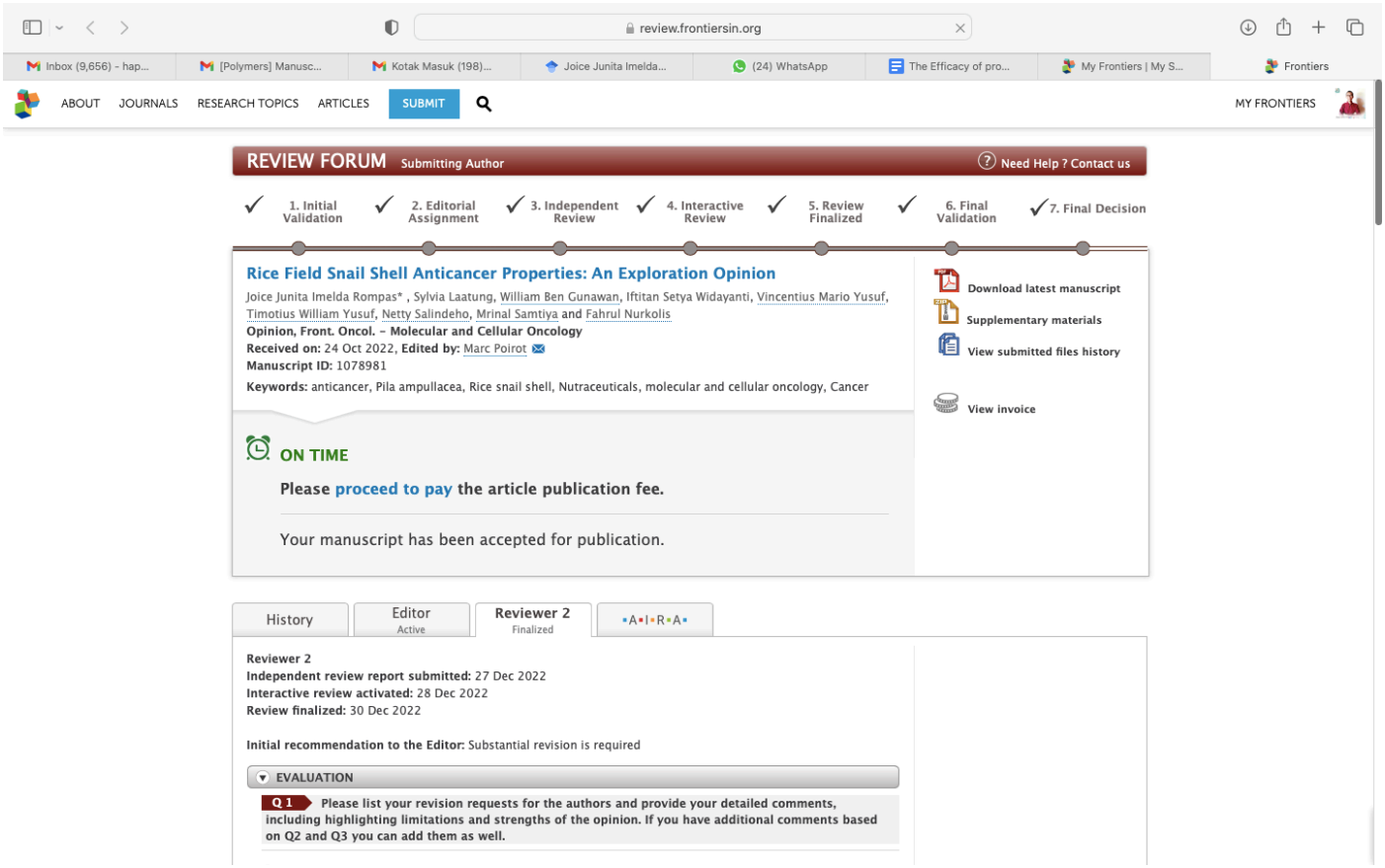
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6. Final Validation
7. Final Decision
Rice Field Snail Shell Anticancer Properties: An Exploration Opinion
Joice Junita Imelda Rompas* , Sylvia Laatung, William Ben Gunawan, Iftitan Setya Widayanti, Vincentius Mario Yusuf, Timotius William Yusuf, Netty Salindeho, Mrinal Samtiya and Fahrul Nurkolis
Opinion, Front. Oncol. - Molecular and Cellular Oncology
Received on: 24 Oct 2022, Edited by: Marc Poirot
Manuscript ID: 1078981
Keywords: anticancer, Pila ampullacea, Rice snail shell, Nutraceuticals, molecular and cellular oncology, Cancer
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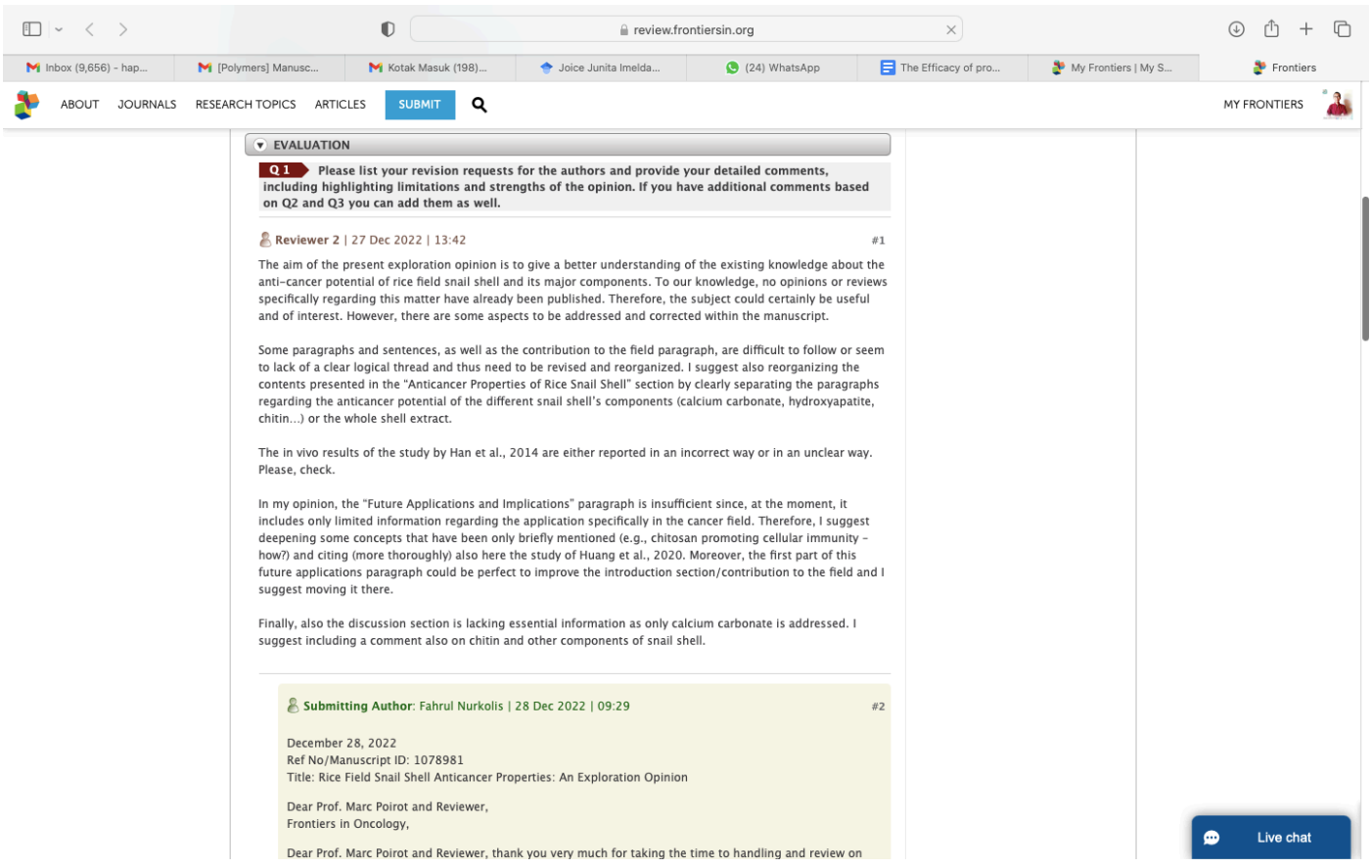
Independent review report submitted: 27 Dec 2022
Interactive review activated: 28 Dec 2022
Review finalized: 30 Dec 2022
Initial recommendation to the Editor: Substantial revision is required
EVALUATION
Q 1 Please list your revision requests for the authors and provide your detailed comments, including highlighting limitations and strengths of the opinion. If you have additional comments based on Q2 and Q3 you can add them as well.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Q 1 Please list your revision requests for the authors and provide your detailed comments, including highlighting limitations and strengths of the opinion. If you have additional comments based on Q2 and Q3 you can add them as well.
Reviewer 2 | 27 Dec 2022 | 13:42 #1
The aim of the present exploration opinion is to give a better understanding of the existing knowledge about the anti-cancer potential of rice field snail shell and its major components. To our knowledge, no opinions or reviews specifically regarding this matter have already been published. Therefore, the subject could certainly be useful and of interest. However, there are some aspects to be addressed and corrected within the manuscript.
Some paragraphs and sentences, as well as the contribution to the field paragraph, are difficult to follow or seem to lack of a clear logical thread and thus need to be revised and reorganized. I suggest also reorganizing the contents presented in the "Anticancer Properties of Rice Snail Shell" section by clearly separating the paragraphs regarding the anticancer potential of the different snail shell's components (calcium carbonate, hydroxyapatite, chitin...) or the whole shell extract.
The in vivo results of the study by Han et al., 2014 are either reported in an incorrect way or in an unclear way. Please, check.
In my opinion, the "Future Applications and Implications" paragraph is insufficient since, at the moment, it includes only limited information regarding the application specifically in the cancer field. Therefore, I suggest deepening some concepts that have been only briefly mentioned (e.g., chitosan promoting cellular immunity - how?) and citing (more thoroughly) also here the study of Huang et al., 2020. Moreover, the first part of this future applications paragraph could be perfect to improve the introduction section/contribution to the field and I suggest moving it there.
Finally, also the discussion section is lacking essential information as only calcium carbonate is addressed. I suggest including a comment also on chitin and other components of snail shell.
Submitting Author: Fahrul Nurkolis | 28 Dec 2022 | 09:29 #2
December 28, 2022
Ref No/Manuscript ID: 1078981
Title: Rice Field Snail Shell Anticancer Properties: An Exploration Opinion
Dear Prof. Marc Poirot and Reviewer,
Frontiers in Oncology,
Dear Prof. Marc Poirot and Reviewer, thank you very much for taking the time to handling and review on
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Dear Prof. Marc Poirot and Reviewer,
Frontiers in Oncology,

Dear Prof. Marc Poirot and Reviewer, thank you very much for taking the time to handling and review on our manuscript.
We greatly appreciate your careful assessment and insightful comments on our manuscript, as well as your recognition of the importance of our study. We have revised extensively and thoroughly, the manuscript with highlights re-submitted. We believe that the manuscript in the revised version is substantially and technically improved as well. Please find below a point-by-point response to the reviewer comments and clarify the important points of your main concerns.

Response to Reviewer:

- The aim of the present exploration opinion is to give a better understanding of the existing knowledge about the anti-cancer potential of rice field snail shells and their major components. To our knowledge, no opinions or reviews specifically regarding this matter have already been published. Therefore, the subject could certainly be useful and of interest. However, there are some aspects to be addressed and corrected within the manuscript.
 # Thank you for allocating your time to review our manuscript. We fully consider your input to further improve the quality of this manuscript.

- Some paragraphs and sentences, as well as the contribution to the field paragraph, are difficult to follow or seem to lack a clear logical thread and thus need to be revised and reorganized.
 # Thank you for noticing this. We have attempted to improve the writing, grammar, and flow of our manuscript.
 # Thank you for your input. We have revised the contribution to the field paragraph as follows:
Calcium carbonate is also the primary material used to synthesize hydroxyapatite, a biocompatible material with high binding activity to proteins and genetic materials. Nanoparticle hydroxyapatite showed in vitro and in vivo anti-proliferative potential against cancer cells (Kargozar, S. et al., 2020; Zhao, H. et al., 2018). Various studies have shown that snail shells also contain bioactive compounds like chitin - the primary material of chitosan - that offers antipathogenic, antioxidant properties, as well as pharmaceutical additive potential (Jatto, O.E. et al., 2010; Abd El-Hack. M.E. et al., 2020). Furthermore, chitin and its derivatives were found to have a significant immunomodulating response against cancer and antitumor

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- Some paragraphs and sentences, as well as the contribution to the field paragraph, are difficult to follow or seem to lack a clear logical thread and thus need to be revised and reorganized.
 # Thank you for noticing this. We have attempted to improve the writing, grammar, and flow of our manuscript.
 # Thank you for your input. We have revised the contribution to the field paragraph as follows:
Calcium carbonate is also the primary material used to synthesize hydroxyapatite, a biocompatible material with high binding activity to proteins and genetic materials. Nanoparticle hydroxyapatite showed in vitro and in vivo anti-proliferative potential against cancer cells (Kargozar, S. et al., 2020; Zhao, H. et al., 2018). Various studies have shown that snail shells also contain bioactive compounds like chitin - the primary material of chitosan - that offers antipathogenic, antioxidant properties, as well as pharmaceutical additive potential (Jatto, O.E. et al., 2010; Abd El-Hack. M.E. et al., 2020). Furthermore, chitin and its derivatives were found to have a significant immunomodulating response against cancer and antitumor activity through the downregulation of tumor angiogenesis factors, apoptotic effects stimulation, and decreased cell adhesion (Satitsri, S. and Muanprasat, C., 2020). However, the bioactive component's profile of snail shells is partially influenced by their habitat, surrounding environment, mineral content, and microorganisms (Sundalian, M. et al., 2021). Therefore, this article specifically aims to summarize the recent findings on potential anticancer properties in molecular and cellular oncology mechanisms of rice field snail shells.

- I suggest also reorganizing the contents presented in the "Anticancer Properties of Rice Snail Shell" section by clearly separating the paragraphs regarding the anticancer potential of the different snail shell's components (calcium carbonate, hydroxyapatite, chitin...) or the whole shell extract.
 # Thank you for your input. We have reorganized the "Anticancer Properties of Rice Snail Shell" section as follows:
1st Paragraph - Whole Shell
2nd Paragraph - Hydroxyapatite
3rd Paragraph - Minerals
4th Paragraph - Miscellaneous

- The in vivo results of the study by Han et al., 2014 are either reported in an incorrect way or in an unclear way. Please, check.
 # Thank you, we have revised this part. We appreciate your input.

- In my opinion, the "Future Applications and Implications" paragraph is insufficient since, at the moment, it includes only limited information regarding the application specifically in the cancer field. Therefore, I suggest deepening some concepts that have been only briefly mentioned (e.g., chitosan promoting cellular immunity - how?) and citing (more thoroughly) also here the study of Huang et al., 2020

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immunity – how?) and citing (more thoroughly) also here the study of Huang et al., 2020.
 # Thank you for your great suggestions. We have incorporated some details into the respective section.

– Moreover, the first part of this future applications paragraph could be perfect to improve the introduction section/contribution to the field and I suggest moving it there.
 # We agree with your input regarding this. Therefore, we have restated the sentence in the introduction section.

– Finally, also the discussion section is lacking essential information as only calcium carbonate is addressed. I suggest including a comment also on chitin and other components of a snail shell.
 # Thank you for your input. We have improved the discussion section.

We believe these actions address the deficiencies and comments noted by the reviewer. We hope that you will be pleased with this revision and that the revised manuscript will better meet the requirements of the 'Frontiers in Oncology' for publication. If any changes need to be made, don't hesitate to contact us again. Your kind help in this submission is highly appreciated!
Your decision is much appreciated!

Kind Regards,

Dr. Joice Junita Imelda Rompas

Fahrul Nurkolis

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Ambassador of Preclinicaltrials.eu; Premium Member of European Society of Cardiology; Associate Members of Royal Society of Biology; Member of The Nutrition Society; Member of American Society for Nutrition.

Q 2 **Check List**

Reviewer 2 | 27 Dec 2022 | 13:42 #1

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Q 2 **Check List**

Reviewer 2 | 27 Dec 2022 | 13:42 #1

a. Is the quality of the figures and tables satisfactory?
– Yes

b. Does the reference list cover the relevant literature adequately and in an unbiased manner?
– Yes

c. Does this manuscript refer only to published data? (unpublished or original data is not allowed for this article type)
– Yes

d. Is the opinion supported by evidence?
– Yes

Submitting Author: Fahrul Nurkolis | 28 Dec 2022 | 09:29 #2

Dear Reviewer,

Thank you for allocating your time to review our manuscript. We fully consider your input to further improve the quality of this manuscript. We believe these actions address the deficiencies and comments noted by the reviewer. We hope that you will be pleased with this revision and that the revised manuscript will better meet the requirements of the 'Frontiers in Oncology' for publication. If any changes need to be made, don't hesitate to contact us again. Your kind help in this submission is highly appreciated!
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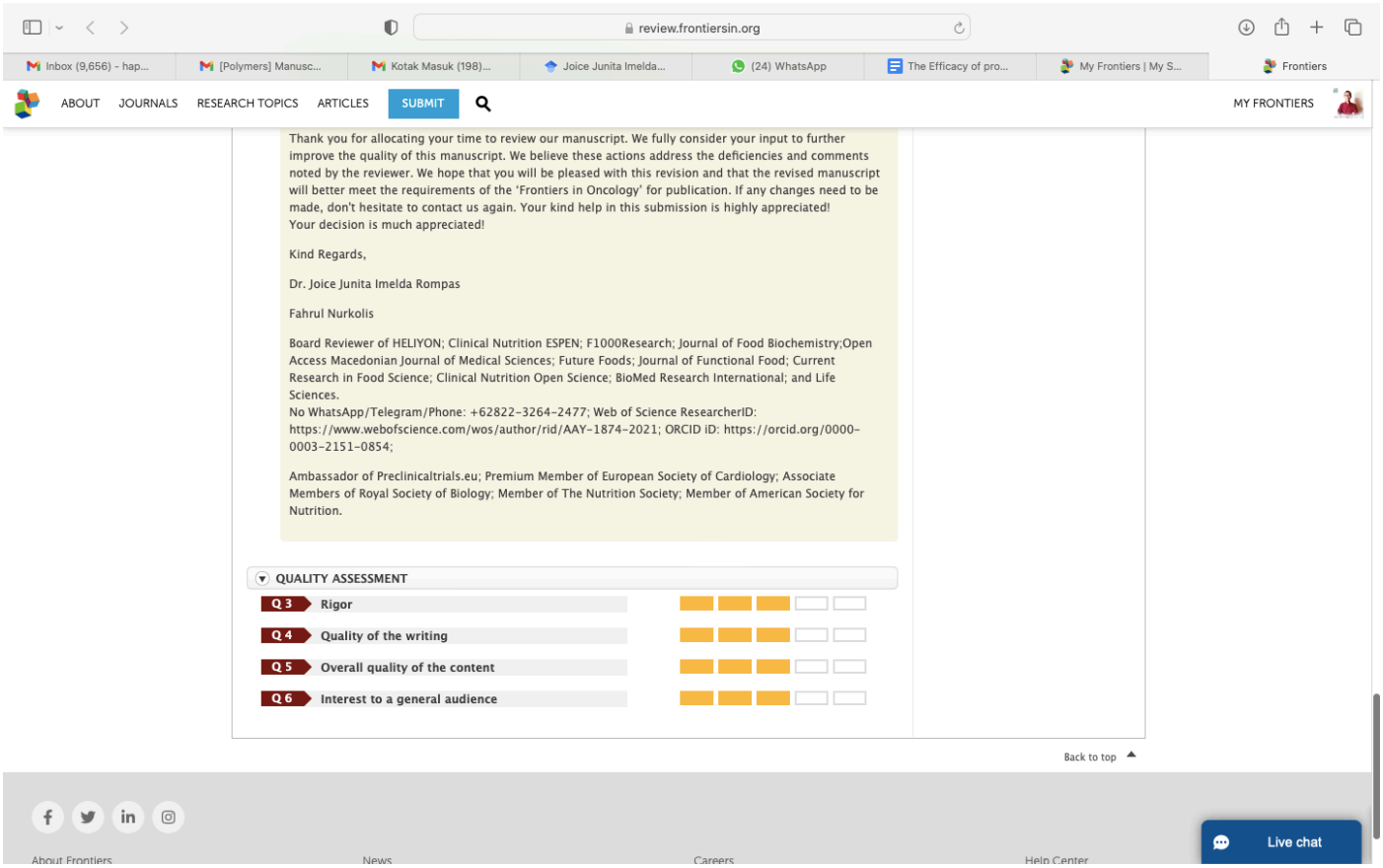
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Q 4 Quality of the writing
Q 5 Overall quality of the content
Q 6 Interest to a general audience
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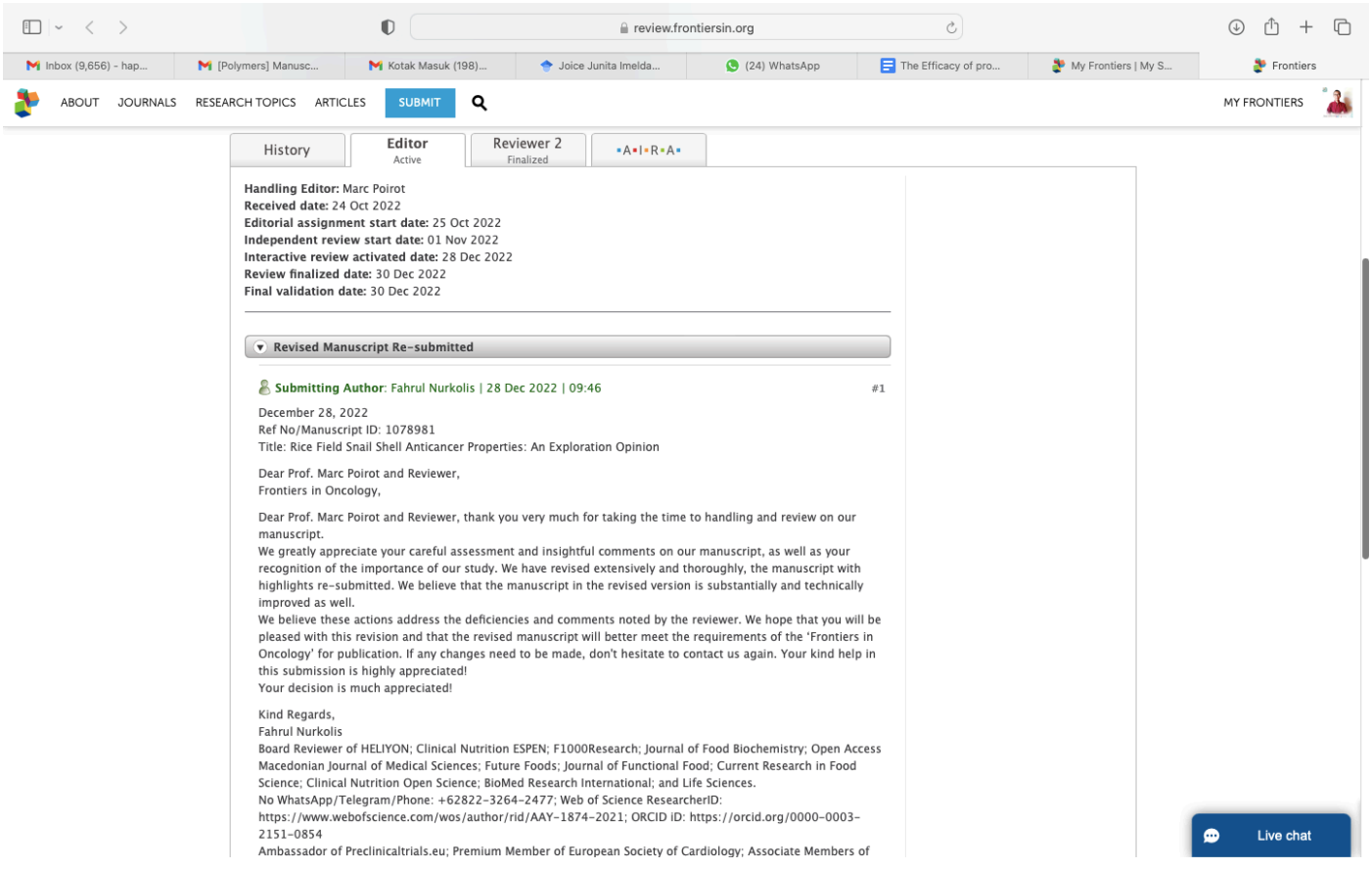
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Review finalized date: 30 Dec 2022
Final validation date: 30 Dec 2022
Revised Manuscript Re-submitted
Submitting Author: Fahrul Nurkolis | 28 Dec 2022 | 09:46
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December 28, 2022
Ref No/Manuscript ID: 1078981
Title: Rice Field Snail Shell Anticancer Properties: An Exploration Opinion
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