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OPEN PEER REVIEW

Exploring Herbal Compounds as Targeted Therapies for Breast Cancer: Insights from Network Pharmacology, Molecular Docking, MD Simulation, ADME-Toxicity and DFT Profiles

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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Contents

1 Original submission 2
2 Revision 1 Associate Editor 3
Authors' reply to reviewers 4
Reviewer and editor comments 11

1 Original submission

0 comments

No public comments in this round.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewers' Comments:

Reviewer 1: (All the modifications are highlighted with yellow colour)

The manuscript entitled "Exploring Herbal Compounds as Targeted Therapies for Breast" (153579,) Cancer: Insights from 2 Network Pharmacology, Molecular Docking, MD Simulation, ADME-Toxicity and DFT 3 Profiles" was about using a herbal database and docking them toward three therapeutic anticancer targets. The compound with best docking score selected for further in silico evaluation My comments are as follows:

1) Could the author please clarify how the docking method employed in this study has been validated? This is crucial to ensure the reliability and accuracy of the results obtained.

Authors response: Thank you for pointing out this issue. Indeed, three compounds/drugs were added for validation purposes [Lapatinib for 1XKK (EGFR), Exemestane for 3S7S (Aromatase) and Alpelisib for 7PG6 (PI3K alpha)]. We have added these data in Table 1 and explained in details in Results Section. They are highlighted with yellow colour.

2) I suggest that the docking results of the compounds should be compared with the results obtained from docking each protein with its co-crystallized ligand. This comparison should include docking scores and interaction analyses to better assess the validity and significance of the findings.

Authors response: As advised, we have added the docking scores of the co-crystallized ligand for comparison in Table 1 and Table S2 [Lapatinib for 1XKK (EGFR), Table S3 [Exemestane for 3S7S (Aromatase)] and Table S4 [Alpelisib for 7PG6 (PI3K alpha)]. The same has been compared in the Results Section and discussed in the Discussion Section. They are highlighted with yellow colour.

3) In the discussion section, it is recommended to reinforce the findings with evidence from previous studies mentioned in the literature. This will help substantiate the results and demonstrate their alignment with existing research.

Authors response: As advised, we have discussed as suggested in the discussion added 3 new references. It is highlighted with yellow colour.

Reviewer 2: (All the modifications are highlighted with Grey colour)

Authors explored Herbal Compounds as Targeted Therapies for Breast Cancer. They used Network Pharmacology, Molecular Docking, MD Simulation, ADME-Toxicity and DFT Profiles. There are some comments that authors should consider.

1) Did the authors use the OPLS_2005 FF for both protein and ligand?

Authors response: Yes, and the OPLS_2005 FF has been optimized for compatibility with both proteins and protein-ligand complexes**.** As pointed out by the reviewer, we have added this statement which is highlighted with grey colour in the Methods Section (MD Simulation).

2) What is the reason for using orthorhombic box in MD simulation?

Authors response: Orthorhombic box allows the simulation to enclose the molecular system more tightly than a cubic box thereby reducing the amount of empty space and improving the computational efficiency. In short Orthorhombic box is a flexible option that ensures a good balance between efficiency and accuracy in MD simulations. As advised by the reviewer, the technical details has been added in the Methods (MD simulation section) which is highlighted with grey colour.

3) In DFT analysis, authors mention to Gaussian 8.0. Is there this version?

Authors response: Thank you for pointing out this mistake. It is corrected as Gaussian 9.0.

4) Authors should mention to MolDock score unit.

Authors response: As advised, all the docking score units have been added (kcal/mol).

5) Charts like RMSD analysis are important. Therefore, they should be

mentioned in the text of the manuscript and not in the Supplementary Material.

Authors response: As advised, the RMSD analysis is moved in the main manuscript as Fig. 4. and Fig. 3 is move to Supplementary as Fig. S5. The incorporations are highlighted with grey colour.

6) Authors should prepare a workflow that includes a brief step-by-step description of the methods/approaches.

Authors response: As advised, a flowchart on the workflow of the study is added as Fig. 1.

7) Unfortunately, the authors only reported many of the results and did not discuss them (as in Figure 2). The same is for ADME analysis. The authors should discuss the values and indicate the threshold limit.

Authors response: As advised, we have elaborated many of the results in the Discussion Section. We have also added a detailed analysis of ADME in Results section. They are highlighted with grey colour.

8) Why do the authors include most of the results in the Supplementary Material? This does not make sense.

Authors response: Thank you for pointing out this issue. Earlier, all the figures and tables were included in main manuscript, however the journal permits only 4-5 Figures and 1-2 Tables. Hence, most of the Figures and Tables were moved to Supplementary Material.

9) Simulation time is very short. Authors should extend it to at least 100 ns.

Authors response: As advised by the reviewer simulation time is increased to 100 ns.

Reviewer 3: (All the modifications are highlighted with Green colour)

1) Please provide the chemical structures of all ligands used in the study. This is essential for clarity and for a better understanding of the docking results.

Authors response: As advised, the chemical structures of all the ligands have been added in Supplementary Info table S1.

2) In the docking section, please elaborate on the key pharmacological groups of the ligands that influence their interactions with enzyme active sites. This will help in explaining the mechanism of action in greater detail.

Authors response: Key pharmacological groups are phenols, coumarind and flavonoids. As advised by the reviewer, these has been elaborated in the Results section (Molecular Interaction Analysis). They are highlighted with Green Colour.

3) Please Conduct and compare the docking interactions of the weak ligand with the potent ligands, highlighting the differences in binding affinities and interaction patterns

Authors response: Three reference compounds were added for validation purposes [Lapatinib for 1XKK (EGFR), Exemestane for 3S7S (Aromatase) and Alpelisib for 7PG6 (PI3K alpha)]. We have added these data in Table 1 and explained in details in Results Section. The same has been compared in the Results Section and discussed in the Discussion Section

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Reviewer 4: (All the modifications are highlighted with Pink colour)

This article presents a computational approach to identifying herbal compounds as potential breast cancer therapies. However, there are areas where further improvement can enhance the quality and impact of this study. While generally well-written, there are minor grammatical issues that need revision.

1) In the abstract section, Shorten the methodology description and focus more on the implications of the findings.

Authors response: Revised as suggested and highlighted in pink colour.

2) In the introduction section, there's a lack of clarity on why Epidermal Growth Factor Receptor (EGFR), Aromatase, and PI3K alpha were chosen as targets.

Authors response: We have added three lines in the introduction for choosing these targets as advised by the reviewer. They are highlighted with pink colour.

3) In the methods section, describe how compounds were highlighted for docking and ADME analysis. The ADME-Toxicity analysis mentions SWISS-ADME but lacks details on the metrics used.

Authors response: As advised by the reviewer, we have added these details in the ADME-Toxicity section of the Methods. The incorporations are highlighted with pink colour.

4) In result section, while the molecular interaction maps are useful, they could be explained more clearly. For example, in Figures S1 and S2, elaborate on what the hydrogen bond acceptor (HBA) and donor (HBD) regions mean in the context of drug design.

Authors response: As advised by the reviewer, we have added few lines about HBA/HBD and electrostatic map in the Results Section (Molecular Interaction Analysis Section). It is highlighted with pink colour.

5) The discussion section requires deeper scientific analysis. If possible, Add a brief section on the inherent limitations of molecular docking and virtual screening, such as the lack of real biological environments in silico in discussion section.

Authors response: Added as suggested by the reviewer in the last paragraph of the discussion section. The incorporations are highlighted with pink colour.

6) The conclusion summarizes the study but could be more impactful by discussing future directions. please refine the conclusion.

Authors response: Refined as suggested by the reviewer. The modifications are highlighted with pink colour.

7) Overall, this paper lacks some detailed explanations, particularly regarding target selection, interaction network construction, and

docking parameter choices. More clarity on these would improve the understanding of the approach and its reproducibility.

Authors response: Updated in the methodology as advised. They are highlighted with pink colour.

8) Some figure captions are unclear and don't fully explain the significance of the findings.

Authors response: As advised, the significance of the figures is explained in the figure captions

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Associate Editor's Comments:

Associate Editor 1:
Dear author
We have received the reports from our advisor on your manuscript, "Exploring Herbal Compounds as Targeted Therapies for Breast Cancer: Insights from Network Pharmacology, Molecular Docking, MD Simulation, ADME-Toxicity and DFT Profiles", which you submitted to the IJPR.
Based on the advice received, you should be prepared to incorporate major revisions in your manuscript. If you decide to revise the work, please submit a list of changes or rebuttals against each point that is being raised when you submit the revised manuscript.

Authors response: We have thoroughly revised the manuscript and answered to all queries raised by all the reviewers.

Reviewer Assistant Comments:

These comments were generated by AI based on your manuscript. Please review them and consider incorporating the suggestions to enhance your article.

Overall Assessment

The study provides valuable insights into the potential of herbal compounds as targeted therapies for breast cancer. However, it lacks detailed methodological rigor in reporting, particularly in the areas of study selection, data collection, and analysis. The authors should consider addressing the following points to enhance the manuscript:

1) Clearly define eligibility criteria and the selection process for the compounds.

Authors response: As Advised, the criteria and selection process for the compounds already written in methods section. They are highlighted in pink colour in the Methods section (Target Proteins of breast cancer).

2) Provide a detailed search strategy and information sources.

Authors response: As Advised, the search strategy and the url link is included in Methods section (TCM Chemical Compounds) which is highlighted with pink colour.

3) Include a discussion on the limitations of the study and the implications for future research.

Authors response: Included in the discussion section in last para which is highlighted in pink color.

4) Address funding sources and potential conflicts of interest.

Authors response: All added, as advised. They are highlighted with pink colour

5) In conclusion, while the study presents interesting findings, it requires significant improvements in reporting standards to meet the criteria outlined in the PRISMA, MOOSE, and STROBE guidelines. Further experimental validation of the findings is recommended to substantiate the claims made in the study.

Authors response: As advised, we have improved the manuscript. Regarding experimental validation, we value your insights and are dedicated to improving the quality of our study in our future work.

2 Revision 1

1 comment · 17 Nov 2024

Associate Editor

ACCEPT 17 Nov 2024

Dear author
We appreciate your submitting this valuable manuscript "Exploring Herbal Compounds as Targeted Therapies for Breast Cancer: Insights from Network Pharmacology, Molecular Docking, MD Simulation, ADME-Toxicity and DFT Profiles" to the IJPR. The answers were convincing, and the article was well-revised; now the manuscript is ready for publication. We are waiting for you to submit your future interesting work to the IJPR.