glacial acetic acid solution (pH 2.6) was then added to this mixture. This test was carried out at 37 ^{o}C for 24 hours. The microtube was then centrifuged at 8000 rpm for 10 minutes, the sediment was then washed with 200 µl of DMSO three times at 8000 rpm for 10 minutes. The β-hematin crystalline precipitated was dissolved in 200 µl of NaOH 0.1 M to form alkaline hematin. A 100 µl of the alkaline hematin solution was transferred to 96-well microplates and the absorbance was read by ELISA reader at a wavelength of 405 nm. The effects of each test substance on β-hematin production were calculated and compared with negative controls."

26. "Making a standard hematin curve started from making a 1 mM hematin solution in 0.2 M NaOH."– is a poorly constructed sentence. What is meant by hematin curve? What is the difference between hematin and beta hematin?

ANSWER:

We have revised the sentence in in the method section of Heme polymerization inhibition test in the revised manuscript [lines 273–279].

In this assay we performed a standard curve of hematin by preparing a dilution concentration of hematin solution. Standard curve of hematin was used to calculate the amount porphyrin which equivalent to the test activity of compound in inhibiting the heme polymerization by 50% (IC_{50}).

The difference of hematin and β-hematin: Heme is toxic byproduct during hemoglobin degradation by malaria parasites. The explanation is written below.

"Malaria parasites consume hemoglobin from erythrocytes during their life cycle, however, parasites are unable to digest iron-containing heme molecule. Heme is toxic due to the reactivity of iron. Therefore, parasite has developed the mechanism to detoxify it by polymerization of heme to form hemozoin or malaria pigmen (6, 7). The structure of hemozoin through X-ray diffraction and IR spectroscopy has been found to be similar to β-hematin (8) β-hematin is synthetic hemozoin which chemically (8), spectroscopically (9) and crystalographically (10) similar to hemozoin which consists of Ferriprotoporphyrin units linked into a polymer by propionate oxygen-iron bonds (8, 11)." [lines 84–93]

27. Table 2. The percentage inhibition of chloroform fractions of *C. spectabillis* DC leaf against *P. falciparum* 3D7 strain: there is no meaning of percentage inhibition of chloroform fractions. Are you inhibiting the fractions???

ANSWER:

The structure of sentence was wrong. The sentence has been revised [lines 317–319].

"Table 2. The percentage growth inhibition of *P. falciparum* 3D7 by chloroform fractions of *C. spectabillis* DC leaf"

28. All tables showing % parasitemia must be replaced with graphs showing the same data.

ANSWER:

We have added the suggested content to the manuscript [lines 339–341].

"The purification of sub-fractions SFC.8.3 resulted in two compounds called compound C.8.3.1 and C.8.3.2 and their antiplasmodial activity is shown in Table 4 and Figure 2."

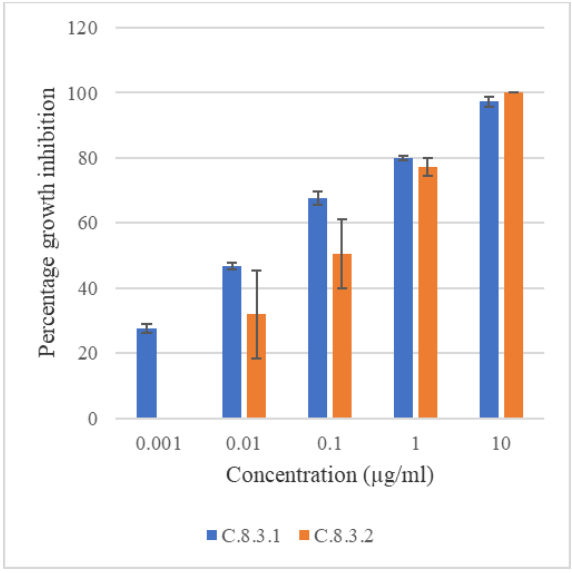

Figure 2. Percentage growth inhibition of *P. falciparum* 3D7 strain by compounds C.8.3.1 and C.8.3.2 of *C. spectabilis* DC leaf

29. Table 2: has 12.44 ± 17.59. What does it mean? Was standard deviation more than the mean? What is the reliability of data that has standard deviation greater than the mean?

ANSWER:

We are sorry, that was wrong, the correct data is 24.03 ± 1.19.

30. "Isolation from chloroform extract obtained nine fractions" – is a poorly constructed sentence. Give details of what exactly was done.

ANSWER:

As suggested by the reviewer, we have changed this sentence in the manuscript [lines 330–332].

"During isolation of compound, chloroform was used to fractionate the extract. Chloroform fractionation resulted in nine fractions called C.1-C.9."

31. The spectral characteristics given must be replaced with the NMR spectra obtained and commented upon.

ANSWER:

We have added the suggested content to the manuscript [lines 353–369].

"Identification using ^{1}H-NMR spectroscopy showed a characteristic signal of two hydroxyl protons at δ 3.60 ppm (1H, s); and δ 3.69 ppm (1H, s), two protons from the CH_2 group of benzene at δ 1.91 ppm (2H, s, H-4) and δ 1.68 ppm (2H, s, H-5), one methyl group at δ 2.13 ppm (3H, s, H-12′), and some cassettes of the CH_2 groups of the aliphatic chain at δ 1.38 ppm (2H, s, H-1′); at δ 1.22 ppm (2H, s, H-2′- H-8′); at δ 1.51 ppm (2H, s, H-9′), and at δ 2.35 ppm (2H, t, H-10′). Identification using ^{13}C-NMR spectroscopy showed the presence of one carbon with a ketone group at δ 179.0 ppm, carbon in the benzene group at δ 56.96 ppm; δ 67.13 ppm; δ 29.23 ppm; δ 25.77 ppm; and δ 48.29 ppm, carbon in the aliphatic chain at δ 34.32 ppm; δ 25.87 ppm; δ 29.23 ppm; δ 29.33 ppm; δ 22.89 ppm; and δ 38.87 ppm, one carbon in the methyl group at δ 30.23 ppm, and one carbon in the hydroxyl group at δ 65.27 ppm."

32. Table 5 has Ring, Trophozoite and Sporozoite. This is quite strange because it is not clear from where did the authors get the Sporozoites. The table mentions DMSO. Does it mean that authors have tested DMSO against the parasite?

ANSWER:

This is a mistyped. "Sporozoite" has been changed to "Schizont".

DMSO was used to dissolve the extract, therefore, DMSO was added to the cultures as negative control groups. Now, the DMSO has been changed to 'negative control'.

33. "leaf was shown in Table 6" must be "is shown in table 6".

ANSWER:

The sentence has been revised as advised [line 432].

34. Table 6: 100 mg adult human dose: why was human dose given to a mouse?

ANSWER:

This is a mistyped. The human dose has been erased. The dose of doxycycline used in the test was 13 mg/kg based on the human dose which has been converted to mouse dose.

35. Table 8 has "level of hematin (mm)" – what is mm?

ANSWER:

There was a typo by the author. "mm" must be "mM" mean "millimolar".

36. 36. There is need to have structure for 7-hydroxycassine.

ANSWER:

We have added the suggested content to the manuscript [lines 475–477].

"In the ^{1}H-NMR spectra, compound C.8.3.1 showed similarities to the compound (-)-7-hydroxycassine (Figure 6) in the presence of several similar chemical shifts (26)."

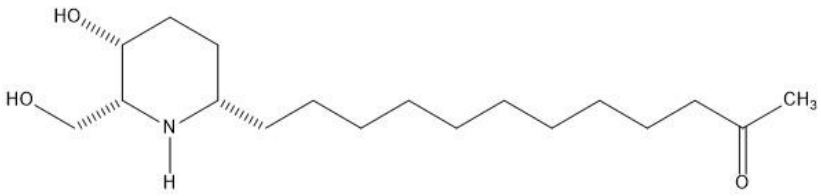

Figure 6. Molecular structure of (-)-7-hydroxycassine.

37. Discussion needs significant qualitative improvement with decrease in number of words used. The data used to suggest that combination of Artesunate with leaf extract will reduce requirement for Artesunate is not strong enough. In fact, there is enough evidence to suggest that the use of whole leaf of A annua is more potent and promising than the same amount of Artemisinin coming as pure Artemisinin. (Dried whole-plant Artemisia annua slows evolution of malaria drug resistance and overcomes resistance to artemisinin. Mostafa A. Elfawala, Melissa J. Towlerb, Nicholas G. Reichc, Pamela J. Weathersb, and Stephen M. Richa, PNAS 2014). So instead of combining C. spectabillis with artesunate/artemisinin why can't people chew the leaves of A annua itself?

ANSWER:

We have modified the sentences in the discussion section [lines 531–587].

In the study we evaluated the combination of *C. spectabilis* DC and artesunate with the aimed to determine the suppression of percentage of parasitemia of extract in combination with standard drug (artesunate) compare to single treatment of standard drug only. This data provided an importance information for developing C. *spectabilis* as anti-malarial drug.

However, we could not suggest people to consume by crewing the *A. annua* due to the unclear dose and unstandardized of bioactive compounds which may give the difference effects.

38. List of abbreviations has ELISA and HRFABMS: but there seems to be neither data nor mention of these in the text.

ANSWER:

We have removed these abbreviations in the revised manuscript.

Your submission to BMC Complementary Medicine and Therapies - BCAM-D-20-00299R3 - [EMID:7d949d56275ec4e2]

1 messages

BMC Complementary & Alternative Medicine - Editorial Office <em@editorialmanager.com>
Mon, Jan 4, 2021 at 6:56 PM

Reply-To: BMC Complementary & Alternative Medicine - Editorial Office <eloisa.hadenolasco@springernature.com>
To: Wiwied - Ekasari <wiwied-e@ff.unair.ac.id>

BCAM-D-20-00299R3
Antiplasmodial Activity of Ethanolic Extract of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification
Wiwied - Ekasari, Ph.D; Dewi Resty Basuki, Master Degree; Heny - Arwati, Doctor Degree; Tutik Sri Wahyuni, Doctor Degree
BMC Complementary Medicine and Therapies

Dear Dr Ekasari,

Your manuscript "Antiplasmodial Activity of Ethanolic Extract of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification" (BCAM-D-20-00299R3) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in BMC Complementary Medicine and Therapies, once you have carried out some essential revisions suggested by our reviewers.

Their reports, together with any other comments, are below. Please also take a moment to check our website at https://www.editorialmanager.com/bcam/ for any additional comments that were saved as attachments. Once you have made the necessary corrections, please submit a revised manuscript online at:

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A decision will be made once we have received your revised manuscript, which we expect by 18 Jan 2021.

We look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any

questions.

Best wishes,

Anne Menard
BMC Complementary Medicine and Therapies
https://bmccomplementalternmed.biomedcentral.com/

Editor Comments:
We apologise for the delays you have faced, neither of the original reviewers were able to re-review, and so we had to seek an independent reviewer, who was informed that this was a revision, and asked to assess the manuscript as such.

Their comments can be found below.

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Reviewer 3: "PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses one or several testable research questions? (Brief or other article types: is there a clear objective?)
Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
Yes - the approach is appropriate

EXECUTION - Are the experiments and analyses performed with sufficient technical rigor to allow confidence in the results?
Yes - experiments and analyses were performed appropriately

STATISTICS - Is the use of statistics in the manuscript appropriate?
Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
Yes - the author's interpretation is reasonable

OVERALL MANUSCRIPT POTENTIAL - Has the author addressed your concerns sufficiently for you to now recommend the work as a technically sound contribution? If not, can further revisions be made to make the work technically sound?
Yes - current version is technically sound

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The revised MS has been improved considerably as compared to the initial version, whereby the first reviewer has provided an extensive evaluation. Authors have tried best to answer queries and concerns raised from previous reviewer. I have checked all comments and found the rebuttals and corrections to my satisfaction. The quest for new antimalarial is always a hot topic and it is anticipated this study will open new avenues for drug development. The research background is satisfactory where authors have identified the research gap. Aims are well defined. Methods are well described and supported with appropriate references to replicate experiments. Results section is good with a mixture of tables and figures. The discussion is well balanced and conclusion supported by the data amassed.
ADDITIONAL REQUESTS/SUGGESTIONS:
I have checked the whole MS and revision undertaken. The revised version meet the threshold for publication in this journal. One minor non mandatory revision is the conclusion. Currently, it is only two lines. Authors can consider elaborating more, e.g. elaborating on the possible compounds that might be responsible for the observed biological activity as elaborated in the discussion section."

****

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Declarations
- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
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- Funding
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Your submission to BMC Complementary Medicine and Therapies - BCAM-D-20-00299R4 - [EMID:abb0de84ecd7c490]

1 messages

BMC Complementary & Alternative Medicine - Editorial Office Thu, Jan 28, 2021 at 11:00 PM
<em@editorialmanager.com>
Reply-To: BMC Complementary & Alternative Medicine - Editorial Office <eloisa.hadenolasco@springernature.com>
To: Wiwied - Ekasari <wiwied-e@ff.unair.ac.id>

BCAM-D-20-00299R4
Antiplasmodial Activity of Ethanolic Extract of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification
Wiwied - Ekasari, Ph.D; Dewi Resty Basuki, Master Degree; Heny - Arwati, Doctor Degree; Tutik Sri Wahyuni, Doctor Degree
BMC Complementary Medicine and Therapies

Dear Dr Ekasari,

Your manuscript "Antiplasmodial Activity of Ethanolic Extract of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification" (BCAM-D-20-00299R4) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in BMC Complementary Medicine and Therapies, once you have carried out some essential revisions.

Their reports, together with any other comments, are below. Please also take a moment to check our website at https://www.editorialmanager.com/bcam/ for any additional comments that were saved as attachments. Once you have made the necessary corrections, please submit a revised manuscript online at:

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We look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,
Kate Gaines
On behalf of,
Esther Fagelson
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Editor Comments:

1. Thank you for your Availability of Data and Materials statement. However, we note you have not included your raw data.

We strongly encourage all authors to share their raw data, either by providing it in a supplementary file or depositing it in a public repository and providing the details on how to access it in this section. If you do not wish to share your data, please clearly state this in this section along with a justification. Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

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Where a mandatory section is not relevant to your study design or article type, for example, if your manuscript does not contain any individual persons data, please write "Not applicable" in these sections.

For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must state that data will not be shared, and provide reasons for this in the manuscript text. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page - http://www.biomedcentral.com/ submissions/editorial-policies#availability+of+data+and+materials.

Declarations
- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements
- Authors' Information

Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

This letter contains confidential information, is for your own use, and should not be forwarded to third parties.

3. ARTIKEL DITERIMA UNTUK PUBLIKASI

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

Decision on your Submission to BMC Complementary Medicine and Therapies - BCAM-D-20-00299R5 - [EMID:ada1f4496c948b7f]

2 messages

BMC Complementary & Alternative Medicine - Editorial Office Tue, Feb 2, 2021 at 6:22 PM
<em@editorialmanager.com>
Reply-To: BMC Complementary & Alternative Medicine - Editorial Office <eloisa.hadenolasco@springernature.com>
To: Wiwied - Ekasari <wiwied-e@ff.unair.ac.id>

BCAM-D-20-00299R5
Antiplasmodial Activity of Ethanolic Extract of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification
Wiwied - Ekasari, Ph.D; Dewi Resty Basuki, Master Degree; Heny - Arwati, Doctor Degree; Tutik Sri Wahyuni, Doctor Degree
BMC Complementary Medicine and Therapies

Dear Dr Ekasari,

I am pleased to inform you that your manuscript "Antiplasmodial Activity of Ethanolic Extract of Cassia spectabilis DC Leaf and Its Inhibition Effect in Heme Detoxification" (BCAM-D-20-00299R5) has been accepted for publication in BMC Complementary Medicine and Therapies.

If any final comments have been submitted from our reviewers or editors, these can be found at the foot of this email for your consideration.

Before publication, our production team will also check the format of your manuscript to ensure that it conforms to the standards of the journal. They will be in touch shortly to request any necessary changes, or to confirm that none are needed.

Articles in this journal may be held for a short period of time prior to publication.
If you have any concerns please contact the journal.

Please do not hesitate to contact us if you have any questions regarding your manuscript and I hope that you will consider BMC Complementary Medicine and Therapies again in the future.

If you wish to co-submit a data note to be published in BMC Research Notes (https://bmcresnotes.biomedcentral.com/about/introducing-data-notes) you can do so by visiting our submission portal http://www.editorialmanager.com/resn/. Data notes support open data (https://www.springernature.com/gp/open-research/open-data) and help authors to comply with funder policies on data sharing. Please note that this additional service is entirely optional.

Best wishes,

Esther Fagelson
BMC Complementary Medicine and Therapies
https://bmccomplementalternmed.biomedcentral.com/

Comments:

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Please also take a moment to check our website at field https://bmccomplementalternmed.biomedcentral.com/ .

We operate a transparent peer review process for this journal where reviewer reports are published with the article but the reviewers are not named (unless they opt in to include their name). ---

Our flexible approach during the COVID-19 pandemic

If you need more time at any stage of the peer-review process, please do let us know. While our systems will continue to remind you of the original timelines, we aim to be as flexible as possible during the current pandemic.

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wiwied ekasari <wiwied-e@ff.unair.ac.id> **Wed,** Feb 3, 2021 at 10:28 AM To: BMC Complementary & Alternative Medicine - Editorial Office <eloisa.hadenolasco@springernature.com>

Dear Mrs. Esther Fagelson
BMC Complementary Medicine and Therapies.

Thank you very much for your email.
I am very happy to hear from you about my manuscript which is finally accepted for publication in this journal.

Best regards.
Dr. Wiwied Ekasari, MSi
[Quoted text hidden]

Proof approval - BMC Complementary Medicine and Therapies : BCAM-D-20-00299R5 / 10.1186/s12906-021-03239-9

3 messages

Lovelia Deciar <lovelia.deciar@springernature.com> **Tue,** Feb 16, 2021 at 1:41 AM To: "wiwied-e@ff.unair.ac.id" <wiwied-e@ff.unair.ac.id>, "wiwiedeka@hotmail.com" <wiwiedeka@hotmail.com>

Title : Antiplasmodial activity of Ethanolic extract of *Cassia spectabilis* DC leaf and its inhibition effect in Heme detoxification

MS ID: BCAM-D-20-00299R5

Dear Dr. Wiwied Ekasari,

We are reaching out to you with reference to your article, which will soon be published in *BMC Complementary Medicine and Therapies*.

In connection to Query 3, missing citation of Figure 5, figures are renumbered accordingly in order to comply journal standard that figures should be cited in ascending numerical order in the main body text.

We are attaching the revised proof for your final checking and approval. Please carefully check if the latest changes have been implemented correctly within the revised proof. If there are any changes you wish to make, kindly indicate/annotate them directly in the attached proof.

You can help us facilitate rapid publication by returning the response to the revised proof within 48 hours.

Please feel free to reach out to us if you have any additional questions.

With kind regards,

(Ms) Lovelia E. Deciar

Production Editor

BMC

lovelia.deciar@springernature.com

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wiwied ekasari <wiwied-e@ff.unair.ac.id> Wed, Feb 17, 2021 at 2:12 PM
To: Lovelia Deciar <lovelia.deciar@springernature.com>

Dear (Ms) Lovelia E. Deciar,
Production Editor

Thank you for your email.

Here I send you the revision of the final proofs of my article.

Best regards,

Dr. Wiwied Ekasari., MSi., Apt

[Quoted text hidden]

12906_2021_3239_OnlinePDF_rev.pdf
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Lovelia Deciar <lovelia.deciar@springernature.com> Wed, Feb 17, 2021 at 8:01 PM
To: wiwied ekasari <wiwied-e@ff.unair.ac.id>

Dr. Wiwied Ekasari,

Thank you for your email.

This is to acknowledge receipt of the attached corrected proof. We shall proceed this accordingly.

With kind regards,

(Ms) Lovelia E. Deciar

Production Editor

BMC

lovelia.deciar@springernature.com

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From: wiwied ekasari <wiwied-e@ff.unair.ac.id>
Sent: Wednesday, 17 February 2021 3:13 pm
To: Lovelia Deciar <lovelia.deciar@springernature.com>
Subject: Re: Proof approval - BMC Complementary Medicine and Therapies : BCAM-D-20-00299R5 / 10.1186/s12906-021-03239-9

[External - Use Caution]

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4. ARTIKEL DITERBITKAN

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

Your article published in BMC Complementary Medicine and Therapies is nowonline

5 messages

Springer <SpringerAlerts@springeronline.com> Mon, Feb 22, 2021 at 6:32 AM
Reply-To: springeralerts@springeronline.com
To: wiwied-e@ff.unair.ac.id

Publication of your article 2021-02-22

Dear Author,

We are pleased to inform you that your open access article has now been published:

BMC Complementary Medicine and Therapies

Antiplasmodial activity of Ethanolic extract of Cassia spectabilis DC leaf and its inhibition effect in Heme detoxification

Wiwied Ekasari, Dewi Resty Basuki, Heny Arwati, Tutik Sri Wahyuni

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Thank you for publishing with BMC. We look forward to your future contributions!

Best regards,
Rachel Burley
Publishing Director, BMC

For further information or enquiries please use our contact page details.
Contact page

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wiwied ekasari <wiwied-e@ff.unair.ac.id> Mon, Feb 22, 2021 at 8:25 AM
To: springeralerts@springeronline.com

Dear Mr. Rachel Burley
Publishing Director, BMC

Thank you very much for your information.
Yes , I hope we can contribution in next publication

Best regards
Dr. Wiwied Ekasari., MSi
[Quoted text hidden]
