

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

peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade B. The manuscript is reviewed by a native English speaker. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by National Natural Science Foundation of China (General Program). The topic has not previously been published in the WJV. 5 Issues raised: (1) The "Author Contributions" section is missing. Please provide the author contributions; (2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (4) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and (5) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Recommendation: Conditional acceptance.

Response:

Thank you for carefully analyzing our manuscript.

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.

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.