Review of: "Effects of the SARS-CoV-2 Spike protein on in vitro aggregation of alpha synuclein- probable molecular interactions and clinical implications"

Najib Sani

Potential competing interests: No potential competing interests to declare.

Reviewer comments:

The authors did a very good work on accessing the interaction effects of spike and α-synuclein proteins from SARS-CoV-2 and Parkinson's diseases (PD) respectively, and their clinical implication on PD. The work is insightful following emphasis of an increase in movement disorders and rapidly progressive dementia following COVID-19 vaccination. This is imperative for further scientific research.

Here are some suggestions:

1. In the Abstract, summary of the docking scores could be stated as it relates to the *in vitro* analysis, this is the basis for comparing aggregation process of α-synuclein *in silico* and *in vitro*
2. Any validation protocol for the protein-protein docking analysis of spike and α-synuclein proteins? Is the confidence score an indication for validation? If it is, it should be emphasized that it indicates validity of the docking score. Validation is key in any docking process, indicating reliability of any *in silico* study. Therefore, summary of the validation could be emphasized in the abstract or results (Castro-Alvarez, Costa, & Vilarrasa, 2017; Kanitkar et al., 2021; Ramírez & Caballero, 2018)
3. Root means square deviation (RMSD) for docking scores should be within certain range. For most docking scores, RMSD within the acceptable range of ≤ 2.0 validates the docking protocols as reliable. (Castro-Alvarez et al., 2017; Ramírez & Caballero, 2018). What is the acceptable range of RMSD in this study that could be used as validation protocol?
4. In PD, before motor symptoms appearance, fibrils within Lewy's bodies must be formed. Since, an increase in motor symptoms (movement disorders and dementia) were observed following vaccination of SARS-CoV-2 vaccines, therefore, fibrils or Lewy's bodies could be used as reference makers to establish a link between PD and SARS-CoV-2 (Spillantini et al., 1997)

Overall, the study is informative and well structured. Authors have demonstrated constructive comparison and discussion.

References

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