Response to Reviewer

We would like to thank the reviewer for helpful comments and suggestions. The following changes have been made to address the concerns, where all the changes have been highlighted in yellow in the manuscript.

The Reviewer 1 comments that

This manuscript "Protein-Protein Interactions: Methods, Databases and Applications in Virus-Host Study" reported a very good overview of the protein-protein interactions databases and application in the field of virology. However, I will recommend some minor suggestions to further improve the manuscript. Discussion on some practical examples showing experimental proofs on the use of these databases in designing therapeutics would benefit the readers. How the review may help researcher in the fight against COVID-19. Minor English editing is also needed.

Response:

Thank you for your kind suggestion. The manuscript has been updated according the reviewer's suggestions. We have added descriptions on some practical examples showing experimental proofs on the use of these databases in designing therapeutics and in fighting against Covid-19 to the section of "Applications of PPIs in disease networks and in virus-host relationships". All the changes have been highlighted in the   section. Additionally, we also have a native-English speaker edit the manuscript and make language polishing.

Targeting protein-protein interactions for designing therapeutics was once considered a difficult and impossible task. However, during the past two decades, the concept has changed and PPI drug targets have gained considerable interest from the scientific community. Some researchers have been conducting drug target studies in both wet and dry labs, hoping to find potential hot spot regions in PPIs' binding interfaces for designing therapeutic drugs. The discovery of small molecule PPI modulators by the emergence of new technologies has made the PPIs significant drug targets (73, 79). Until now, three databases have been dedicated to modulators of PPIs: (i) 2P2I database (80), (ii) TIMBAL (81) and (iii) iPPI-DB (82), and more than 40 PPIs have been targeted successfully (83). To our knowledge, some of the druggable hotspots for well-studied PPI targets identified by various studies are: MDM2/p53, IL-2/IL-2Ra, HPV-11 E2/HPV-11 E1, TNF-α/TNFR1 and several others (84).

Currently a lot of focus has been diverted towards the recent Covid-19 coronavirus pandemic, and many researches have been carried out to combat the deadly virus experimentally and computationally. Gordon *et al.* (85) performed affinity purification-mass spectrometry and identified 332 physical interactions between human proteins and SARS-CoV-2 proteins. The study helped researchers to dig deep down into the host molecular machineries and identify potential hotspots for developing therapeutic compounds to treat Covid-19. PPI identification will also help in predicting the behavior of the virus and the biological processes targeted by the virus. Khorsand *et al.* (86) developed a three-layered network model to predict SARS-CoV-2-human PPIs and reported the most central human proteins in the network by investigating host proteins that are targeted by the viral proteins.

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LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Response:

Thank you for your kind suggestion. We have had a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so as to let the manuscript's language meet the direct publishing needs.

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: 1 Scientific quality: The manuscript describes a Review of the protein-protein interactions in virus-host study. The topic is within the scope of the WJV. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: The authors should add some practical examples in discussion section. Minor English editing is also needed. The questions raised by the reviewers should be answered; (3) Format: There are 2 tables and 4 figures; (4) References: A total of 79 references are cited, including 11 references published in the last 3 years; (5) Self-cited references: There is no self-cited reference; and (6) References recommendations (kindly remind): The authors have the right to refuse to cite improper references recommended by the

Response:

Thank you for carefully analyzing our manuscript.

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The "Author Contributions" section has been added to the manuscript.

We have provided the supportive foundations.

All the images in the manuscript have been prepared and arranged in the PowerPoint.

The manuscript follows NLM referencing format, and PMID and DOI numbers have been mentioned in the reference list. DOI of every paper is mentioned but PMID is missing in some of the references as they have not been cited in PubMed.

No image has been copied from anywhere, and all the ideas are taken from literatures but images have been made by the authors.