nanik siti aminah <nanik-s-a@fst.unair.ac.id>

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20-Mar-2021

Dear Dr Aminah:

TITLE: Exploration of stilbenoid trimers as a potential inhibitor of Sirtuin1 enzyme using molecular docking and molecular dynamics simulation approach

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2 messages

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Reply-To: advances@rsc.org
To: nanik-s-a@fst.unair.ac.id

26-Apr-2021

Dear Dr Aminah:

Manuscript ID: RA-ART-03-2021-002233
TITLE: Exploration of stilbenoid trimers as a potential inhibitor of Sirtuin1 enzyme using molecular docking and molecular dynamics simulation approach

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I look forward to receiving your revised manuscript.

Yours sincerely,
Prof Manojit Pal
Associate Editor, RSC Advances

****
REVIEWER REPORT(S):
Referee: 1

Recommendation: Major revisions

Comments:
Comments to authors
The work is interesting to the audience of this journal and can be considered for publication after addressing the following concerns.

First, please correct your English throughout the manuscript. I found a lot of typos

methodology
molecular docking

In the methodology, it is not much clear whether you used PDB ID 4ZZI or 1NS, you mentioned that you obtained but in the docking you mentioned that you used 1NS.., please clarify

You mentioned that the compounds were previously isolated, however, it is not clear whether the TS1 was isolated in this study or previous study. If isolated in this study, please provide the details on the isolation and characterization techniques used including nmr etc, and if not, please, provide a suitable reference.

In the methodology, you wrote "… Besides, to fix the missing residue in the receptor (loop) using Modeller 9.21 package, which is integrated with Chimera version 1.13…" this sentence to me is incomplete and hanging. Please check the English and correct.

In the mothodology, docking you wrote "… The comparison of EVDW and Eele between
the native ligand of the crystal structure (reference) and the native ligand docking (pose). …" this is also hanging

molecular dynamics
The methodology here is not clear at all and have a lot of typos. This section has a lot of language problems, the english used brings a lot of confusing to the reader, I have found a lot of problem in the methodology and cannot be understood properly.

For example, Not clear whether the production was done at an NVT or NPT ensemble, it is important that author be explicit for reproduceability of their work. The minimization process is not much explicity, did the authors minimize the each system individually and then combined the minimized system..? why..? why did not work on the complex ..?

I suggest that the whole work be read by an english expert, in its current form can not be accepted until the english has been edited.

qm/mm-gbsa
what is the changes in binding energy for the other ns e.g from 50-100, 100-150, 150-200 ns? something can happen in between. It is also important to understand what is happening…?

Results
It could be important to see how the binding of the ligand changes the secondary structure of the protein, e.g how the apo and holo protein structure changes, also by comparing to the least inhibitor and strong binding molecule.

In figure 4, TS3 shows fluctuations at 180-190 or near 200 ns, similar to 1NS shows fluctuations near 90-100 ns, what is happening at this point..? authors need to tell the physical features taking place at this region.

Is the ligand moving out the pocket..? what is the binding energy at this rgions..? how is the protein changing its structure..? what is happening to the ligands..changing its conformation...?

what is reason for having large std dev in the total energy of the system..? eg -146,966 +/-803.55 , what is the units of this energy..? kcal/mol..? or kJ/mol..?, please, specify..?

How is this protein flexible in the absence of the ligand..?

Figure 6. To have a good picture on the effects of the ligand, it is good to compare the holo and the apo protein, I suggest that the authors compared this stability relatively to the free protein as well. this will establish the effects of the ligand upon binding to a protein. You have to do it for the rmsd as well and the rmsf too and other reaction coordinates you think are useful e.g distances.

It will be useful if you can show the binding energy decomposition and residue contribution obtained from qm/mm-GBSA and compared with those obtained from the docking /MD simulation.

To support fig 7 and 8, authors should compute the free energy as the function of the distance between the ligand and the protein using selected reaction coordinates e.g h-bond distances use the relationship
F = -kBT ln (p), where P is the probability..

Additional Questions:
Does the work significantly advance the understanding or development in this field?: Yes

Is this work of relevance to the chemistry community?: Yes

Are the conclusions of the work convincing and sufficiently supported by experimental evidence?: Yes

Does the data provided fulfil the journal's data requirements?

See Journal specific guidelines: https://www.rsc.org/journals-books-databases/about-journals/rsc-advances/#Characterisation-of-new-compounds: Yes

Is the experimental section sufficiently detailed to allow others to reproduce the work?: No

Are the reported claims adequately discussed in the context of the literature?: Yes

Are the number of tables and figures in the manuscript appropriate and clear?: Yes

Referee: 2

Recommendation: Major revisions

Comments:
I have gone through your manuscript and I have few comments to make:

In as much as docking is first step for HTVS studies, validation of the docking protocol is necessary. In this work, redocking approach has been performed. However, many atimes the selection of top hits maybe biased and as such, additional techniques can be implemented. This includes perfoming a Receiver Operating Characteristic (ROC) which determines the sensitivity of the protocol in picking up potential positive hits from non-potential ones. I recommend that this is performed.

Additionally, is it possible to validate these results uding wet-laboratory assays?

Additional Questions:
Does the work significantly advance the understanding or development in this field?: Yes

Is this work of relevance to the chemistry community?: Yes

Are the conclusions of the work convincing and sufficiently supported by experimental evidence?: No

Does the data provided fulfil the journal's data requirements?

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Are the reported claims adequately discussed in the context of the literature?: Yes

Are the number of tables and figures in the manuscript appropriate and clear?: Yes

Referee: 3

Recommendation: Major revisions

Comments:
The manuscript entitled “Exploration of stilbenoid trimers as a potential inhibitor of Sirtuin1 enzyme using molecular docking and molecular dynamics simulation approach” seemed to be interesting and may be considered further for RSC Advances after some revision

1. The English language and grammar needs substantial improvements throughout the manuscript.
2. Page 1, the sentence “Stilbenoid trimer is a class of polyphenol compounds that have been known to have the potential to inhibit the SIRT1 enzyme 11,12” needs further elaboration as I could not find anything significant related to this topic in ref 11 and 12. In fact I doubt if ref 11 has any relevance to this statement. Please check.
3. Next authors have commented “Structurally, the stilbenoid trimers consist of three resveratrol monomers,…..”. In my opinion resveratrol are known to be activators of Sirt1 whereas authors studied the Sirt1 inhibitory potential of stilbenoid trimers. Please clarify.
4. The coverage of background literature is poor. The recent literature on identification of Sirt 1 inhibitors must be included in the introduction section.
5. Authors have mentioned that Stilbenoid trimers can be isolated from the Dryobalanops oblongifolia plant but it is not clear if TS1, TS2 and TS3 have been isolated and characterized earlier. This needs proper elaboration.
6. Fig 1: the trans isomer should be TS3?
7. Fig 2D: the chemical structure shown is awkward, please address the problem. Same issue with Fig S 2. Also TS2 and TS3 are same (trans isomer) in this figure.
8. One or two well-known inhibitor(s) of Sirt1 should have been used as reference compound(s) in the molecular modelling studies.
9. Besides docking studies in silico it is desirable to assess and analyse the ADMET properties of the current compounds in silico.
10. The graphical abstract or TOC is missing.

Additional Questions:
Does the work significantly advance the understanding or development in this field?: Yes

Is this work of relevance to the chemistry community?: Yes

Are the conclusions of the work convincing and sufficiently supported by experimental evidence?: No

Does the data provided fulfil the journal’s data requirements?

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Title
Exploration of stilbenoid trimers as a potential inhibitor of Sirtuin1 enzyme using molecular docking and molecular dynamics simulation approach

Authors
Abdjan, Muhammad
Aminah, Nanik
siswanto, Imam
Kristanti, Alfinda Novi
Takaya, Yoshiaki
Choudhary, Muhammad

Date Submitted
11-May-2021

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Title
Exploration of stilbenoid trimers as a potential inhibitor of Sirtuin1 enzyme using molecular docking and molecular dynamics simulation approach

Authors
Abdjan, Muhammad
Aminah, Nanik
siswanto, Imam
Kristanti, Alfinda Novi
Takaya, Yoshiaki
Choudhary, Muhammad

Date Submitted
20-May-2021

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20-May-2021

Dear Dr Aminah:

TITLE: Exploration of stilbenoid trimers as a potential inhibitor of Sirtuin1 enzyme using molecular docking and molecular dynamics simulation approach
AUTHORS: Abdjan, Muhammad; Aminah, Nanik; siswanto, Imam; Kristanti, Alfinda Novi; Takaya, Yoshiaki; Choudhary, Muhammad

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21-May-2021

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