

### **Bukti Korespondensi**

**Judul Artikel: Screening Carica Papaya Compounds as an Antimalarial Agent: In Silico Study**

<b>No</b>	<b>Proses</b>	<b>Tanggal</b>
1	Artikel di ajukan ke jurnal <i>Tropical Journal of Natural Product Research</i>	9-3-2023
2	Revisi pertama: <i>accepted with moderate corrections</i>	18-3-2023
3	Editor mengirim hasil review artikel • Review form	8-5-2023
4	Author mengirimkan hasil revisi artikel • Response to reviewer • Plagiarism check • Revised article	9-5-2023
5	Manajer editor mengirimkan <i>galley proof</i>	13-5-2023
6	Author mengirimkan kembali kepada manajer editor hasil revisi <i>galley proof</i>	13-5-2023
7	Artikel dipublikasi pada <i>Tropical Journal of Natural Product Research</i> . Vol. 7, Issue 5, Juni 2023. Hal: 2895-2903	2-6-2023

**Dr. apt. Rollando, S.Farm., M.Sc.**  
Pengajuan ke Lektor Kepala

- 1. Artikel di ajukan ke jurnal Tropical Journal of Natural Product  
Research  
(9-3-2023)**

**Dr. apt. Rollando, S.Farm., M.Sc.**  
Pengajuan ke Lektor Kepala

Submitted Article\_Rollando

Dr. apt. Rollando , S.Farm, M.Sc. <ro.lando@machung.ac.id>

Thu 3/9/2023 8:51 AM

To:Editor-in-Chief Tjnpr <editor.tjnpr@gmail.com>;Managing Editor TJNPR <p.editor.tjnpr@gmail.com>

📎 5 attachments (1 MB)

Abstract.docx; Authors Contributor.docx; Cover latter.doc; Potential Reviewer.docx; Rollando\_Submitted.docx;

Dear Prof. Abiodun Falodun, PhD

I am herewith submitting the manuscript entitled "Screening Carica Papaya Compounds as an Antimalarial Agent: In Silico Study" for publication in Tropical Journal of Natural Product Research.

The manuscript has not been currently submitted for review to any other journal and will not be submitted elsewhere before a decision is made by this journal. We look forward for your positive response.

Kind regards

Dr. Rollando, M.Sc.  
Program of Pharmacy  
Ma Chung University  
65151 Malang  
Indonesia

**Dr. apt. Rollando, S.Farm., M.Sc.**  
Pengajuan ke Lektor Kepala

Re: Submitted Article\_Rollando

Editor-in-Chief Tjnpr <editor.tjnpr@gmail.com>

Thu 3/9/2023 1:21 PM

To: Dr. apt. Rollando, S.Farm, M.Sc. <ro.lando@machung.ac.id>

Dear Dr Rollando,

Thank you for submitting your original manuscript to the Tropical Journal of Natural Product Research ([www.tjnpr.org](http://www.tjnpr.org)) <https://www.scopus.com/sourceid/21100933230> SCOPUS **Q4**, published by the University of Benin and Natural Product Research Group.

The peer-review process will commence immediately, as the manuscript will be passed to an editor for initial assessment as soon as possible. If there are any problems with your submission, we will contact you. Also, note that manuscripts submitted and undergoing peer review will not be accepted for withdrawal or retraction.

Title: **Screening *Carica Papaya* Compounds as an Antimalarial Agent: In Silico Study**

Best regards

Abiodun

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Professor Abiodun Falodun, PhD

Editor-in-Chief:

Tropical Journal of Natural Product Research (TJNPR)  
Head, Natural Product Research Group, University of Benin  
Email: [editor.tjnpr@uniben.edu](mailto:editor.tjnpr@uniben.edu); [editor.tjnpr@gmail.com](mailto:editor.tjnpr@gmail.com)  
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Professor of Pharmaceutical Chemistry  
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Deputy Vice-Chancellor (Academic) 2014-2016  
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TROPICAL JOURNAL of  
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**Dr. apt. Rollando, S.Farm., M.Sc.**  
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(TJNPR) Manuscript Undergoing Peer-Review Process

Editor-in-Chief Tjnpr <editor.tjnpr@gmail.com>

Thu 3/9/2023 1:25 PM

To: Dr. apt. Rollando, S.Farm, M.Sc. <ro.lando@machung.ac.id>

Cc: Fatimah Maulada <611810015@student.machung.ac.id>; apt. Muhammad Hilmi Afthoni, S.Farm., M.Farm. <muhammad.hilmi@machung.ac.id>; Dr. Yuyun Yuniati, ST, MT <yuyun.yuniati@machung.ac.id>

The manuscript submitted to the Tropical Journal of Natural Product Research <https://www.scopus.com/sourceid/21100933230> SCOPUS by the corresponding author is undergoing the peer-review process.

Title: *Screening Carica Papaya Compounds as an Antimalarial Agent: In Silico Study*

Journal: Tropical Journal of Natural Product Research [www.tjnpr.org](http://www.tjnpr.org)

Corresponding Author: Rollando Rollando

Co-authors: Fatimah Maulada, Muhammad Hilmi Afthoni, Yuyun Yuniati

Manuscript No: TJNPR FEB257ARN

If you have any objections, please contact the editorial office as soon as possible. If we do not hear from you, we will assume you agree with your co-authorship.

If you did not co-author this submission, please contact the corresponding author directly

Thank you very much.

Best regards

Abiodun

---

Professor Abiodun Falodun, PhD

Editor-in-Chief:

Tropical Journal of Natural Product Research (TJNPR)  
Head, Natural Product Research Group, University of Benin

Email: [editor.tjnpr@uniben.edu](mailto:editor.tjnpr@uniben.edu); [editor.tjnpr@gmail.com](mailto:editor.tjnpr@gmail.com)

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Professor of Pharmaceutical Chemistry

Fellow, Fulbright (USA)

Deputy Vice-Chancellor (Academic) 2014-2016

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**Dr. apt. Rollando, S.Farm., M.Sc.**  
Pengajuan ke Lektor Kepala

**2. Revisi pertama: accepted with moderate corrections**  
**(18-3-2023)**

**Dr. apt. Rollando, S.Farm., M.Sc.**  
Pengajuan ke Lektor Kepala

(TJNPR) Editor Decision

Editor-in-Chief Tjnpr <editor.tjnpr@gmail.com>

Sat 3/18/2023 9:27 PM

To: Dr. apt. Rollando, S.Farm, M.Sc. <ro.llando@machung.ac.id>

1 attachments (201 KB)

Provisional acceptance 257.pdf;

Dear Dr Rollando,

The manuscript submitted to the Tropical Journal of Natural Product Research [www.tjnpr.org](http://www.tjnpr.org) <https://www.scopus.com/sourceid/21100933230> has been carefully reviewed by competent experts.

I am pleased to inform you that the manuscript has been accepted for publication in Tropical Journal of Natural Product Research.

Find attached the details of the decision.

Please send your response urgently to the Editor-in-Chief, to enable us to process your manuscript for the next issue Vol 7 Issue 3, 2023. Kindly acknowledge the receipt of the mail.

**Title:** Screening Carica Papaya Compounds as an Antimalarial Agent: *In Silico* Study

**Authors:** Rollando Rollando\*, Fatimah Maulada, Muhammad Hilmi Afthoni, Yuyun Yuniati

TJNPR Editorial Decision: accepts with moderate revisions

Thank you very much for choosing to publish with Tropical Journal of Natural Product Research.

Best regards

Abiodun

---

Professor Abiodun Falodun, PhD

Editor-in-Chief:

Tropical Journal of Natural Product Research (TJNPR)

Head, Natural Product Research Group, University of Benin

Email: [editor.tjnpr@uniben.edu](mailto:editor.tjnpr@uniben.edu); [editor.tjnpr@gmail.com](mailto:editor.tjnpr@gmail.com)

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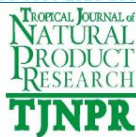
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Dr. apt. Rollando, S.Farm., M.Sc.  
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## Tropical Journal of Natural Product Research

Official Journal of the Natural Product Research Group

Faculty of Pharmacy, University of Benin 300001, Benin City, Nigeria

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SCOPUS indexed, SCImago Sjr 0.13

Ref. No. 7820901802471

DATE: 17<sup>th</sup> March 2023

Pharmacy Department, Faculty of Science and Technology, Ma Chung University, Malang  
65151, Indonesia, Malang 65151, Indonesia.

Dear Dr Rollando,

### **Provisional Acceptance letter for Article Manuscript Number TJNPR FEB257ARN**

**Title: Screening Carica Papaya Compounds as an Antimalarial Agent: *In Silico* Study**

**Authors:** Rollando Rollando\*, Fatimah Maulada, Muhammad Hilmi Afthoni, Yuyun Yuniati

I am pleased to inform you that your manuscript sent to the Tropical Journal of Natural Product Research has been reviewed and recommended for publication as a full article.

However, before the issues raised by the Reviewers are forwarded, to enable you revise your manuscript accordingly, please pay a publication charge of **\$ USD270**. The actual publication of the paper will be in the upcoming issue (**Vol 7 issue 3, 2023**).

Please, the manuscript number (TJNPR ----) should be included in the bank transfer.

Congratulations.

The money should be remitted in favour of:

<b>Name of account:</b>	<b>Abiodun FALODUN</b>
<b>Bank Name:</b>	Access Bank Plc
<b>Account Number:</b>	1456136521.
<b>Sort Code:</b>	044040699
<b>Swift code:</b>	ABNGNGLA
<b>Address of Bank:</b>	Ransome Kuti Road, University of Benin, Benin City, Edo State, Nigeria

Sincerely,

**Professor Abiodun Falodun**  
Editor-in-Chief

---

Editor-in-Chief: Professor Abiodun Falodun, PhD (Nigeria) Fulbright Fellow, USA  
Associate Editors: Professor Dr Peter Langer PhD Hannover (Germany)  
Professor FO Ekhaise, PhD Bayreuth (Germany)



**3. Editor mengirim hasil review artikel**  
**(8-5-2023)**

**Dr. apt. Rollando, S.Farm., M.Sc.**  
Pengajuan ke Lektor Kepala

Editorial and Reviewer comments

Editor-in-Chief Tjnpr <editor.tjnpr@gmail.com>

Mon 5/8/2023 2:14 PM

To: Dr. apt. Rollando, S.Farm, M.Sc. <ro.llando@machung.ac.id>

2 attachments (1 MB)

cr1-REVIEW FORM Tjnpr (2).docx; cr2-TJNPR FEB257AR (1).docx;

Please see the editorial comments (below) and attached copies of the reviewer comments for manuscript title "**Screening *Carica Papaya* Compounds as an Antimalarial Agent: In Silico Study.**"

Editorial comments to authors

**Title: Names (First and Last name in full, middle name as initials) and affiliations of authors should be written correctly. Correspondence authors' contact address (email and telephone number) should also be stated.**

Combine the results and discussion into a single section.

Move all figures and tables under the reference section.

For no-integers, use decimal points **not commas**

All botanical and zoological names should be **italicized**

**References:** Cite relevant and related references from the published articles of TJNPR [www.tjnpr.org](http://www.tjnpr.org)

Adhere strictly to the Journal's style for listing references. Abbreviate all journal names and List names of all Authors in place of **et al**;  
Falodun A, Siraj R, Choudhary MI. GC-MS Insecticidal Leaf essential oil of *P. staudtii* Hutch and Dalz (Icacinaceae). Trop J. Pharm Res. 2009; 82:139-143.

Okolie NP, Falodun A, Oluseyi D. Evaluation of the antioxidant activity of root extract of pepper fruit (*Dennetia tripetala*), and its potential for the inhibition of Lipid peroxidation. Afr J. Trad Compl and Altern Med. 2014; 11(3):221-227. Doi: 10.4314/ajtcam. v11i3.31

All comments/corrections made by reviewers should be completely addressed, point by point, and make appropriate changes in the manuscript, or provide a suitable rebuttal to any specific request for change that has not been made.

All corrections/changes made in the manuscript should be highlighted in **yellow** when submitting the manuscript in the revised **form on or before 11th May 2023**

The authors should carefully revise and correct the manuscript taking into consideration the comments of all the reviewers. **50% of the references cited should be between 2016-2020. The revised and corrected manuscript should be subjected to plagiarism checker (17% allowed in TJNPR) and English language editing. Evidence of the checks should be attached when submitting the revised/corrected manuscript.**

During submission of the revised manuscript include another file labelled "**Responses to reviewers' comments**" (a matrix) clearly showing your responses to each of the issues raised by the reviewers; mention the section, page and paragraph/lines where and how the changes/corrections have been made.

Strictly adhere to the author guidelines. Make sure that all the facts and information provided in the manuscript are correct. Check grammar, spelling, spacing, other information and facts including scientific names, formulae, symbols, equations, etc.

Ensure that all the references are correctly cited in the text and list. Verify all the references from their original sources. Confirm correctness of the citation info such as authors' names (surnames, initials, spelling, arrangements, etc), year, title, journal, volume, pages, punctuation, etc. The numbers and units must be presented according to the journal style. Use clearly distinguishable patterns for the illustrations/figures (e.g., graphs and charts) such that they should be legible even for black and white printing or when reduced in size.

Proofread the whole document after effecting all the corrections. The revised version should be approved by all the co-authors before submitting it.

A manuscript not complying with these and other instructions will not be processed and may be rejected.

Please find the attached review comments for your revisions.

Best regards

Abiodun

-----  
Professor Abiodun Falodun, PhD: FAAS, FISPON

Editor-in-Chief:

Tropical Journal of Natural Product Research (TJNPR)

Head, Natural Product Research Group, University of Benin

Email: [editor.tjnpr@gmail.com](mailto:editor.tjnpr@gmail.com)

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Professor of Pharmaceutical Chemistry, FAAS

Fellow, Fulbright (USA)

Deputy Vice-Chancellor (Academic) 2014-2016

Faculty of Pharmacy



**REVIEW FORM**

The Editorial Team of the Tropical Journal of Natural Product Research kindly request you to review the enclosed article. Please complete the form and return to the Editor-in-Chief, [editor.tjnpr@gmail.com](mailto:editor.tjnpr@gmail.com)

**A. MANUSCRIPT**

Journal	<b>Tropical Journal of Natural Product Research</b>
Manuscript Number	TJNPR FEB257AR
Type of paper	Research article
Title of paper	Screening <i>Carica Papaya</i> Compounds as an Antimalarial Agent: In Silico Study
Name of Authors	

**B. REVIEWER'S SPECIFIC COMMENTS PER SECTION OF MANUSCRIPT**

Title	<p>The author(s) should consider rephrasing the title to capture major components of the research</p> <ul style="list-style-type: none"> <li>• The abstract needs to be improved</li> </ul>
Abstract	<p>The abstract word count is &lt; 250. The language of the abstract need to be improved, the abstract should be grammar checked.</p> <ul style="list-style-type: none"> <li>• The abstract captures the entirety of the manuscripts (i.e. the abstract covers the research scope) and the style of writing is appropriate however, the abstract need to be grammar checked.</li> </ul>
Introduction	<p>The introduction section needs to be grammar checked. Punctuation errors need to be corrected. The aim and objectives of the research is clear however, the author(s) should highlight the novelty of the research. The introduction contains limited information therefore, the author(s) should discuss in details both previous and recent research on the use of <i>C. papaya</i> leaf and compounds identified from them in the treatment of malaria. Also, the author(s) should consider comparative analysis of <i>C. papaya</i> leaf and other plant parts of <i>C. papaya</i> as well as other plants used in the treatment of malaria</p> <ul style="list-style-type: none"> <li>• The introduction is concise.</li> </ul>
Methodology	<p>The language of the methodology is inappropriate. The author(s) should improve on the language of the methodology. Periods/ full stop should not come before the citation as in ...<b>the compound and receptor's accuracy.</b><sup>9</sup>... etc. this error was obvious throughout the manuscript. The title of some of the subheading is inappropriate and should be rephrased. The methodology should be grammar checked. Spelling errors should be corrected. The author(s) should extensively discuss the method used in the molecular dynamics simulation study. What are the periodic conditions employed in the MD simulation study? They claimed to have sourced their library from compounds identified in <i>C. papaya</i> leaf however, no mention of the criteria used in the selection/screening of the library to obtain</p>

	<p>the compounds used in the study was mentioned in the methodology however, it was mentioned in the results section so the author(s) should also, mention these criteria in the methodology. Pyrx is not sufficient for a molecular docking study, the author(s) should consider autodock tools for the docking analysis or use Pyrx in conjunction with other software to validate the docked conformation results. The method for the ADMET analysis was not mentioned in the methodology section but its results were presented and discussed?</p> <ul style="list-style-type: none"> <li>• Vital information on the methodology is lacking especially in the MD simulation study.</li> </ul>
Results	<p>The selection criteria for the compounds used in the study was elusive. The author(s) should give detailed information about these criteria. They should cite the literature source of the journals (publishers, indexing and source etc.) they should give valid reason the compounds were selected for the study and provide web link to the library to the editorial team. ... <b>A total of 55 compounds were found to exhibit antimalarial activity based on the screening criteria</b>.... What were the screening criteria? You only reported 14 compounds in table 1, what happened to the remaining 41 compounds? What criteria was used to screen them out? ... <b>The pkCSM test yielded thirty predictive data on fourteen compounds (Table 2.)</b> where are the remaining 24 data from the pkCSM analysis? Since, you only reported six in the table other data associated with the research should be provided as supplementary documents if they cannot fit into the table.</p> <ul style="list-style-type: none"> <li>• The results are not well presented. Most of the results not contained in the manuscript should be provided as a supplementary document</li> </ul>
Discussion	<p>The author(s) should stick to discussing results contained in the manuscript or its supplementary documents. The manuscript discussion is detailed. The discussion contains a lot of grammatical error which should be corrected. The spellings should all be checked. The author(s) choice of words in communicating some parts of the manuscript is poor. Is 3i65 and 3I65 same protein? ....The amino acid residue TYR528, <b>produced</b> by both the control ligand and Kaempferol-3-O-rhamnose compounds.... Instead of using <u>produced</u> the author(s) should consider using "amino acid residue interacted with..." give the full meaning of an abbreviation before subsequent mention in the manuscript. What criteria was used in selecting the protein used in the molecular docking assay? What criteria was used to select the specific compounds docked to specific proteins as reported? The authors selected different proteins for their docking however, no specific criteria was given for the choice of the reported results.</p> <ul style="list-style-type: none"> <li>• The discussion of the results of the molecular docking experiment is ambiguous and vague</li> <li>• The author(s) needs to improve on the discussion of the results of the MD simulation study</li> <li>• The author(s) should use the unit of Angstroms rather than words such</li> </ul>

	<p>as ... 2.5 Angstroms...</p> <ul style="list-style-type: none"><li>• The author(s) should supply the .txt document of their docking results as supplementary documents, also all the docked conformation of the 14 compounds with the protein should be supplied as a supplementary document.</li><li>• The 3D/stereo/ pose view of the docked compound in the active/allosteric/binding site of the protein should be reported in the manuscript for comprehensive and aesthetic purpose</li></ul>
Conclusion	The conclusion is not concise and doesn't represent the entire information contained in the manuscript. The authors didn't highlight the future prospects of the research and they were no recommendations for further study.
References	Author(s) should ensure that the reference count for the body of the manuscript is same with those at the reference section. The author(s) should report the reference based on the journal guideline for author
Figures	<p>Figure 5 was not mentioned in the body of the manuscript. Figure 6 was used twice for "the Molecular docking visualization of quercetin 3-[rhamnosyl-(1-&gt;2)-rhamnosyl-(1-&gt;6)-glucoside] with 6C4G protein and for the Analysis result of RMSD protein 6M20" authors should correct the errors. If numbered correctly figure 7 should be figure 8. The figure should be reported based on the journal author guideline.</p> <ul style="list-style-type: none"><li>• The numbering of the figures should be corrected</li><li>• The authors should improve the graphics of the molecular docking results</li></ul>
Tables	The tables should be presented based on the journal author guideline.

### C. REVIEWER'S GENERAL COMMENTS AND REMARKS

The author(s) screened "*Carica Papaya* Compounds as an Antimalarial Agent" using in silico technique such as ADMET, molecular docking and molecular dynamics simulation analysis. The literature review though concise but needs to be improved to reflect key areas of the research. The method used in the analysis is sufficient for the results obtained in the study. The results presentation is concise but the discussion of the obtained results are vague and ambiguous. The research conclusion needs to be improved.

The author(s) should provide a link to the library of selected *C. papaya* used in the research. The graphics for the docking results should be improved.

In some sections of the manuscript, the language used is inappropriate. The author(s) needs to improve on the choice of language of writing of the manuscript. The manuscript should be grammar checked and spell checked for errors.

All the corrections highlighted in the manuscript should be effected prior to acceptance.

- The research is interesting and worthy of publication after all concerns raised are addressed by the author(s)

**D. REVIEWER'S RECOMMENDATION**

Please mark with "X" one of the options.

You state the article should:

Publish as it is	
Accept with minor revisions (editor will check), specific comments to the editor below  The authors should improve on the language and choice of words used in reporting the manuscript, the manuscript should be grammar checked and spelling errors should be corrected. If possible the author(s) should employ a manuscript editing service to improve the manuscript. The graphics of the molecular docking should be improved. All supplementary documents should be provided.  <ul style="list-style-type: none"><li>• All other recommendation are contained in the other sections of the form and in the body of the reviewed manuscript.</li></ul>	<b>X</b>
Accept with moderate revisions as recommended by reviewer	
Accept with major corrections (the article should be thoroughly changed)	
<b>Full article</b>	
<b>Short communication</b>	
Reject for reasons noted by the reviewer (please be specific)	

**Dr. apt. Rollando, S.Farm., M.Sc.**

Pengajuan ke Lektor Kepala

**E. REVIEWER'S INFORMATION**

Name	<b>Kingsley Ikechukwu Ijoma</b>
Official title	<b>Dr.</b>
Affiliation	<b>Nnamdi Azikiwe University</b>
Specialization	<b>Analytical Organic Chemistry (Sub: Natural Product and Computational Chemistry)</b>
Country	<b>Nigeria</b>
E-mail	<a href="mailto:ikechukwuijoma@gmail.com"><b>ikechukwuijoma@gmail.com</b></a>
Phone	<b>+2348144250562</b>
Signature	

**4. Author mengirimkan hasil revisi artikel**  
**(9-5-2023)**



**Dr. apt. Rollando, S.Farm., M.Sc.**  
Pengajuan ke Lektor Kepala

Re: Editorial and Reviewer comments

Dr. apt. Rollando , S.Farm, M.Sc. <ro.llando@machung.ac.id>

Tue 5/9/2023 6:18 PM

To:Editor-in-Chief Tjnpr <editor.tjnpr@gmail.com>

📎 2 attachments (1 MB)

Responses to reviewers' comments.docx; Rollando\_Revised 1.docx;

Dear Editor In Chief of Tropical Journal of Natural Product Research,

I hope this email finds you well. I am writing to inform you that the manuscript entitled "Screening Carica Papaya Compounds as an Antimalarial Agent: In Silico Study" has been revised according to the feedback received from the reviewers. I am pleased to say that we have made significant improvements to the manuscript and we believe that it is now suitable for publication in your esteemed journal.

We appreciate the constructive feedback provided by the reviewers, which has helped to enhance the quality and accuracy of our research. We have carefully considered each comment and have made the necessary changes to the manuscript. We have also included a point-by-point response to the reviewers' comments to demonstrate how we have addressed each issue.

In summary, the revised manuscript includes the following changes:

- We have restructured the manuscript to make it more concise and focused.
- We have clarified the methodology used in our study and have included additional data to support our findings.
- We have addressed all the issues raised by the reviewers, including those related to the interpretation of our results and the presentation of our data.
- We have fixed the references style.

We would like to express our gratitude to the reviewers for their time and effort in reviewing our manuscript. We also appreciate the opportunity to revise our manuscript and submit it for consideration for publication in the Tropical Journal of Natural Product.

Thank you for your consideration. We look forward to hearing from you soon.

Best regards,  
Rollando

---

**Dr. apt. Rollando, S.Farm., M.Sc.**

Pengajuan ke Lektor Kepala

Prof. Abiodun Falodun

Editor in Chief

Tropical Journal of Natural Product Research

Dear Abiodun,

I would like to submit our revised manuscript entitled” **Screening Carica Papaya Compounds as an Antimalarial Agent: In Silico Study**” for the consideration of publication in the tropical journal of natural product research.

I also have answered a point by point questions, comments and suggestions from the reviewer to improve our article quality as written along with this letter. I really appreciate for all these valuable comments and suggestions.

I hope very much that you would consider this manuscript for the publication in your esteemed journal. Your kind consideration would be gratefully acknowledged.

Thank you

Your sincerely

Rollando

**Responses to reviewers' comments**

<p>The author(s) should consider rephrasing the title to capture major components of the research</p> <ul style="list-style-type: none"> <li>• The abstract needs to be improved</li> </ul>	<p>We have fixed the grammatical error in the article. We have improved the English language. Proofread certificate already exists.</p>
<p>The abstract word count is &lt; 250. The language of the abstract need to be improved, the abstract should be grammar checked.</p> <ul style="list-style-type: none"> <li>• The abstract captures the entirety of the manuscripts (i.e. the abstract covers the research scope) and the style of writing is appropriate however, the abstract need to be grammar checked.</li> </ul>	<p>The abstract section has added words and research objectives.</p>
<p>The introduction section needs to be grammar checked. Punctuation errors need to be corrected. The aim and objectives of the research is clear however, the author(s) should highlight the novelty of the research. The introduction contains limited information therefore, the author(s) should discuss in details both previous and recent research on the use of C. papaya leaf and compounds identified from them in the treatment of malaria. Also, the author(s) should consider comparative analysis of C. papaya leaf and other plant parts of C. papaya as well as other plants used in the treatment of malaria</p> <ul style="list-style-type: none"> <li>• The introduction is concise.</li> </ul>	<p>We have fixed text referencing.</p>
<p>The language of the methodology is inappropriate. The author(s) should improve on the language of the methodology. Periods/ full stop should not come before the citation as in ...the compound and receptor's accuracy.?<sup>9</sup>... etc. this error was obvious throughout the manuscript. The title of some of the subheading is inappropriate and should be rephrased. The methodology should be grammar checked. Spelling errors</p>	<p>We have fixed reference writing.</p>

<p>should be corrected. The author(s) should extensively discuss the method used in the molecular dynamics simulation study. What are the periodic conditions employed in the MD simulation study? They claimed to have sourced their library from compounds identified in <i>C. papaya</i> leaf however, no mention of the criteria used in the selection/screening of the library to obtain the compounds used in the study was mentioned in the methodology however, it was mentioned in the results section so the author(s) should also, mention these criteria in the methodology. Pyrx is not sufficient for a molecular docking study, the author(s) should consider autodock tools for the docking analysis or use Pyrx in conjunction with other software to validate the docked conformation results. The method for the ADMET analysis was not mentioned in the methodology section but its results were presented and discussed?</p> <p>Vital information on the methodology is lacking especially in the MD simulation study.</p>	
<p>The selection criteria for the compounds used in the study was elusive. The author(s) should give detailed information about these criteria. They should cite the literature source of the journals (publishers, indexing and source etc.) they should give valid reason the compounds were selected for the study and provide web link to the library to the editorial team. ... <b>A total of 55</b></p>	<p>We have fixed reference writing.</p>

<p>compounds were found to exhibit antimalarial activity based on the screening criteria.... What were the screening criteria? You only reported 14 compounds in table 1, what happened to the remaining 41 compounds? What criteria was used to screen them out? ... The pkCSM test yielded thirty predictive data on fourteen compounds (Table 2.) where are the remaining 24 data from the pkCSM analysis? Since, you only reported six in the table other data associated with the research should be provided as supplementary documents if they cannot fit into the table. The results are not well presented. Most of the results not contained in the manuscript should be provided as a supplementary document</p>	
<p>The author(s) should stick to discussing results contained in the manuscript or its supplementary documents. The manuscript discussion is detailed. The discussion contains a lot of grammatical error which should be corrected. The spellings should all be checked. The author(s) choice of words in communicating some parts of the manuscript is poor. Is 3i65 and 3I65 same protein? ....The amino acid residue TYR528, produced by both the control ligand and Kaempferol-3-O-rhamnose compounds.... Instead of using produced the author(s) should consider using “amino acid residue interacted with...” give the full meaning of an abbreviation before</p>	<p>We have fixed reference writing.</p>

<p>subsequent mention in the manuscript. What criteria was used in selecting the protein used in the molecular docking assay? What criteria was used to select the specific compounds docked to specific proteins as reported? The authors selected different proteins for their docking however, no specific criteria was given for the choice of the reported results.</p> <ul style="list-style-type: none"><li>• The discussion of the results of the molecular docking experiment is ambiguous and vague</li><li>• The author(s) needs to improve on the discussion of the results of the MD simulation study</li><li>• The author(s) should use the unit of Angstroms rather than words such as ... 2.5 Angstroms...</li><li>• The author(s) should supply the .txt document of their docking results as supplementary documents, also all the docked conformation of the 14 compounds with the protein should be supplied as a supplementary document.</li></ul> <p>The 3D/stereo/ pose view of the docked compound in the active/allosteric/binding site of the protein should be reported in the manuscript for comprehensive and aesthetic purpose</p>	
<p>The conclusion is not concise and doesn't represent the entire information contained in the manuscript. The authors didn't highlight the future prospects of the research and they were no recommendations for further study.</p>	<p>We have fixed text referencing.</p>
<p>Author(s) should ensure that the reference count for the body of the manuscript is same</p>	<p>We have fixed text referencing.</p>

<p>with those at the reference section. The author(s) should report the reference based on the journal guideline for author</p>	
<p>Figure 5 was not mentioned in the body of the manuscript. Figure 6 was used twice for “the Molecular docking visualization of quercetin 3-[rhamnosyl-(1-&gt;2)-rhamnosyl-(1-&gt;6)-glucoside] with 6C4G protein and for the Analysis result of RMSD protein 6M20” authors should correct the errors. If numbered correctly figure 7 should be figure 8. The figure should be reported based on the journal author guideline.</p> <ul style="list-style-type: none"><li>• The numbering of the figures should be corrected</li></ul> <p>The authors should improve the graphics of the molecular docking results</p>	<p>We have fixed text referencing.</p>
<p>The tables should be presented based on the journal author guideline.</p>	<p>We have fixed text referencing.</p>

**Dr. apt. Rollando, S.Farm., M.Sc.**  
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Cc: Editor-in-Chief Tjnpr <editor.tjnpr@gmail.com>

 1 attachments (1 MB)

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Dear Author,

See the attached **galley proof** manuscript with title " *Screening Carica Papaya Compounds as an Antimalarial Agent: In Silico Study*" for authors  
perusal



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I send my revised galley proof.

Regards  
Rollando

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- 7. Artikel dipublikasi pada Tropical Journal of Natural Product Research. Vol. 7, Issue 5, Juni 2023. Hal: 2895-2903  
(2-6-2023)**



Screening *Carica Papaya* Compounds as an Antimalarial Agent: *In Silico* Study

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ABSTRACT

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Malaria is a highly prevalent infectious disease caused by the Plasmodium parasite transmitted through *Anopheles* mosquitoes, which poses a significant public health challenge worldwide, including in Indonesia. Therefore, a study was conducted to identify potential drug compounds from the *Carica papaya* plant that could inhibit various antimalarial proteins or receptors, such as Plasmodium falciparum DXR reductase complex with fosmidomycin, Plasmeprin V Plasmodium vivax, P. falciparum dihydroorotate dehydrogenase, P. falciparum hexose transporter, P. falciparum protein kinase 5, and P. falciparum dihydrofolate reductase-thymidylate synthase. The researchers used the Pyrx application to dock the C. papaya compounds with the targeted antimalarial proteins to determine the binding affinity values. Additionally, they used the Yasara dynamics application to conduct molecular dynamics simulation to ensure the stability of the bonds formed between the ligands and proteins. The results showed that 14 compounds found in C. papaya, particularly flavonoids and terpenoids, had the potential to inhibit the six antimalarial proteins with the lowest binding affinity values. Furthermore, the molecular dynamics simulation on 6M20 and 1V0P proteins indicated that the compounds effectively inhibited Plasmodium proteins, as they had an RMSD value below 2.5 Angstrom. The study suggests that C. papaya could be a potential source of antimalarial compounds, which could be developed into new drugs to combat this disease.

**Keywords:** Antimalaria, *Carica papaya*, Molecular Docking, Molecular Dynamic

Introduction

Malaria is a widespread infectious disease that affects many people worldwide, with an estimated 300 million cases reported annually.<sup>1</sup> Indonesia is one of the countries where malaria is endemic, and it is a significant concern for elimination, alongside other diseases like TB and HIV/AIDS. However, the number of malaria cases had decreased from 2018, around 202,176 cases, to only 94,610 cases in 2021.<sup>2</sup> Malaria remains one of the deadliest infectious diseases, caused by Plasmodium protozoan parasites, including Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, and Plasmodium knowlesi.<sup>3</sup> In Indonesia, C. papaya, also known as papaya leaf, is a traditional plant commonly used to treat malaria.<sup>4</sup> It belongs to the Caricaceae family, and some of its species have been used as medicinal plants for various ailments, including antimalarials. *In vitro* studies have demonstrated that C. papaya exhibits high and effective antiplasmodial activity against P. falciparum, indicating that it is well-suited for traditional malaria treatment.<sup>5</sup>

*In silico* experiments refer to experiments carried out using a computer. These tests can help determine the interaction between a compound and its molecular target, such as a receptor.<sup>6</sup> Using computational methods, the interaction between compounds and receptors can be visualized, which can aid in identifying the pharmacophore of a compound that can be screened and assist in the synthesis process.<sup>7</sup>

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In the plasmodium synthesis process, the chain cleavage leads to a lack of energy required for metabolism, which ultimately leads to its death. This study aims to identify potential candidate compounds from C. papaya, which can be further explored in the search for new antimalarial drugs.

Material and Methods

Materials

The materials used in this study include a Lenovo laptop with 4GB RAM, an Intel Core i3 processor, and software such as Windows 10 operating system, Pyrx, Biovia (Discovery Studio 2021 client), PDB (Protein Data Bank used for searching for plasmodium proteins), and secondary metabolites obtained from papaya leaves, which were downloaded from Pubchem website in the PDB format.

Preparation of Ligand Compounds

To obtain the structure of a compound, the Pubchem program on the website [pubchem.ncbi.nlm.nih.gov](http://pubchem.ncbi.nlm.nih.gov) can be used.<sup>8</sup> This website provides information, including Simplified Molecular Input Life Entry System (SMILE). The downloaded compound structure should be in 3D format with SDF. After obtaining the SMILES from the C. papaya compound can be copied and pasted into the PASS Test. The PASS test can be performed on the way2drug.com website by entering the SMILES in the provided box and clicking the "Get prediction" button to view the prediction results. To see the predicted biological activity of a compound, click on the "Pa>0.7" button. A pre-ADMET test can also be performed on the <https://PkCSM.com/> website by entering the SMILES in the box and clicking the black pre-ADMET button.

Preparation of Proteins Related to Malaria

To prepare the malaria protein for docking, the protein is obtained from the PDB database through the website [www.rcsb.org](http://www.rcsb.org). When selecting the protein, it is essential to consider the resolution limit of 1-3, with a lower limit preferred to avoid missing residues. Additionally, the