Dear Reviewer, # 3,

Thank you for the review of our manuscript (ijms-3199965) titled "***Syzygium aromaticum*** **extract mitigates doxorubicin-induced hepatotoxicity via targeting ferroptosis and NRF 2/SLC7A-11/GPX-4 pathway in male rats**". The whole manuscript has been revised carefully and we have considered all your comments. These revisions are highlighted in the manuscript by track changes and are summarized below.

Reviewer # 3	
Comment 1	**Response**
The title of the manuscript: lack of evidence on the crucial genes to be knocked out or down, the authors cannot claim that Syzygium aromaticum extract can target ferroptosis or NRF-2/SLC7A-11/GPX-4 pathway. Their data presented only supports that there is a positive correlation between the SAE treatment and NRF-2/SLC7A-11/GPX-4 pathway and related response.	In the revised manuscript, the title changed to *Syzygium aromaticum* extract mitigates doxorubicin-induced hepatotoxicity in male rats
Comment 2	**Response**
combined 2.1 and 2.2	In the revised manuscript, 2.1. was combined with 2.2. and 2.1 became: Phytochemical Constitutes and GC-MS Analysis of SAE.
Comment 3	**Response**
All the abbreviations in Figure2 should be shown in full form in legend, and all the abbreviations in the first column in Table3 should be shown in full form. The results in Figure2 and Table3 should be described in more detailed in In Silico ADMET Analysis.	Thanks for your comment, in the revised manuscript, all abbreviations in Figure2 were fully written in the figure legend, and all the abbreviations in the first column in Table3 were shown in full form. Furthermore, the results in Figure2 and Table3 were described in more detail in In Silico ADMET analysis.
Comment 4	**Response**
Combined 2.5 and 2.6, and deleted Figure6. Check Figure6A cited on line193, is it Figure7A? Changed Figure7A into relative body weight on vertical axis, check the values of Figure7B, why do the relative liver weights only reach less than 5?	In the revised manuscript, 2.5 and 2.6 were combined and Figure 6 was deleted. On line193, figure citation was corrected to Figure 6 A, Figure 6 B. Figure 6A was corrected in the vertical axis to relative body weight. Our data showed that the relative liver weights only reach less than 5, this was the obtained data and agreed with previous studies investigated the effect of DOX and natural products on the relative liver weight. This finding could be due to the hepatotoxic effect of DOX.
Comment 5	**Response**
The statistical significance at a level of P or p <0.05? It presents in two different forms in Line 190 and 192, it should be typed in Italic style in the whole manuscript.	The statistical significance at a level of P was corrected and typed in Italic style through the whole manuscript.
Comment 6	**Response**
Changed the title of 2.9, the result only showed The effect of SAE on ferroptosis and NRF-2/SLC7A-11/GPX-4 pathway	In the revised manuscript, the title of 2.9 was changed to SAE Treatment Modulate NRF-2/SLC7A-11/GPX-4 Pathway in DOX-Exposed

	Rats.
Comment 7	**Response**
Figure9 and 10, parts of them are missing.	In the revised manuscript, Figure9 and 10, were rearranged and corrected.
Comment 8	**Response**
Combined 2.9 and 2.10, and moved Table6 into Support information together with 4.9 section, the authors should address how did they measure protein levels in Figure9 and Figure10. Delete Figure10A.	In the revised manuscript, 2.9 and 2.10 were combined. Table6 was moved to support information with 4.9 section. Figure 10A was deleted and we added the measurement of protein levels: "The total protein levels in the hepatic tissues were measured by the method of Lowry et al. (1951) using bovine serum albumin (BSA) as a standard [75]."
Comment 9	**Response**
Delete each in the note of Table 8 on Line301, there is only one column. Give full name of all the abbreviations in Figure11.	The note of Table 8 on Line301 was deleted and full name of all the abbreviations in Figure11 was added in the resubmitted manuscript
Comment 10	**Response**
The experiment design lacks different dosage of SAE, whether the responses are in dose-dependent manner has not been shown, and no information on the dose ranges of SAE and its effective responses.	In our study, we used the sublethal dose after determining the oral median lethal dose of SAE LD_{50} using the probit analysis. The LD_{50} of SAE oral administration was determined using different doses after 24 hours of treatment in rats. Different groups were gavaged with different doses (1000 to 5000 mg/kg). The probit analysis results reported that the oral LD_{50} of SAE was 3400 mg/kg. We used 1/10 of this LD_{50}.
Comment 11	**Response**
The results referred in discussion should be cited.	The result citations that were referred in discussion were added in the revised manuscript.
Comment 12	**Response**
Why only male rats were chosen to be used in the present study should be stated in Method section or other appropriate part.	In the revised manuscript, in materials and methods section, 4.7. Animals and Experimental Design. We added: "Male rats were used to avoid the fluctuating hormone levels and the menstrual cycle that could make data difficult to interpret, results more variable".
Comment 13	**Response**
The discussion section is lengthy, it should be simplified as far as possible. Especially, delete Line339-346. - Rewrite Line415 *which confirmed the confirmed the clove hepatoprotective action of clove.* - Delete Line415-416 *"Therefore, it's plausible that SAE hepatoprotective mechanism results from its antioxidant activity".* - Line434-435 "*SAE could mitigate liver injury by inhibiting liver ferroptosis through activating the SLC7A-11/GPX-4*	We would like to thank you for your comment, we agreed with you, in the revised manuscript, the discussion section was simplified, Lines from 339-346 were deleted. - The sentences "*which confirmed the confirmed the clove hepatoprotective action of clove"* was corrected to "*which confirmed the hepatoprotective action of clove"* - Line415-416 *"Therefore, it's plausible that SAE hepatoprotective mechanism results from its antioxidant activity"* was deleted.

pathway in DOX-administered rats. I suggested the sentence should be deleted; the results have not given any direct evidence. - *Enzymes called cytoplasmic reductase and cytochrome*	- The sentence "*SAE could mitigate liver injury by inhibiting liver ferroptosis through activating the SLC7A-11/GPX-4 pathway in DOX-administered rats.* Was omitted. - *Enzymes called cytoplasmic reductase, and cytochrome* was rewritten to *"Cytochrome enzymes"*.
Comment 14	**Response**
Conclusion: rewrite Line573-575 *and can be used as a new potent ferroptosis inhibitor in the liver tissues of rats injected with DOX. The combination of SAE and DOX could serve as a new strategy for efficient chemotherapy.* The sentence seems over claimed the results.	The conclusion was rewritten to Collectively, the SAE may be a highly effective protective agent against hepatotoxicity brought on by DOX therapy. This effect of SAE is through inhibiting oxidative stress, inflammation, and upregulating the NRF-2/SLC7A-11/GPX-4 signaling pathway. Further preclinical and clinical studies should optimize SAE doses and investigate the effects of SAE against other toxicities induced by DOX

We would like to thank you for helping to increase the quality of this paper. We hope the changes that have been made were appropriate and the manuscript can now be accepted for publication. Please address all correspondence to the author indicated below.

Sincerely Yours,

Corresponding author

Prof. Dr. Karim Samy El-Said