

DOKUMEN KORESPONDENSI

International Food Research Journal (IFRJ)

<http://www.ifrj.upm.edu.my>

Nephrotoxicity effect of Ginseng Bugis (*Talinum paniculatum* (Jacq) Gaertn) leaves ethanolic extract on creatinine, urea, and kidney histopathological features

Authors: Emelda, A., Santi, I., Besse, S. C. D., Aderafni, A. and Yuliana, D.

International Food Research Journal 31(2): 417 - 422 (April 2024)

A. Resume of step by step correspondences:

No.	Time	Activities
1.	10 August 2022	Create an account in IFRJ website
2.	12 August 2022	Submit manuscript with cover letter
3.	27 August 2022	Reply to editorial
4.	07 September 2022	Editorial Review, an initial check against formal technical criteria's
5.	29 September 2022	Submit the revised of editorial reviews
6.	03 July 2023	Decision of reviewer is Minor Revision: Detail of reviewer comments in the manuscript.
7.	18 August 2023	Reminder to submit a revised manuscript of reviewer comments
8.	23 August 2023	Submit the revised manuscript and Cover Letter with response to the Editor's and Reviewer's comments
9.	04 January 2024	Editorial review comment to send manuscript to English Editing Service
10.	15 January 2024	Submit revised manuscript and certificate of English Editing
11.	22 January 2024	Decision on manuscript IFRJ22495.R1: Accepted (LoA),
12.	23 January 2024	Submit a Copyright agreement
13.	04 April 2024	APC Charge for Accepted Article (IFRJ22495.R1)
14.	09 April 2024	Paid the APC
15.	16 April 2024	Galley Proof - IFRJ Issue 2, 2024
16.	April 2024	Publish the manuscript in Volume 31: Issue 2, 2024

B. Detail of Step by Step Correspondences

(1) 10 August 2022: Create an account in IFRJ website



Andi Emelda <andi.emelda@umi.ac.id>

International Food Research Journal - Account Created in ScholarOne Manuscripts

1 message

International Food Research Journal <onbehalfof@manuscriptcentral.com>

Wed, Aug 10, 2022 at 10:44 PM

Reply-To: ifrj@upm.edu.my

To: andi.emelda@umi.ac.id

10-Aug-2022

Dear Dr. Emelda:

Welcome to International Food Research Journal - ScholarOne Manuscripts site for online submission and review.

Your USER ID for your account at <https://mc.manuscriptcentral.com/upm-ifrj> is as follows:

USER ID: andi.emelda@umi.ac.id

If you are unsure of the password that you set when you created your account you should click the link below which will take you directly to the option for setting a new password.

https://mc.manuscriptcentral.com/upm-ifrj?URL_MASK=58f5ca0567ea4fef84c1112c5b7e3526

Please note that the single use link will expire on 13-Aug-2022 2:44:38 PM GMT / 13-Aug-2022 10:44:38 PM SGT.

If the single use link has expired, you can generate a single use password by entering your email address into the Password Help function on your site log in page:

<https://mc.manuscriptcentral.com/upm-ifrj>

Regards,

International Food Research Journal Editorial Office

Log in to Remove This Account - https://mc.manuscriptcentral.com/upm-ifrj?URL_MASK=bade37658233493ca9798dc26046ca74

(2) 12 August 2022: Submit manuscript (manuscript ID is IFRJ22495)

International Food Research Journal



Nephrotoxicity Study of Ethanol Extract of Ginseng Bugis Leaves (*Talinum paniculatum* (Jacq) Gaertn on Creatinine and Urem Levels and Kidney Histopathological Features

Journal:	International Food Research Journal
Manuscript ID	IFRJ22495
Manuscript Type:	Original Article
Keyword:	Talinum paniculatum, Nephrotoxic, Creatinine, Urem, Histopathology

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Manuscripts

Cover Letter

Andi Emelda
Universitas Muslim Indonesia
Jl. Urip Sumiharjo Km.5 Makassar Indonesia

August 12. 2022

Dear Prof. Dr. Tan Chin Ping
Editor in Chief of The International Food Research Journal (IFRJ)

We wish to submit an original research article entitled “Nephrotoxicity study of Ethanol Extract of Ginseng Bugis Leaves (*Talinum paniculatum* (Jacq) Gaertn on Creatinine and Ureum Levels and Kidney Histopathological Features” for consideration by The International Food Research Journal (IFRJ).

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

This study uses a ginseng plant, *Talinum paniculatum* (Jacq) Gaertn, which grows locally and is used by the community in daily life for food, vegetables, or medicines. Several studies have found that these plants provide various activities including tonic, antimicrobial, and immune systems. Therefore, toxicity testing is needed to determine a safe dose to use. This research was carried out with a nephrotoxic test with ureum, creatinine, and histopathology parameters in order to obtain a safe dose based on these parameters.

We have no conflicts of interest to disclose.

Please address all correspondence concerning this manuscript to me at the email address:
andi.emelda@umi.ac.id

Thank you for your consideration of this manuscript.

Sincerely yours,

Andi Emelda



Andi Emelda <andi.emelda@umi.ac.id>

International Food Research Journal - Manuscript IFRJ22495

International Food Research Journal <onbehalf@manuscriptcentral.com>

Fri, Aug 12, 2022 at 7:32 PM

Reply-To: ifrj@upm.edu.my

To: andi.emelda@umi.ac.id, irma.santi@umi.ac.id, bessesasmitacitra@yahoo.com, aderafniamaliah@gmail.com, dewi.yuliana@umi.ac.id

12-Aug-2022

Dear Dr. Emelda

Your manuscript entitled 'Nephrotoxicity Study of Ethanol Extract of Ginseng Bugis Leaves (*Talinum paniculatum* (Jacq) Gaertn on Creatinine and Ureum Levels and Kidney Histopathological Features' has been successfully submitted online and will be given full consideration for publication in International Food Research Journal.

Your manuscript ID is IFRJ22495. Please mention this manuscript ID in all future correspondence or when contacting the Editorial Office for questions.

You can also view the status of your manuscript at any time by checking your Author Centre after logging in.

If there are any changes in your email address, please log in to ScholarOne Manuscripts at <https://mc.manuscriptcentral.com/upm-ifrj> and edit your details as appropriate.

We confirm that, if accepted for publication, Article Processing Charges (APC) will apply to your article with the amount of USD250. Please confirm that you support open access publishing and that you will pay the APC if your manuscript is accepted.

Thank you in advance for your cooperation. I look forward to hearing from you.

Regards,
Editorial Office, International Food Research Journal

(3) 27 August 2022: Reply to editor



Andi Emelda <andi.emelda@umi.ac.id>

International Food Research Journal - Manuscript IFRJ22495

Andi Emelda <andi.emelda@umi.ac.id>

Sat, Aug 27, 2022 at 9:36 PM

To: ifrj@upm.edu.my

Manuscript ID: **IFRJ22495**

Dear Editorial Team of International Food Research Journal.

Thank you very much for your accepting our manuscript for the next process in the IFRJ.
We confirm that we support open-access publishing and will pay the APC if our manuscript is accepted.

Best regards,
Dr. Andi Emelda

(4) 07 September 2022: Editorial Review, an initial check against formal technical criteria's



Andi Emelda <andi.emelda@umi.ac.id>

International Food Research Journal - IFRJ22495 has been unsubmitted

International Food Research Journal <onbehalf@manuscriptcentral.com>

Wed, Sep 7, 2022 at 3:02 PM

Reply-To: ifrj@upm.edu.my

To: andi.emelda@umi.ac.id

07-Sep-2022

Dear Dr. Emelda,

Thank you for submitting your manuscript to International Food Research Journal. Before submitting the manuscript for the reviewing process, we perform an initial check against formal technical criteria's. We regret to inform you that your manuscript does not meet the required standards. Please make changes/corrections as detailed in the comments below.

Your manuscript is located in the 'Unsubmitted Manuscripts' section in the 'My Manuscripts' area of your Author Centre. Find the submission that needs updating and click on the 'Continue Submission' button. Please DO NOT delete the manuscript.

Please contact the Editorial Office if you have any queries regarding this process, and I sincerely apologize for the delay and any inconvenience caused due to the high number of submissions received recently.

Comments:

- 1) Please add another two names for the author recommended reviewers part, preferably from different institutions.
- 2) Please send the manuscript file in word format.
- 3) Please revise in text citation following IFRJ's guideline. Do italic 'et al' and arrange based on older to latest year for in text citation.
- 4) For reference part, please follow IFRJ's guideline accordingly. An example how it should be following IFRJ's guideline:

Abeliotis, K., Lasaridi, K., Costarelli, V. and Chroni, C. 2015. The implications of food waste generation on climate change: The case of Greece. Sustainable Production and Consumption 3: 8–14.

- 5) Please arrange tables and figures to be at a separate page after reference part in the main manuscript.

Thank you.

Regards,

Ms. Norhafizah Mohamad Noh

Editorial Assistant

International Food Research Journal Editorial Office

(5) 29 September 2022: Submit the revised manuscript of editorial reviews



Andi Emelda <andi.emelda@umi.ac.id>

International Food Research Journal - Manuscript IFRJ22495

International Food Research Journal <onbehalf@manuscriptcentral.com>

Thu, Sep 29, 2022 at 11:28 PM

Reply-To: ifrj@upm.edu.my

To: andi.emelda@umi.ac.id, irma.santi@umi.ac.id, bessesasmitacitra@yahoo.com, aderafniamaliah@gmail.com, dewi.yuliana@umi.ac.id

29-Sep-2022

Dear Dr. Emelda

Your manuscript entitled 'Nephrotoxicity Study of Ethanol Extract of Ginseng Bugis Leaves (*Talinum paniculatum* (Jacq) Gaertn on Creatinine and Ureum Levels and Kidney Histopathological Features' has been successfully submitted online and will be given full consideration for publication in International Food Research Journal.

Your manuscript ID is IFRJ22495. Please mention this manuscript ID in all future correspondence or when contacting the Editorial Office for questions.

You can also view the status of your manuscript at any time by checking your Author Centre after logging in.

If there are any changes in your email address, please log in to ScholarOne Manuscripts at <https://mc.manuscriptcentral.com/upm-ifrj> and edit your details as appropriate.

We confirm that, if accepted for publication, Article Processing Charges (APC) will apply to your article with the amount of USD250. Please confirm that you support open access publishing and that you will pay the APC if your manuscript is accepted.

Thank you in advance for your cooperation. I look forward to hearing from you.

Regards,
Editorial Office, International Food Research Journal

(6) 03 July 2023: Decision on reviewer is Minor Revision: Detail of reviewer comments in the manuscript



Andi Emelda <andi.emelda@umi.ac.id>

International Food Research Journal - Decision on Manuscript IFRJ22495

1 message

International Food Research Journal <onbehalf@manuscriptcentral.com>

Mon, Jul 3, 2023 at 11:29 AM

Reply-To: ifrj@upm.edu.my
To: andi.emelda@umi.ac.id

03-Jul-2023

Dear Dr. Emelda

Manuscript IFRJ22495, entitled 'Nephrotoxicity Study of Ethanol Extract of Ginseng Bugis Leaves (Talinum paniculatum (Jacq) Gaertn on Creatinine and Ureum Levels and Kidney Histopathological Features', which you submitted to International Food Research Journal, has been reviewed. The comments of the reviewers appear below.

Based on the advice received, your manuscript could be reconsidered for publication should you be prepared to incorporate MINOR REVISIONS.

When preparing and submitting your revised manuscript (which should be labelled as such), you will be able to respond to the comments made by the reviewers, the Associate Editor and the Editor in the space provided. You can use this space to document the changes you make to the original manuscript and submit a list of responses to the comments and suggestions, item by item.

Your list of responses should also be uploaded as a separate file (i.e. Word) in addition to your comments in the system. For the separate uploaded file, please explicitly and clearly state where and how you have addressed the referees' criticisms or provide your reasons for rebuttal of the criticisms. Please submit 'Responses to Reviewers' Comments' for each of the point raised by each referee with numbering system (include line and page numbers), and to cross reference it with the revised manuscript. Please also highlight the changes to your manuscript within the document by highlighting the text or using colored text.

Please note that there is/are comments on the English grammar. Therefore, please make sure to send the manuscript to English Editing Services, and attach the certificate or evidence that you are doing so.

Please download a copy of your manuscript from the system at STEP 3: File Upload after clicking 'CREATE REVISION' and use the file to do the revision. This is because the file has been edited according to the Journal's format.

The manuscript must be submitted electronically within 60 days, or it may be considered withdrawn.

Thank you for submitting your manuscript to International Food Research Journal; I look forward to receiving your revision. Instructions on how to revise your manuscript are included at the end of this letter.

Regards,
Dr. Ahmad Faizal Abdull Razis
Editor, International Food Research Journal

Reviewers' Comments to Author:

Reviewer: 1

Comments to the Author
your manuscript is a good and need minor revision for more better.

HOW TO REVISE YOUR MANUSCRIPT

To revise your manuscript, log in to <https://mc.manuscriptcentral.com/upm-ifrj> and enter your Author Centre, where you will find this manuscript listed under 'Manuscripts with Decisions'. Under 'Actions', click on 'Create a Revision'.

You can also click the link below to start the revision process (or continue the process if you have already started your revision) for your manuscript. If you use the link below you will not be required to log in to ScholarOne Manuscripts.

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https://mc.manuscriptcentral.com/upm-ifrj?URL_MASK=68f5c440b2634f9780cf235df723560e

(7) 18 August 2023: Reminder to submit a revised manuscript of reviewer comments



Andi Emelda <andi.emelda@umi.ac.id>

REMINDER: International Food Research Journal - submission of revised manuscript

1 message

International Food Research Journal <onbehalf@manuscriptcentral.com>

Fri, Aug 18, 2023 at 4:23 PM

Reply-To: ifrj@upm.edu.my
To: andi.emelda@umi.ac.id

18-Aug-2023

Dear Dr. Emelda:

Recently, you received a decision on Manuscript ID IFRJ22495, entitled "Nephrotoxicity Study of Ethanol Extract of Ginseng Bugis Leaves (Talinum paniculatum (Jacq) Gaertn on Creatinine and Ureum Levels and Kidney Histopathological Features." The manuscript and decision letter are located in your Author Center at <https://mc.manuscriptcentral.com/upm-ifrj>.

This e-mail is simply a reminder that your revision is due in two (2) weeks from 01-Sep-2023. If it is not possible for you to submit your revision within one week, your paper will be withdrawn and we will consider your paper as a new submission.

You may also click the below link to start the revision process (or continue the process if you have already started your revision) for your manuscript. If you use the below link you will not be required to login to ScholarOne Manuscripts.

*** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/upm-ifrj?URL_MASK=26b3b5bf5814f08b72ef12a79700a1d

Regards,

Norhafizah Mohamad Noh
International Food Research Journal Editorial Office
ifrj@upm.edu.my

(8) 23 August 2023: Submit the revised manuscript and Cover Letter with response to the editor's and reviewer's comments



Andi Emelda <andi.emelda@umi.ac.id>

International Food Research Journal - Manuscript IFRJ22495.R1

1 message

International Food Research Journal <onbehalf@manuscriptcentral.com>

Wed, Aug 23, 2023 at 3:17 AM

Reply-To: ifrj@upm.edu.my
To: andi.emelda@umi.ac.id, irma.santi@umi.ac.id, bessesasmitacitra@yahoo.com, aderafniamaliah@gmail.com, dewi.yuliana@umi.ac.id

23-Aug-2023

Dear Dr. Emelda

Your revised manuscript entitled 'Nephrotoxicity Study of Ethanol Extract of Ginseng Bugis Leaves (Talinum paniculatum (Jacq) Gaertn on Creatinine, Ureum Levels and Kidney Histopathological Features' has been successfully submitted online and will be given full consideration for publication in International Food Research Journal.

Your manuscript ID is IFRJ22495.R1. Please mention this manuscript ID in all future correspondence or when contacting the Editorial Office for questions.

You can also view the status of your manuscript at any time by checking your Author Centre after logging in.

If there are any changes in your email address, please log in to ScholarOne Manuscripts at <https://mc.manuscriptcentral.com/upm-ifrj> and edit your details as appropriate.

Due to high volume of submissions, please expect some delays.

Thank you for submitting your manuscript to International Food Research Journal.

Regards,
International Food Research Journal Editorial Office

Response to Editor's and Reviewer's Comments

Dear Editor of the International Food Research Journal (IFRJ),

We are grateful to the editors and reviewer for their time and constructive comments on our manuscript "Nephrotoxicity study of ethanol extract of Ginseng Bugis leaves (*Talinum paniculatum* (Jacq) Gaertn) on creatinine, ureum levels, and kidney histopathological features". We have implemented all the comments and suggestions and wish to submit a revised version of the manuscript for further consideration in the journal. Changes in the initial version of the manuscript are highlighted with red color for added sentences in the revised version. Below, we provide a point-by-point response explaining how we have addressed each of the editor's or reviewers' comments. We look forward to the outcome of your assessment.

Sincerely Yours,
Dr. Andi Emelda

Editor's comments and Answers

- 1) Please add another two names for the author recommended reviewers part, preferably from different institutions.
- 2) Please send the manuscript file in word format.
- 3) Please revise in text citation following IFRJ's guideline. Do italic 'et al' and arrange based on older to latest year for in text citation.
- 4) For reference part, please follow IFRJ's guideline accordingly. An example how it should be following IFRJ's guideline:
Abeliotis, K., Lasaridi, K., Costarelli, V. and Chroni, C. 2015. The implications of food waste generation on climate change: The case of Greece. Sustainable Production and Consumption 3: 8–14.
- 5) Please arrange tables and figures to be at a separate page after reference part in the main manuscript.

Our answer:

1. We added 2 names in menu *add reviewer* in submission online system.
2. All the comments (2-5) have been done in revised manuscript.

Reviewers' Comments and Answers:

1. Your manuscript is good and need minor revision for better.

Our answer: Thank you very much your comments and decision to improve our paper

2. Maybe you can use updated references (**Page: 2; Line:39**)

(Andarwulan et al., 2012; Kotta et al., 2013; Luis et al., 2015; Santoso et al., 2016).

Our answer (Page:2; Line:47): The references have been updated. (Moura et al., 2020; Menezes et al., 2021).

3. I didn't found on the references (Katno and Pramono 2008). (**Page:2; Line: 43**)

Our answer (Page: 3; Line:50): The reference has been added with an updated reference (Bose et al., 2021).

4. Maybe you can add about the dose of your sample, why you used that dose (0.8; 1.6; 2.4 g/KgBW) (**Page 6; Line: 142**)

Our answer (Page: 7; Line:140-145): This study used various extract doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW on male Wistar rats. The selection of dose variations was based on a previous study in which extract doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW provided immunomodulatory and anti-inflammatory activity (Emelda et al., 2019). Therefore, this study aimed to determine the nephrotoxic effect of these doses.

5. Why do you use male animals (Wistar strain) (**Page: 6; line:142**)

Our answer (Page:7; line: 146-152): The experimental animals used in this study were male rats (*Rattus norvegicus*) of the Wistar strain commonly often used in studies due to their wide availability. According to previous reports, male rats have a more stable hormonal system than females. This study preferred male rats over females in the experiment due to concerns about female hormone cycles causing behavioral variations that could skew the results (Lovick et al., 2021; Mohd Azam et al., 2022).

(9) 04 January 2024: Editorial review comment to send manuscript to English editing Service



Andi Emelda <andi.emelda@umi.ac.id>

International Food Research Journal - IFRJ22495.R1 has been unsubmitted

International Food Research Journal <onbehalf@manuscriptcentral.com>

Thu, Jan 4, 2024 at 3:17 PM

Reply-To: ifrj@upm.edu.my

To: andi.emelda@umi.ac.id

04-Jan-2024

Dear Dr. Emelda,

Thank you for submitting your manuscript to International Food Research Journal. Before submitting the manuscript for the reviewing process, we perform an initial check against formal technical criteria's. We regret to inform you that your manuscript does not meet the required standards. Please make changes/corrections as detailed in the comments below.

Your manuscript is located in the 'Unsubmitted Manuscripts' section in the 'My Manuscripts' area of your Author Centre. Find the submission that needs updating and click on the 'Continue Submission' button. Please DO NOT delete the manuscript.

Please contact the Editorial Office if you have any queries regarding this process, and I sincerely apologize for the delay and any inconvenience caused due to the high number of submissions received recently.

Comments:

Please kindly send your manuscript to English Editing Services, and attach the certificate or evidence that you are doing so as it is compulsory for IFRJ.

Thank you.

Regards,
Ms. Norhafizah Mohamad Noh
Editorial Assistant
International Food Research Journal Editorial Office

(10) 15 January 2024: Submit revised manuscript and certificate of English Editing



Andi Emelda <andi.emelda@umi.ac.id>

International Food Research Journal - Manuscript IFRJ22495.R1

1 message

International Food Research Journal <onbehalfof@manuscriptcentral.com>

Mon, Jan 15, 2024 at 1:13 PM

Reply-To: ifrj@upm.edu.my

To: andi.emelda@umi.ac.id, irma.santi@umi.ac.id, aderafniamaliah@gmail.com, dewi.yuliana@umi.ac.id

15-Jan-2024

Dear Dr. Emelda

Your revised manuscript entitled 'Nephrotoxicity Effect of Ginseng Bugis Leaves (*Talinum paniculatum* (Jacq) Gaertn) Ethanol Extract on Creatinine, Urea, and Kidney Histopathological Features' has been successfully submitted online and will be given full consideration for publication in International Food Research Journal.

Your manuscript ID is IFRJ22495.R1. Please mention this manuscript ID in all future correspondence or when contacting the Editorial Office for questions.

You can also view the status of your manuscript at any time by checking your Author Centre after logging in.

If there are any changes in your email address, please log in to ScholarOne Manuscripts at <https://mc.manuscriptcentral.com/upm-ifrj> and edit your details as appropriate.

Due to high volume of submissions, please expect some delays.

Thank you for submitting your manuscript to International Food Research Journal.

Regards,
International Food Research Journal Editorial Office

EST.		2013
Certificate of Proofreading		
Manuscript Title		
Nephrotoxicity Effect of Ginseng Bugis Leaves (<i>Talinum paniculatum</i> (Jacq) Gaertn) Ethanol Extract on Creatinine, Urea, and Kidney Histopathological Features		
Author(s)		
Emelda, A., Santi, I., Besse, S.C.D., Aderafni, A. and Yuliana, D.		
Date Issued		
January 14, 2024		
Native Proofreading Service (NPS) <u>www.native-proofreading.com</u>		
This document certifies that the manuscript listed above was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English speaking editors at Native Proofreading Service (NPS)		

1 Nephrotoxicity Effect of Ginseng Bugis Leaves (Talinum paniculatum
2 (Jacq) Gaertn) Ethanol Extract on Creatinine, Urea, and Kidney
3 Histopathological Features

4
5 ^{1*}Emelda, A., ²Santi, I., ³Besse, S.C.D., ⁴Aderafni, A. and ⁵Yuliana, D.
6
7 ^{1,2,3,4,5}Faculty of Pharmacy, Universitas Muslim Indonesia, Jl. Urip Sumiharjo
8 KM.05, Makassar 90231 Indonesia
9
10 *e-mail: andi.emelda@umi.ac.id
11
12
13

13 **Abstract**

14 The prolonged use of traditional medicines in large doses is known to potentially
15 cause organ failure, with the kidneys being particularly susceptible. Therefore,
16 this study aimed to determine the effect of Talinum paniculatum (Jacq.) Gaertn
17 leaves ethanol extract on serum creatinine and urea parameters, as well as
18 kidney histopathological features in an animal model. The rats used were
19 separated into four groups. Group I (control) was given Na CMC 1% w/v, while
20 groups II, III, and IV were administered ethanol extract of ginseng Bugis with
21 doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW, respectively. The extract
22 was induced orally for 28 days, while the serum creatinine and urea levels were
23 measured using Human Analyzer on days 0 and 29. Additionally, a necropsy for
24 organ retrieval of the kidneys was conducted on day 15. Tissue processing was
25 then carried out for histopathological examination by Hematoxylin Eosin (HE)
26 staining. The results showed that based on the One Way Anova statistical

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55 analysis on creatinine and urea levels, ethanol extract of ginseng Bugis leaves
56 in doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW had no nephrotoxic
57 effects. Regarding the histopathological features of the kidneys, the dose of 0.8
58 g/KgBW caused no abnormalities.

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60 **Keywords:** *Talinum paniculatum*, Nephrotoxic, Creatinine, Urea,
61 Histopathological

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Formatted: Indonesian

63 Introduction

64 Indonesia is renowned as a rich source of raw materials for tropical
65 medicines with potential healing properties for various diseases. The use of
66 plants as medicine has been practiced for a long period, but historical
67 documentation on this subject is limited (Nugroho *et al.*, 2022). One of the
68 indigenous plants in Indonesia is *Talinum paniculatum* Gaertn. The plant has
69 roots similar to the Panax ginseng plant, resulting in the name Ginseng. In South
70 Sulawesi Province, the plant is called ginseng Bugis (Emelda *et al.*, 2020). The
71 root is known to possess a tonic effect and is believed to have benefits for the
72 body system (Santoso *et al.*, 2016; Sulistiono *et al.*, 2017). Ginseng leaves
73 contain protein, magnesium, potassium, ascorbic acid, phenolic, flavonoids, and
74 numerous iron which provide beneficial effects (Moura *et al.*, 2020; Menezes *et*
75 *al.*, 2021). The use of medicinal herbs or traditional medicine is assumed to be
76 safe, but potential toxicity might occur either at a low or high dose during long-

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98 term usage. Therefore, studies on toxicity to plants are needed to ensure proper
99 use of medicinal plants (Bose *et al.*, 2021).

100 Inappropriate use of natural materials potentially damages the organs
101 with the kidneys being particularly susceptible. Therefore, testing the toxicity of
102 a plant is essential for its therapeutic use (Sani *et al.*, 2021).

103 A common plant often used in medication is ginseng Bugis (*Talinum*
104 *paniculatum* (Jacq). Gaertn). Previous studies reported that ginseng Bugis
105 leaves have immunomodulatory activity along with anti-rheumatoid arthritis
106 effect at doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW (Emelda *et al.*,
107 2019).

108 The kidneys, responsible for filtering approximately 25% to 30% of
109 cardiac output, are particularly vulnerable to damage due to their role in
110 processing blood containing toxic substances from the systemic circulation.
111 Therefore, the kidneys acting as a filter system are susceptible to significant
112 pathological changes (Vázquez *et al.*, 2022).

113 The safety assessment of medicinal plants is a crucial step during drug
114 development. Determining the toxicity of medicinal plants is necessary for
115 application in bioassay screening (Abubakar *et al.*, 2020).

116 Serum creatinine and urea are the standard parameters to measure
117 kidney function. Creatinine is a waste product of creatinine phosphate
118 metabolism formed in the muscles while urea is produced in the liver from amino
119 acids (Astawibawa *et al.*, 2022). Elevated levels of creatinine and urea show

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154 potential damage and a decline in kidney function. Kidney cell breakdown further
155 impairs the filtration system, leading to increased creatinine and urea levels
156 (Wolfensohn and Lloyd, 2013).

157 An alternative method to examine the kidney function is to observe the
158 histological features. This method enables the observation of crystal damage,
159 hydrops degeneration, edema, fat degeneration, congestion, necrosis,
160 inflammation, and hemorrhage. Changes in the histological features of the
161 kidneys may result in an influx of numerous compounds into the body
162 (Chinnappan *et al.*, 2019). Therefore, this study used nephrotoxicity testing to
163 investigate the effects of ethanol extract. The outcomes were evaluated using
164 creatinine and urea parameters as well as kidney histopathological changes in
165 white rats.

167 Materials and methods

168 Equipment and Materials

169 The tools used were rotavapor (rotary vacuum evaporator), (IKA®),
170 maceration vessels, animal scales (Ohaus®), digital scales (Ohaus®),
171 centrifuges (PLC series), micropipettes (Huawei®), Human Analyzer (microlab
172 300), glass objects, and microtomes.

173 The materials used included aquadest, ginseng Bugis leaves (*Talinum*
174 *paniculatum* (Jacq.) Gaertn) from South Sulawesi, 70% ethanol, Na-CMC
175 (Sodium Carboxymethyl Cellulose), urea and creatinine reagents, alcohol, xylol,

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202 hematoxylin and eosin staining (HE), paraffin, and formalin buffer.

203

204 *Methods*

205 *Extraction*

206 Simplicia powder of *Talinum paniculatum* (Jacq.) Gaertn was macerated
207 using ethanol 70%. The macerate was separated by filtration, then the solution
208 was evaporated and lyophilized to obtain a dry extract (Emelda *et al.*, 2017).

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209

210 *Suspension of ethanol extract*

211 Suspension of ethanol extract was conducted by adding successive
212 amounts of 2.4 g, 4.8 g, and 7.2 g. Subsequently, the samples were suspended
213 into 30 ml Na-CMC 1%.

Deleted: extraction process of *Talinum paniculatum* (Jacq.) Gaertn ...

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214

215 *Animal model*

216 The animal model in this study was *Rattus norvegicus* with
217 characteristics of being male, healthy and clean, Wistar strain, 8-12 weeks old,
218 and weighing 150-230 grams. Before conducting the treatment, the rats were
219 adapted to their environment within two weeks, followed by weighing and
220 marking.

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221

222 *Assay*

223 After the adaptation process, the rats fasted for 16 to 18 hours before

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238 the treatment. The blood samples were taken for the initial stage of creatinine
239 and urea measurement. Furthermore, the rats were divided into four groups,
240 each consisting of six members. Group I (control) was injected with 1% of Na-
241 CMC, while groups II, III, and IV (tested groups) were injected with ethanol
242 extract of *Talinum paniculatum* (Jacq.) Gaertn at doses of 0.8 g/KgBW, 1.6
243 g/KgBW, and 2.4 g/KgBW respectively. All the treatment steps were conducted
244 once a day for 28 days through oral injection. Finally, blood collection as well as
245 initial and final rate measurement of creatinine and urea were conducted on day
246 29 using Human Analyser (No. ethical clearance: UMI011907271).

247
248 *The production of Kidney Histology Prepare*

249 The histopathological examination was conducted through fixation of
250 kidneys using a Formalin Neutral Buffer solution of 10% followed by cutting and
251 putting into a plastic specimen pan. Furthermore, the dehydration process was
252 performed on three different concentrations of alcohol, namely 70%, 80%, and
253 90%. The next step was the purification process using xylol followed by placing
254 into paraffin and storing in a refrigerator. A microtome was used to cut paraffin
255 blocks into thin slices in the range of 5-6 µm. Finally, the slices were floated into
256 warm water, 60°C, to hinder multiplying tissues for 24 hours. Afterward, the
257 slices were lifted, placed into a glass object for Hematoxylin and Eosin (HE)
258 staining, and observed under a microscope (Abebe *et al.*, 2021; Lazuardi *et al.*,
259 2022).

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- Deleted: Absolute alcohol I, absolute II, and absolute III for 3 minutes each (Yuniartu *et al.*, 2023).
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Results and Discussion

This study used various [extract](#) doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW [on](#) male Wistar rats. The selection of [dose variations](#) [was based on](#) [a previous study in](#) which [extract](#) doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW [provided](#) immunomodulatory and anti-inflammatory activity (Emelda *et al.*, 2019). [Therefore](#), this study [aimed to determine](#) the nephrotoxic effect of these doses.

The experimental [animals](#) used in this [study were](#) male [rats](#) (*Rattus norvegicus*) [of the Wistar strain](#) [commonly often used in studies due to their wide availability](#). [According to previous reports](#), male rats have a more stable hormonal system than [females](#). [This study preferred](#) male rats over [females](#) in the experiment due to concerns [about](#) female hormone cycles [causing](#) behavioral variations that could skew the results (Lovick *et al.*, 2021; Mohd Azam *et al.*, 2022). The [effect of the extract on](#) serum creatinine and [urea](#) levels in all treatment groups [is shown in Tables 1 and 2](#).

Table 1 shows the [measurement](#) results [for](#) initial creatinine levels before treatment. Group I (control) produced a creatinine value of 0.658 ± 0.074 mg/dL [while groups II, III, and IV yielded](#) 0.653 ± 0.080 mg/dL, 0.585 ± 0.077 mg/dL, and 0.618 ± 0.069 mg/dL respectively. [These results signified that initial](#) creatinine levels for all groups were within the normal range [of](#) 0.2-0.8 mg/dL. The final creatinine level in group I (control) [was](#) 0.621 ± 0.064 mg/dL [while groups II, III,](#)

Deleted: in...n male Wistar rats. The selection of the dose variations used ...as based on a previous research...tudy in which showed that extracts at the extract doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW were able to provide...rovided immunomodulatory and anti-inflammatory activity (Emelda *et al.*, 2019), so.... Therefore, this study aims...imed to know...etermine the nephrotoxic effect at the use ... [1]

Deleted: animal...nimals used in this research was the study were male rat...ats (*Rattus norvegicus*) wistar...f the Wistar strain which is the strain most ... [2]

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and IV obtained values of 0.606 ± 0.109 mg/Kg dl, 0.660 ± 0.103 mg/dl and 0.636 ± 0.086 mg/dl respectively. Based on the results, the final creatinine level decreased in the control and the 0.8 g/KgBW extract group. An increase was observed in the extract group at a dose of 1.6 g/KgBW and 2.4 g/KgBW, but within normal values.

Deleted: which were given the extract successively at doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW for 28 days ...obtained a final creatinine value...alues of 0.606 ± 0.109 mg/Kg dl, 0.660 ± 0.103 mg/dl and 0.636 ± 0.086 mg/dl. The...respectively. Based on the results, the final creatinine level showed a decrease in creatinine levels...ecreased in the control and the 0.8 g/KgBW extract group and the 0.8 g/KgBW extract group. There was an increase in creatinine levels... An increase was observed in the extract group at a dose of 1.6 g/KgBW and 2.4 g/KgBW,...but the increase that occurred was still

... [5]

Table 2 shows the measurement results of initial urea levels before treatment. Group I (control) produced a urea value of 19.30 ± 1.55 mg/dl, while groups II, III, and IV obtained values of 19.81 ± 1.74 mg/dl, 19.51 ± 1.94 mg/dl, and 19.43 ± 1.83 mg/dl respectively. These results signified that the initial urea levels for all groups were within the normal range (8-23 mg/dl). The final urea levels in group I (control) was 19.43 ± 1.83 mg/dl, while groups II, III, and IV yielded values of 19.90 ± 1.87 mg/dl, 19.81 ± 1.88 mg/dl, and 20.0 ± 1.16 mg/dl respectively. These results showed that the final urea level had increased but within the normal range.

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... [6]

Based on the final serum creatinine and urea levels, it was concluded that the rats did not experience kidney damage. This is based on references stating that elevated concentrations of urea and creatinine in the serum show a decrease in kidney function. An increase in blood urea concentration is associated with a decrease in kidney function, resulting in decreased glomerular filtration rate and impaired excretion (Emeribe et al., 2021).

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... [7]

The results of creatinine and urea levels were statistically processed using one-way ANOVA. Both levels had $p > 0.05$, implying no significant

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... [8]

573 differences among the treatment groups.

574 Figure 1 shows the histopathological examination results of the kidneys
575 obtained using a microscope. Based on the results, there were no abnormalities
576 in the histological appearance in the control and the extract group of 0.8 g/KgBW
577 dose. However, abnormalities such as hydrophilic degeneration and
578 inflammation were observed in the extract groups of 1.6 g/KgBW and 2.4
579 g/KgBW.

580 Hydropic degeneration is characterized by inflammation of the cytoplasm
581 resulting from an accumulation of excess fluid due to a failure in maintaining
582 homeostasis and fluid regulation in cells. This condition manifests as cell
583 swelling, empty spaces (vacuoles), enlarged and condensed cells. Furthermore,
584 hydropic degeneration is a reversible cell injury with intracellular accumulation
585 that is more severe in the presence of albumin. The etiology is similar to cell
586 swelling but the intensity of pathological stimuli is more severe and the exposure
587 time is longer as commonly observed in epithelial cells.

588 Inflammatory processes are natural immune reactions crucial for the
589 defense system of the body against various hazards. This process also
590 improves the structure and function of the tissue caused by the hazard.

591 The nephrotoxic effect assessment for ginseng Bugis leaves extract at
592 doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW showed that the treatment
593 was safe for test animals up to 28 days based on the creatinine and urea
594 parameters. Further observations were carried out on the histopathological

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628 features of the kidneys. Observations in the control group and at a dose of 0.8
629 g/KgBW did not show any abnormalities. At doses of 1.6 g/KgBW and 2.4
630 g/KgBW, hydrophilic degeneration and inflammation were observed as a natural
631 body defense system response to disturbances.

632 In previous studies, extract doses of 0.05 g/KgBW, 0.1 g/KgBW, and
633 0.15 g/KgBW, showed immunomodulatory and anti-rheumatoid activity.
634 Additionally, the extract has shown aphrodisiac effects on the libido of Wistar
635 male rats (*Rattus norvegicus*) at a dose of 55 mg given orally (Emelda *et al.*,
636 2020; Septiani *et al.*, 2021). Based on the results, extract doses below 0.8
637 g/KgBW do not have a nephrotoxic effect.

638
639 **Conclusion**

640 In conclusion, the administration of ginseng bugis leaves (*Talinum*
641 *paniculatum* (Jacq.) Gaertn) ethanol extract at doses of 0.8 g/KgBW, 1.6
642 g/KgBW, and 2.4 g/KgBW for 28 days in white rats (*Rattus norvegicus*) had no
643 nephrotoxic effect based on creatinine and urea parameters. In addition, the 0.8
644 g/KgBW dose caused no abnormalities in the renal histology.

645
646 **References**

647 Abebe, S., Asres, K., Bekuretsion., Abebe, A., Bikila, D., Seyoum, G. 2021. Sub-
648 chronic toxicity of ethanol leaf extract of *Syzygium guineense* on the

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Deleted: because it is below 0.8 g/KgBW.¶ Furthermore, cytoplasmic nodules occur due to degenerating hydrophilic because it excesses fluid volume leading to failure in maintaining homeostasis and fluid regulation in cells. Hydrophilic degeneration is characterized by cell swelling, vacant spaces (vacuoles), enlarged and pressed cells. Hydrophilic degeneration is a reversible cell injury with more intracellular accumulation if accompanied by albumin. The nodules on etiology are similar to cells nodule. However, it is slightly heavier on the intensity of pathological stimulation and has a longer period of exposure to pathological stimulation. Hydrophilic degeneration commonly happens in epithelial cells (Wolfensohn and Lloyd, M., 2013). The process of inflammation or an inflammatory reaction is a key body mechanism to defend itself from various risks that impair the body's balance system, improve the structure and hinder it from disrupting the tissue (Chen *et al.*, 2018). This is thought to have occurred at doses of 1.6 g/KgBW and 2.4 g/BW because creatinine and ureum levels at these doses were still at normal levels

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690 biochemical parameters and histopathology of liver and kidney in the
691 rats. Elsevier Toxicology Reports 8: 822-828.

692 Abubakar, A. R., Sani, I. H., Malami, S. and Yaro, A. H. 2020. Sub-chronic safety
693 assessment of crude methanol extract of *Solanum aethiopicum* (L.) fruit
694 in rats. Trends in Science & Technology Journal 5(3): 716-719.

695 Astawibawa, P. O., Suarsana, I. N. and Suartini, G. A. A. 2022. The Influence of
696 peel extract *Musa paradisiaca* formatypica against kidney histology, [urea](#)
697 levels, and creatinine *Rattus novergicus* after intensive exercise. Buletin
698 Veteriner Udayana 14(5): 578-585.

699 Bose, S., Datta R. and Kirilin, W. G. 2021. Toxicity Studies Related to Medicinal
700 Plants. Springer Nature Singapore Pte Ltd.

701 Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X. and
702 Zhao, L. 2018. Inflammatory responses and inflammation associated
703 diseases in organs. Oncotarget 9(6): 7204-7218.

704 Chinnappan, S. M., George, A., Thaggikuppe, P., Choudhary, Y., Vandana, K.
705 C., Ramani, Y. and Dewangan, R. 2019. Nephroprotective effect of
706 herbal extract eurycoma longifolia on paracetamol-induced
707 nephrotoxicity in rats. Evidence-Based Complementary and Alternative
708 Medicine. 2019: 1-6.

709 Emelda, A., Auliawati and Mushli. 2019. Aktivitas daun ginseng bugis (*Talinum*
710 *paniculatum*) terhadap respon hipersensitivitas secara pra klinik.
711 Proceeding of the National Conference on Pharmacy, p. 116-118.

Deleted: ureum

713 Makassar: Indonesia

714 Emelda, A., Auliawati, Arman, Taufik, M. and Kurniawaty, R. 2020.

715 Immunomodulator activity and antirheumatoid arthritis extract of ethyl

716 acetate ginseng Bugis (*Talinum Paniculatum* (Jacq.) Gaertn). Journal of

717 Global Pharma Technology 12(02): 246-251.

718 Emelda, A., Wahid, S., Massi, N. and Wahyudin, E. 2017. Different doses of

719 purified extract of the cacao bean (*Theobroma cacao*) to IgM antibody

720 profile in wistar rat stimulated by ovalbumin antigen. International Food

721 Research Journal 24(3): 1321-1323.

722 Emeribe, A. U., Anyanwu, S. O., Isong, I. K., Bassey, U. R., Inyang, I. J.,

723 Ibeneme, E. O., Asemota, E. A., Okhormhe, Z., Icha, B. and Abdullahi, I.

724 N. 2021. Phytochemical analysis and toxicological evaluation of the

725 ethanolic Leaves extract of *Hypoestes rosea* on the morphology and

726 biochemical indices of the kidneys of albino wistar rats. Saudi Journal of

727 Biological Sciences 28: 6748-6755.

728 Lazuardi, A. Z., Suprihatin, T. and Tana, S. 2022. Histopathology of pre-diabetic

729 white rat (*Rattus norvegicus L.*) renal after treatment with turmeric

730 powder and organic quail eggs. Borneo Journal of Resource Science

731 and Technology 12(2): 119-133.

732 Lovick, T. A. and Zangrossi, J. H. 2021. Effect of estrous cycle on behavior of

733 females in rodent test of anxiety. Frontiers in Psychiatry 12: 1-19.

734 Menezes, F. D. A. B., Ishizawa, T. A., Souto, L. R. F. and Oliveira, T. F. 2021.

735 *Talinum paniculatum* (Jacq.) Gaertn. leaves - source of nutrients,
736 antioxidant and antibacterial potentials. *Acta Scientiarum Polonorum*
737 *Technologia Alimentaria* 20(3): 253-63.

738 Mohd Azam, N. S., Che Soh, N. A., Rapi, H. S., Ismail, N., Jusoh, A. Z., Haron,
739 M. N., Ali, A. M., Maulidiani, M. and Ismail, W. I. 2022. Invivo study of
740 subacute oral toxicity of kelulut honey. *International Food Research*
741 *Journal* 29(5): 1188-1204.

742 Moura, I. O., Santana, C. C., Lourenço, Y. R. F., Souza, M. F., Silva A. R. S. T.,
743 Dolabella, S. S. 2020. Chemical characterization, antioxidant activity and
744 cytotoxicity of the unconventional food plants: sweet potato (*Ipomoea*
745 *batatas* (L.) Lam.) leaf, major gomes (*Talinum paniculatum* (Jacq.)
746 Gaertn.) and caruru (*Amaranthus deflexus* L.). *Waste and Biomass*
747 *Valorization* 12(5): 2407-31.

748 Nugroho, Y., Soendjoto, M. A., Suyanto., Matatula, J., Alam, S. and Wirabuana,
749 P. Y. A. D. 2022. Traditional medicinal plants and their utilization by local
750 communities around lambung mangkurat education forest, South
751 Kalimantan, Indonesia. *Biodiversitas* 23 (1): 306-314.

752 Sani, I. H., Malami, S., Yaro, A. H. and Akbar, A. R. 2021. Sub-chronic safety
753 assessment of crude methanol leaf extract of *Terminalia macroptera*
754 (Guill & Perr) in rats. *Trends in Natural Products Research* 2(1): 46-54.

755 Santoso, A. M., Amin, M., Sumitro, S. B. and Lukiati, B. 2016. Determination of
756 java ginseng (*Talinum paniculatum*) ginsenoside. *Proceeding of the 3rd*

757 International Biology Conference, p.3-6. Bandung: Indonesia.

758 Septiani, D., Angelina, M. and Kusmana, D. 2021. Aphrodisiac activity of java
759 ginseng (*Talinum paniculatum* Gaertn.) leaves ethanolic extract on libido
760 wistar male rats (*Rattus norvegicus*). *Hermia Health Sciences Journal*
761 1(1): 27-32.

762 Sulistiono., Alfinda, N. K. and Agus, M. S. 2017. *Talinum paniculatum* (Jacq)
763 Gaertn (Java ginseng) production using vesicular-arbuscular
764 mycorrhizal. *International Journal of Applied Biology* 1(2): 76-81.

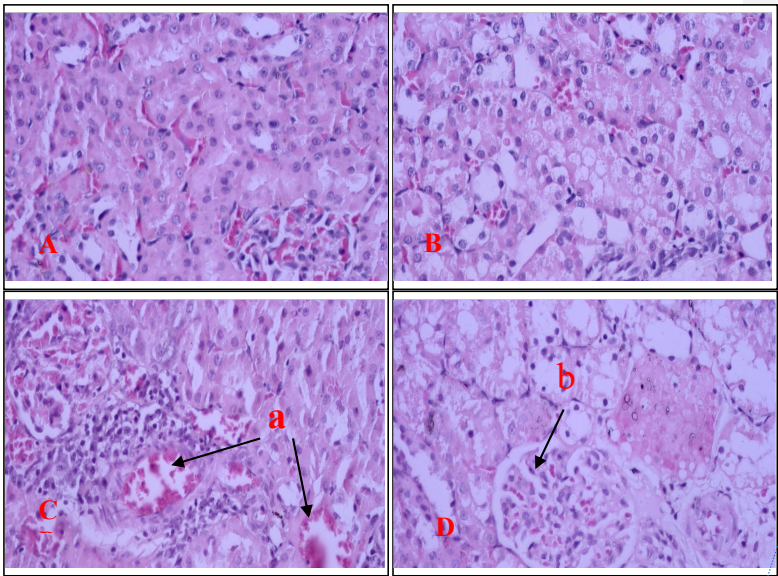
765 Vázquez, M. A. T., Zoé, P., Morreeuw., Hernández, J. E. S., Martínez, A. C.,
766 Sabath, E., Elda, M., Martínez, M., Iqbal, H. M. N. and Saldívar, R. P.
767 2022. Nephroprotective plants: A review on the use in pre-renal and post-
768 renal diseases. *Plants* 11(6): 818.

769 Wolfensohn, S. and Lloyd, M. 2013. *Handbook of laboratory animal*.
770 *management and welfare*. 4th Ed. West Sussex: Wiley-Blackwell.

771 Yuniarti, E., Des, M., Fitria, D. and Mayorita, P. 2023. Cardiac histopathology of
772 male mice (*Mus musculus* L.) given maximum physical exercise and
773 gambir catechin (*Uncaria gambir* Roxb.). *Proceedings of the 3rd*
774 *International Conference on Biology, Science and Education*, p. 113-
775 120. Padang: Indonesia.

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Figure 1. Kidney Histology. A: Control Group; B: Extract 0.8 g/KgBW; C: Extract 1.6 g/KgBW; D: Extract 2.4 g/KgBW; a: [Inflammation](#); b: Hydrophilic degeneration

Table 1. Percent increase in serum creatinine levels in all treatment groups

Treatment Groups	Average Level of creatinine (mg/dL)		% Increasing Level
	Initial $\pm$ SD	Final $\pm$ SD	
I Control	0.658 $\pm$ 0.074	0.621 $\pm$ 0.064	-5.958%
II Extract 0.8 g/KgBW	0.653 $\pm$ 0.080	0.606 $\pm$ 0.109	-7.755%
III Extract 1.6 g/KgBW	0.585 $\pm$ 0.077	0.660 $\pm$ 0.103	12.878%
IV Extract 2.4 g/KgBW	0.618 $\pm$ 0.069	0.636 $\pm$ 0.086	2.830%

Table 2. The results of measuring the average levels of [urea](#) and increased levels of creatinine

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Treatment Groups	Average Levels of Urea (mg/dL)		% Increase Level
	Initial ± SD	Final ± SD	
I Control	19.30±1.55	19.43±1.83	0.66%
II Extract 0.8 g/KgBW	19.81±1.74	19.90±1.87	0.45%
III Extract 1.6 g/KgBW	19.51±1.94	19.81±1.88	1.51%
IV Extract 2.4 g/KgBW	19.43±1.83	20.0±1.16	2.85%

Deleted: Ureum

**Nephrotoxicity Effect of Ginseng Bugis Leaves (*Talinum paniculatum*
(Jacq) Gaertn) Ethanol Extract on Creatinine, Urea, and Kidney
Histopathological Features**

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Abstract

The prolonged use of traditional medicines in large doses is known to potentially cause organ failure, with the kidneys being particularly susceptible. Therefore, this study aimed to determine the effect of *Talinum paniculatum* (Jacq.) Gaertn leaves ethanol extract on serum creatinine and urea parameters, as well as kidney histopathological features in an animal model. The rats used were separated into four groups. Group I (control) was given Na CMC 1% w/v, while groups II, III, and IV were administered ethanol extract of ginseng Bugis with doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW respectively. The extract was induced orally for 28 days, while the serum creatinine and urea levels were measured using Human Analyzer on days 0 and 29. Additionally, a necropsy for organ retrieval of the kidneys was conducted on day 15. Tissue processing was then carried out for histopathological examination by Hematoxylin Eosin (HE) staining. The results showed that based on the One Way Anova statistical

27 analysis on creatinine and urea levels, ethanol extract of ginseng Bugis leaves
28 in doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW had no nephrotoxic
29 effects. Regarding the histopathological features of the kidneys, the dose of 0.8
30 g/KgBW caused no abnormalities.

31

32 **Keywords:** *Talinum paniculatum*, Nephrotoxic, Creatinine, Urea,
33 Histopathological

34

35 **Introduction**

36 Indonesia is renowned as a rich source of raw materials for tropical
37 medicines with potential healing properties for various diseases. The use of
38 plants as medicine has been practiced for a long period, but historical
39 documentation on this subject is limited (Nugroho *et al.*, 2022). One of the
40 indigenous plants in Indonesia is *Talinum paniculatum* Gaertn. The plant has
41 roots similar to the Panax ginseng plant, resulting in the name Ginseng. In South
42 Sulawesi Province of Indonesia, the plant is called ginseng Bugis (Emelda *et al.*,
43 2020). The root is known to possess a tonic effect and is believed to have
44 benefits for the body system (Santoso *et al.*, 2016; Sulistiono *et al.*, 2017).
45 Ginseng leaves contain protein, magnesium, potassium, ascorbic acid,
46 phenonugric, flavonoids, and numerous iron which provide beneficial effects
47 (Moura *et al.*, 2020; Menezes *et al.*, 2021). The use of medicinal herbs or
48 traditional medicine is assumed to be safe, but potential toxicity might occur

49 either at a low or high dose during long-term usage. Therefore, studies on
50 toxicity to plants are needed to ensure proper use of medicinal plants (Bose *et*
51 *al.*, 2021).

52 Inappropriate use of natural materials potentially damages the organs,
53 with the kidneys being particularly susceptible. Therefore, testing the toxicity of
54 a plant is essential for its therapeutic use (Sani *et al.*, 2021).

55 A common plant often used in medication is ginseng Bugis (*Talinum*
56 *paniculatum* (Jacq). Gaertn). Previous studies reported that ginseng Bugis
57 leaves have immunomodulatory activity, along with anti-rheumatoid arthritis
58 effect at doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW (Emelda *et al.*,
59 2019).

60 The kidneys, responsible for filtering approximately 25% to 30% of
61 cardiac output, are particularly vulnerable to damage due to their role in
62 processing blood containing toxic substances from the systemic circulation.
63 Therefore, the kidneys acting as a filter system are susceptible to significant
64 pathological changes (Vázquez *et al.*, 2022).

65 The safety assessment of medicinal plants is a crucial step during drug
66 development. Determining the toxicity of medicinal plants is necessary for
67 application in bioassay screening (Abubakar *et al.*, 2020).

68 Serum creatinine and urea are the standard parameters to measure
69 kidney function. Creatinine is a waste product of creatinine phosphate
70 metabolism formed in the muscles while urea is produced in the liver from amino

71 acids (Astawibawa *et al.*, 2022). Elevated levels of creatinine and urea show
72 potential damage and a decline in kidney function. Kidney cell breakdown further
73 impairs the filtration system, leading to increased creatinine and urea levels
74 (Wolfensohn and Lloyd, 2013).

75 An alternative method to examine the kidney function is to observe the
76 histological features. This method enables the observation of crystal damage,
77 hydrops degeneration, edema, fat degeneration, congestion, necrosis,
78 inflammation, and hemorrhage. Changes in the histological features of the
79 kidneys may result in an influx of numerous compounds into the body
80 (Chinnappan *et al.*, 2019). Therefore, this study used nephrotoxicity testing to
81 investigate the effects of ethanol extract. The outcomes were evaluated using
82 creatinine and urea parameters as well as kidney histopathological changes in
83 white rats.

84

85 **Materials and methods**

86 *Equipment and Materials*

87 The tools used were rotavapor (rotary vacuum evaporator), (IKA®),
88 maceration vessels, animal scales (Ohaus®), digital scales (Ohaus®),
89 centrifuges (PLC series), micropipettes (Huawei®), Human Analyzer (microlab
90 300), glass objects, and microtomes.

91 The materials used included aquadest, ginseng Bugis leaves (*Talinum*
92 *paniculatum* (Jacq.) Gaertn) from South Sulawesi, 70% ethanol, Na-CMC

93 (Sodium Carboxymethyl Cellulose), urea and creatinine reagents, alcohol, xylol,
94 hematoxylin and eosin staining (HE), paraffin, and formalin buffer.

95

96 *Methods*

97 *Extraction*

98 Simplicia powder of *Talinum paniculatum* (Jacq.) Gaertn was macerated
99 using ethanol 70%. The macerate was separated by filtration, then the solution
100 was evaporated and lyophilized to obtain a dry extract (Emelda *et al.*, 2017).

101

102 *Suspension of ethanol extract*

103 Suspension of ethanol extract was conducted by adding successive
104 amounts of 2.4 g, 4.8 g, and 7.2 g. Subsequently, the samples were suspended
105 into 30 ml Na-CMC 1%.

106

107 *Animal model*

108 The animal model in this study was *Rattus norvegicus* with
109 characteristics of being male, healthy and clean, Wistar strain, 8-12 weeks old,
110 and weighing 150-230 grams. Before conducting the treatment, the rats were
111 adapted to their environment within two weeks, followed by weighing and
112 marking.

113

114 *Assay*

115 After the adaptation process, the rats fasted for 16 to 18 hours before
116 the treatment. The blood samples were taken for the initial stage of creatinine
117 and urea measurement. Furthermore, the rats were divided into four groups,
118 each consisting of six members. Group I (control) was injected with 1% of Na-
119 CMC, while groups II, III, and IV (tested groups) were injected with ethanol
120 extract of *Talinum paniculatum* (Jacq.) Gaertn at doses of 0.8 g/KgBW, 1.6
121 g/KgBW, and 2.4 g/KgBW respectively. All the treatment steps were conducted
122 once a day for 28 days through oral injection. Finally, blood collection as well as
123 initial and final rate measurement of creatinine and urea were conducted on day
124 29 using a Human Analyser (Ethical clearance number: UMI011907271).

125

126 *The production of Kidney Histology Prepare*

127 The histopathological examination was conducted through fixation of
128 kidneys using a Formalin Neutral Buffer solution of 10% followed by cutting and
129 putting into a plastic specimen pan. Furthermore, the dehydration process was
130 performed on three different concentrations of alcohol, namely 70%, 80%, and
131 90%. The next step was the purification process using xylol followed by placing
132 it into paraffin and storing in a refrigerator. A microtome was used to cut paraffin
133 blocks into thin slices in the range of 5-6 μ m. Finally, the slices were floated into
134 warm water, 60°C, to hinder multiplying tissues for 24 hours. Afterward, the
135 slices were lifted, placed into a glass object for Hematoxylin and Eosin (HE)
136 staining, and observed under a microscope (Abebe *et al.*, 2021; Lazuardi *et al.*,

137 2022; Yuniarti *et al.*, 2023).

138

139 **Results and Discussion**

140 This study used various extract doses of 0.8 g/KgBW, 1.6 g/KgBW, and
141 2.4 g/KgBW on male Wistar rats. The selection of dose variations was based on
142 a previous study in which extract doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4
143 g/KgBW provided immunomodulatory and anti-inflammatory activity (Emelda *et*
144 *al.*, 2019). Therefore, this study aimed to determine the nephrotoxic effect of
145 these doses.

146 The experimental animals used in this study were male rats (*Rattus*
147 *norvegicus*) of the Wistar strain commonly often used in studies due to their wide
148 availability. According to previous reports, male rats have a more stable
149 hormonal system than females. This study preferred male rats over females in
150 the experiment due to concerns about female hormone cycles causing
151 behavioral variations that could skew the results (Lovick *et al.*, 2021; Mohd
152 Azam *et al.*, 2022). The effect of the extract on serum creatinine and urea levels
153 in all treatment groups is shown in Tables 1 and 2.

154 Table 1 shows the measurement results for initial creatinine levels before
155 treatment. Group I (control) produced a creatinine value of 0.658 ± 0.074 mg/dl,
156 while groups II, III, and IV yielded 0.653 ± 0.080 mg/dl, 0.585 ± 0.077 mg/dl, and
157 0.618 ± 0.069 mg/dl respectively. These results signified that initial creatinine
158 levels for all groups were within the normal range of 0.2-0.8 mg/dl. The final

159 creatinine level in group I (control) was 0.621 ± 0.064 mg/dl, while groups II, III,
160 and IV obtained values of 0.606 ± 0.109 mg/Kg dl, 0.660 ± 0.103 mg/dl and
161 0.636 ± 0.086 mg/dl respectively. Based on the results, the final creatinine level
162 decreased in the control and the 0.8 g/KgBW extract group. An increase was
163 observed in the extract group at a dose of 1.6 g/KgBW and 2.4 g/KgBW but
164 within normal values.

165 Table 2 shows the measurement results of initial urea levels before
166 treatment. Group I (control) produced a urea value of 19.30 ± 1.55 mg/dl, while
167 groups II, III, and IV obtained values of 19.81 ± 1.74 mg/dl, 19.51 ± 1.94 mg/dl,
168 and 19.43 ± 1.83 mg/dl respectively. These results signified that the initial urea
169 levels for all groups were within the normal range (8-23 mg/dl). The final urea
170 levels in group I (control) was 19.43 ± 1.83 mg/dl, while groups II, III, and IV
171 yielded values of 19.90 ± 1.87 mg/dl, 19.81 ± 1.88 mg/dl, and 20.0 ± 1.16 mg/dl
172 respectively. These results showed that the final urea level had increased but
173 within the normal range.

174 Based on the final serum creatinine and urea levels, it was concluded
175 that the rats did not experience kidney damage. This is based on references
176 stating that elevated concentrations of urea and creatinine in the serum show a
177 decrease in kidney function. An increase in blood urea concentration is
178 associated with a decrease in kidney function, resulting in decreased glomerular
179 filtration rate and impaired excretion (Emeribe *et al.*, 2021).

180 The results of creatinine and urea levels were statistically processed

181 using one-way ANOVA. Both levels had $p>0.05$, implying no significant
182 differences among the treatment groups.

183 Figure 1 shows the histopathological examination results of the kidneys
184 obtained using a microscope. Based on the results, there were no abnormalities
185 in the histological appearance in the control and the extract group of 0.8 g/KgBW
186 dose. However, abnormalities such as hydrophilic degeneration and
187 inflammation were observed in the extract groups of 1.6 g/KgBW and 2.4
188 g/KgBW.

189 Hydropic degeneration is characterized by inflammation of the cytoplasm
190 resulting from an accumulation of excess fluid due to a failure in maintaining
191 homeostasis and fluid regulation in cells. This condition manifests as cell
192 swelling, empty spaces (vacuoles), enlarged and condensed cells. Furthermore,
193 hydropic degeneration is a reversible cell injury with intracellular accumulation
194 that is more severe in the presence of albumin. The etiology is similar to cell
195 swelling but the intensity of pathological stimuli is more severe and the exposure
196 time is longer, as commonly observed in epithelial cells.

197 Inflammatory processes are natural immune reactions crucial for the
198 defense system of the body against various hazards. This process also
199 improves the structure and function of the tissue caused by the hazard.

200 The nephrotoxic effect assessment for ginseng Bugis leaves extract at
201 doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW showed that the treatment
202 was safe for test animals up to 28 days based on the creatinine and urea

parameters. Further observations were carried out on the histopathological features of the kidneys. Observations in the control group and at a dose of 0.8 g/KgBW did not show any abnormalities. At doses of 1.6 g/KgBW and 2.4 g/KgBW, hydrophilic degeneration and inflammation were observed as a natural body defense system response to disturbances.

In previous studies, extract doses of 0.05 g/KgBW, 0.1 g/KgBW, and 0.15 g/KgBW showed immunomodulatory and anti-rheumatoid activity. Additionally, the extract has shown aphrodisiac effects on the libido of Wistar male rats (*Rattus norvegicus*) at a dose of 55 mg given orally (Emelda *et al.*, 2020; Septiani *et al.*, 2021). Based on the results, extract doses below 0.8 g/KgBW do not have a nephrotoxic effect.

Conclusion

In conclusion, the administration of ginseng bugis leaves (*Talinum paniculatum* (Jacq.) Gaertn) ethanol extract at doses of 0.8 g/KgBW, 1.6 g/KgBW, and 2.4 g/KgBW for 28 days in white rats (*Rattus norvegicus*) had no nephrotoxic effect based on creatinine and urea parameters. In addition, the 0.8 g/KgBW dose caused no abnormalities in the renal histology.

References

Abebe, S., Asres, K., Bekuretsion., Abebe, A., Bikila, D., Seyoum, G. 2021. Sub-chronic toxicity of ethanol leaf extract of *Syzygium guineense* on the

225 biochemical parameters and histopathology of liver and kidney in the
 226 rats. Elsevier Toxicology Reports 8: 822-828.

227 Abubakar, A. R., Sani, I. H., Malami, S. and Yaro, A. H. 2020. Sub-chronic safety
 228 assessment of crude methanol extract of *Solanum aethiopicum* (L.) fruit
 229 in rats. Trends in Science & Technology Journal 5(3): 716-719.

230 Astawibawa, P. O., Suarsana, I. N. and Suartini, G. A. A. 2022. The Influence of
 231 peel extract *Musa paradisiaca* formatypica against kidney histology, urea
 232 levels, and creatinine *Rattus novergicus* after intensive exercise. Buletin
 233 Veteriner Udayana 14(5): 578-585.

234 Bose, S., Datta R. and Kirlin, W. G. 2021. Toxicity Studies Related to Medicinal
 235 Plants. Springer Nature Singapore Pte Ltd.

236 Chinnappan, S. M., George, A., Thaggikuppe, P., Choudhary, Y., Vandana, K.
 237 C., Ramani, Y. and Dewangan, R. 2019. Nephroprotective effect of
 238 herbal extract *Eurycoma longifolia* on paracetamol-induced
 239 nephrotoxicity in rats. Evidence-Based Complementary and Alternative
 240 Medicine. 2019: 1-6.

241 Emelda, A., Auliawati and Mushli. 2019. Aktivitas daun ginseng bugis (*Talinum*
 242 *paniculatum*) terhadap respon hipersensitivitas secara pra klinik.
 243 Proceeding of the National Conference on Pharmacy, p. 116-118.
 244 Makassar: Indonesia

245 Emelda, A., Auliawati, Arman, Taufik, M. and Kurniawaty, R. 2020.
 246 Immunomodulator activity and antirheumatoid arthritis extract of ethyl

247 acetate ginseng Bugis (*Talinum Paniculatum* (Jacq.) Gaertn). Journal of
 248 Global Pharma Technology 12(02): 246-251.

249 Emelda, A., Wahid, S., Massi, N. and Wahyudin, E. 2017. Different doses of
 250 purified extract of the cacao bean (*Theobroma cacao*) to IgM antibody
 251 profile in wistar rat stimulated by ovalbumin antigen. International Food
 252 Research Journal 24(3): 1321-1323.

253 Emeribe, A. U., Anyanwu, S. O., Isong, I. K., Bassey, U. R., Inyang, I. J.,
 254 Ibeneme, E. O., Asemota, E. A., Okhormhe, Z., Icha, B. and Abdullahi, I.
 255 N. 2021. Phytochemical analysis and toxicological evaluation of the
 256 ethanolic Leaves extract of *Hypoestes rosea* on the morphology and
 257 biochemical indices of the kidneys of albino wistar rats. Saudi Journal of
 258 Biological Sciences 28: 6748-6755.

259 Lazuardi, A. Z., Suprihatin, T. and Tana, S. 2022. Histopathology of pre-diabetic
 260 white rat (*Rattus norvegicus* L.) renal after treatment with turmeric
 261 powder and organic quail eggs. Borneo Journal of Resource Science
 262 and Technology 12(2): 119-133.

263 Lovick, T. A. and Zangrossi, J. H. 2021. Effect of estrous cycle on behavior of
 264 females in rodent test of anxiety. Frontiers in Psychiatry 12: 1-19.

265 Menezes, F. D. A. B., Ishizawa, T. A., Souto, L. R. F. and Oliveira, T. F. 2021.
 266 *Talinum paniculatum* (Jacq.) Gaertn. leaves - source of nutrients,
 267 antioxidant and antibacterial potentials. Acta Scientiarum Polonorum
 268 Technologia Alimentaria 20(3): 253-63.

269 Mohd Azam, N. S., Che Soh, N. A., Rapi, H. S., Ismail, N., Jusoh, A. Z., Haron,
 270 M. N., Ali, A. M., Maulidiani, M. and Ismail, W. I. 2022. Invivo study of
 271 subacute oral toxicity of kelulut honey. International Food Research
 272 Journal 29(5): 1188-1204.

273 Moura, I. O., Santana, C. C., Lourenço, Y. R. F., Souza, M. F., Silva A. R. S. T.,
 274 Dolabella, S. S. 2020. Chemical characterization, antioxidant activity and
 275 cytotoxicity of the unconventional food plants: sweet potato (*Ipomoea*
 276 *batatas* (L.) Lam.) leaf, major gomes (*Talinum paniculatum* (Jacq.)
 277 Gaertn.) and caruru (*Amaranthus deflexus* L.). Waste and Biomass
 278 Valorization 12(5): 2407-31.

279 Nugroho, Y., Soendjoto, M. A., Suyanto., Matatula, J., Alam, S. and Wirabuana,
 280 P. Y. A. D. 2022. Traditional medicinal plants and their utilization by local
 281 communities around lambung mangkurat education forest, South
 282 Kalimantan, Indonesia. Biodiversitas 23 (1): 306-314.

283 Sani, I. H., Malami, S., Yaro, A. H. and Akbar, A. R. 2021. Sub-chronic safety
 284 assessment of crude methanol leaf extract of *Terminalia macroptera*
 285 (Guill & Perr) in rats. Trends in Natural Products Research 2(1): 46-54.

286 Santoso, A. M., Amin, M., Sumitro, S. B. and Lukiati, B. 2016. Determination of
 287 java ginseng (*Talinum paniculatum*) ginsenoside. Proceeding of the 3rd
 288 International Biology Conference, p.3-6. Bandung: Indonesia.

289 Septiani, D., Angelina, M. and Kusmana, D. 2021. Aphrodisiac activity of java
 290 ginseng (*Talinum paniculatum* Gaertn.) leaves ethanolic extract on libido

291 wistar male rats (*Rattus norvegicus*). Hermina Health Sciences Journal
292 1(1): 27-32.

293 Sulistiono., Alfinda, N. K. and Agus, M. S. 2017. *Talinum paniculatum* (Jacq)
294 Gaertn (Java ginseng) production using vesicular-arbuscular
295 mycorrhizal. International Journal of Applied Biology 1(2): 76-81.

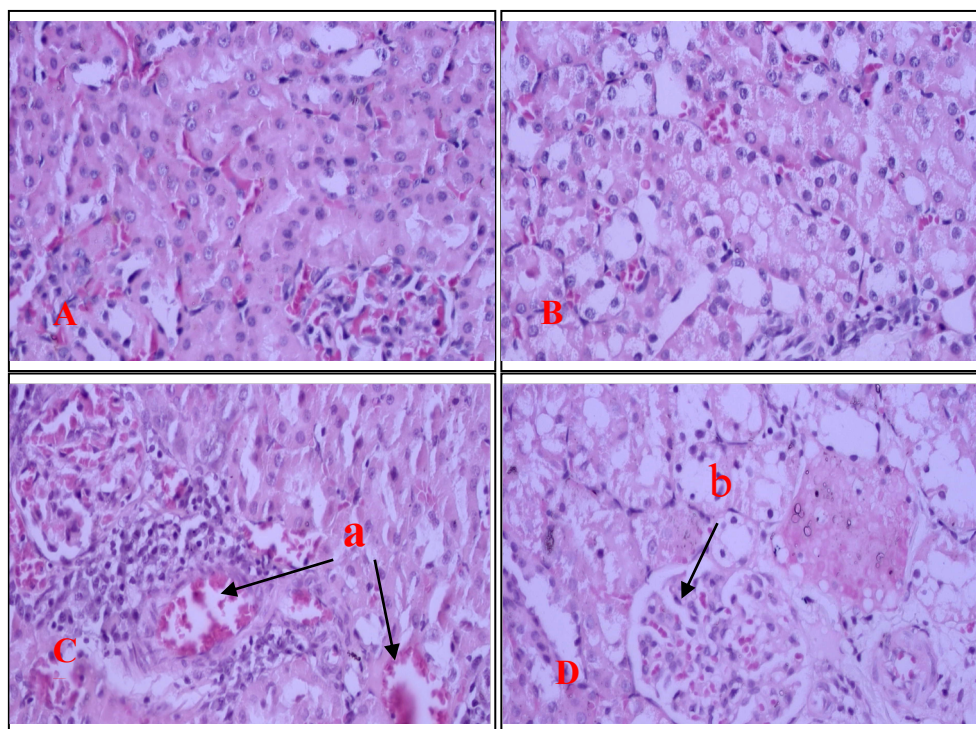
296 Vázquez, M. A. T., Zoé, P., Morreeuw., Hernández, J. E. S., Martínez, A. C.,
297 Sabath, E., Elda, M., Martínez, M., Iqbal, H. M. N. and Saldívar, R. P.
298 2022. Nephroprotective plants: A review on the use in pre-renal and post-
299 renal diseases. Plants 11(6): 818.

300 Wolfensohn, S. and Lloyd, M. 2013. Handbook of laboratory animal.
301 management and welfare. 4th Ed. West Sussex: Wiley-Blackwell.

302 Yuniarti, E., Des, M., Fitria, D. and Mayorita, P. 2023. Cardiac histopathology of
303 male mice (*Mus musculus* L.) given maximum physical exercise and
304 gambir catechin (*Uncaria gambir* Roxb.). Proceedings of the 3rd
305 International Conference on Biology, Science and Education, p. 113-
306 120. Padang: Indonesia.

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Figure 1. Kidney Histology. A: Control Group; B: Extract 0.8 g/KgBW; C: Extract 1.6 g/KgBW; D: Extract 2.4 g/KgBW; a: Inflammation; b: Hydrophilic degeneration

316

Table 1. Percent increase in serum creatinine levels in all treatment groups

317

Treatment Groups	Average Level of creatinine (mg/dL)		% Increasing Level
	Initial $\pm$ SD	Final $\pm$ SD	
I Control	0.658 $\pm$ 0.074	0.621 $\pm$ 0.064	-5.958%
II Extract 0.8 g/KgBW	0.653 $\pm$ 0.080	0.606 $\pm$ 0.109	-7.755%
III Extract 1.6 g/KgBW	0.585 $\pm$ 0.077	0.660 $\pm$ 0.103	12.878%
IV Extract 2.4 g/KgBW	0.618 $\pm$ 0.069	0.636 $\pm$ 0.086	2.830%

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Table 2. The results of measuring the average levels of urea and increased levels of creatinine

Treatment Groups	Average Levels of Urea (mg/dL)		% Increasing Level
	Initial $\pm$ SD	Final $\pm$ SD	
I Control	19.30 $\pm$ 1.55	19.43 $\pm$ 1.83	0.66%
II Extract 0.8 g/KgBW	19.81 $\pm$ 1.74	19.90 $\pm$ 1.87	0.45%
III Extract 1.6 g/KgBW	19.51 $\pm$ 1.94	19.81 $\pm$ 1.88	1.51%
IV Extract 2.4 g/KgBW	19.43 $\pm$ 1.83	20.0 $\pm$ 1.16	2.85%

323

(11) 22 January 2024: Decision on manuscript IFRJ22495.R1: Accepted (LoA)



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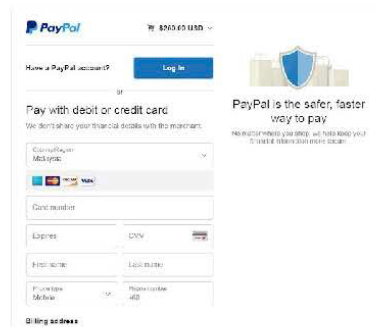
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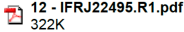
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