Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript (Manuscript NO.: 89639, Basic Study). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in yellow in the revised manuscript. The main corrections in the manuscript and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments: Reviewer #1:

1.Comment: Please explain why "gastric cancer" was used as a keyword for screening in the screening process of Network Pharmacology, but "gastric adenocarcinoma" was used as a screening index for the validation of Differential expression of core target genes, is this too one-sided?

Response: It is really true as the reviewer suggested that there were differences in the screening index in network pharmacology and bioinformatics analysis. Therefore, I would like to make the following explanation: We first collected the related targets of resveratrol and gastric cancer, and conducted PPI network to explore the 20 core targets of resveratrol anti-gastric cancer. The target genes were then further screened by combining bioinformatics analysis. The reason why we used TCGA database to analyze the differential expression of core targets is that it is currently the largest cancer gene database with more comprehensive data. However, the gastric cancer samples in the TCGA database are gastric adenocarcinoma, which may be related to the fact that gastric adenocarcinoma accounts for 95% of all gastric cancer cases, and it is difficult to collect other types of gastric cancer samples. Reminded by the reviewer, we tried to dig up gastric cancer samples of other pathological types, but we have not found suitable samples at present. Therefore, we still used STAD in TCGA database as screening

samples for differential expression analysis of the core target gene.

2. Comment: Please explain why only FOS and MMP9 were docked in the molecular docking validation, and whether there is a loss of other possible results and a lack of comparison.

Response: In the study, the main object of molecular docking is the core targets screened by combining network pharmacology and bioinformatics, so only the docking results of FOS and MMP9 were presented in this manuscript. We also conducted molecular docking simulation on other core targets, and indeed found the docking results of other molecules were all > -5 kcal/mol. Therefore, they were not shown in the manuscript. The molecular docking results of other core targets and resveratrol are attached in the following table:

Target	PDB ID	Docking score (kcal/mol)
AKT1	3MV5	-3.69
TP53	1AIE	-3.74
ALB	1YSX	-3.9
VEGFA	4CL7	-3.67
TNF	1A8M	-4.1
CTNNB1	7AFW	-4.4
EGFR	3POZ	-1.66
INS	1APH	-4.36
ESR1	1XP6	-3.37
MYC	6G6K	-4.0
CASP3	1CP3	-4.97
SRC	1A07	-4.22
PTEN	1D5R	-4.92
CCND1	2W96	-4.51
HSP90AA1	5NJX	-2.96
PPARG	2F4B	-3.26
PTGS2	5F19	-4.37
MTOR	1AUE	-2.67

3. Comment: Title: The title of the paper does not well summarize and reflect the content of the manuscript, and it is recommended that a new title selection be made.

Response: We thank the reviewer for this suggestion. The title has now been changed accordingly: “Identification of anti-gastric cancer effects and molecular mechanisms of resveratrol: From network pharmacology and bioinformatics to experimental validation”. We sincerely hope that the new title will better summarize the content of this study

4. Comment: Introduction: 1. The introduction in the manuscript should adequately and comprehensively describe the background of the study and the current status and significance of the applied technology. 2. There is a duplication of content between the introduction and the first paragraph of the discussion, and it is recommended that it be deleted or replaced.

Response: We are very sorry for our negligence of introduction writing. 1. We have re-written this part according to the reviewer’s suggestion. In the first paragraph of the introduction, we described the research status and the limitations of diagnosis and treatment of gastric cancer; In the second paragraph, we added the content of anti-tumor effects of resveratrol and its recent research progress in gastric cancer; In the last paragraph, we emphasized the importance of network pharmacology-based research on the anti-gastric cancer mechanism of resveratrol. 2. In the first paragraph of the discussion, we have removed the duplication of content already described in the introduction according to the reviewer’s suggestion.

5. Comment: Results: 1. Results section: e.g., Resveratrol suppressed proliferation, colony formation, migration and invasion of AGS cells, Resveratrol arrested cell cycle and induced apoptosis, Resveratrol inhibited AGS cells through regulating FOS and MMP9, are suggested to be subdivided and described. 2. Some of the figures in the manuscript are blurred: e.g., Figures 1, 4 and 7. 3. In the figures, the concentration of drug administered should not be written as "μm", but "μM".

Response: We have made correction according to the comments in the

results section. 1. We have supplemented the results of the study, especially in the experimental result section. We further subdivided the experimental results into “Resveratrol inhibited AGS cell proliferation”, “Resveratrol suppressed AGS cell migration and invasion”, “Resveratrol induced cell cycle S phase arrest and apoptosis in AGS cells”, and “Resveratrol inhibited AGS cells through regulating FOS and MMP9”. 2. According to the reviewer's reminder, we changed the figure clarity and concentration unit writing.

6. Comment: Discussion: 1. In the Discussion section, it is recommended that the discussion of the results follow the order of the results in the manuscript, and the discussion should be more in-depth, with attention paid to the correlation between results. 2. The spaces before paragraphs in the manuscript should be standardized.

Response: 1. We have expanded the content of the discussion section according the suggestions. We adjusted the writing order of the discussion section. The discussion of the results follows the order of the results in the manuscript to correspond the results to the discussion section. Please see the detailed modification content marked in yellow in the manuscript. 2. We have unified the space in each paragraph.

We thank the reviewer for this insightful comment.

Responds to the reviewer's comments: Reviewer #2:

1. Comment: Are there controversies in this field? What are the most recent and important achievements in the field? In my opinion, answers to these questions should be emphasized. Perhaps, in some cases, novelty of the recent achievements should be highlighted by indicating the year of publication in the text of the manuscript.

Response: We thank the reviewer for this excellent suggestion, and we have expanded the content of introduction to address the reviewer's suggestions. The first paragraph described the current situation and treatment of gastric

cancer, and emphasized the limitations of current diagnosis and treatment of gastric cancer. The second paragraph described the advantages of resveratrol as a traditional Chinese medicine monomer in anti-tumor, and focused on the research progress and achievements of resveratrol in gastric cancer in recent years. The last paragraph highlighted the importance and necessity of exploring the mechanism of resveratrol against gastric cancer based on network pharmacology and bioinformatics analysis

2. Comment: The results and discussion section is very weak and no emphasis is given on the discussion of the results like why certain effects are coming in to existence and what could be the possible reason behind them?

Response: We apologize for the weakness of the discussion, and thank the reviewer for the helpful suggestion. We modified the results and discussion section to make the discussion closely fit the research results. In the revised discussion, we sorted out the main points of this study based on the research results: 1. Through network pharmacology, we screened out the core biological targets and potential mechanisms of resveratrol action on gastric cancer. 2. Subsequently, FOS and MMP9 as the target genes with the most therapeutic potential were further screened out by bioinformatics analysis; 3. In vitro experiments proved that resveratrol inhibited proliferation, suppressed migration and invasion, and induced cell cycle arrest and apoptosis of gastric cancer cells. Molecular docking technology and RT-qPCR assays confirmed the molecular effects of resveratrol targeting FOS and MMP9. Taken together, our results suggested that resveratrol could inhibited gastric cancer cell proliferation, migration, and invasion and induced S phase arrest and apoptosis by targeting FOS and MMP9. Literature reports and experimental validation support the prediction of network analysis in this study. In addition, we also point out the limitations of this paper. We sincerely hope that the content of the manuscript can be improved after the revision.

3. Comment: Conclusion: not properly written.

Response: We are very sorry for our incorrect writing about the conclusion section, and we have revised this part to sum up the paper. We summarized the content of this study in concise sentences: "In conclusion, the mechanisms of action of resveratrol against GC were systematically elucidated based on network pharmacology and bioinformatics. Our results demonstrate that resveratrol inhibited proliferation, migration, and invasion and induced cell cycle arrest and apoptosis in GC cells by targeting FOS and MMP9, thereby playing an important role in regulating the progression of GC."

4. Comment: Results and conclusion: The section devoted to the explanation of the results suffers from the same problems revealed so far. Your storyline in the results section (and conclusion) is hard to follow. Moreover, the conclusions reached are really far from what one can infer from the empirical results.

Response: We are sorry that those part in the original manuscript has confused the reviewer. We should have subdivided the research results and analyzed the experimental results in depth. We have revised the contents of results and conclusion sections to make them clearer and more relevant

5. Comment: The discussion should be rather organized around arguments avoiding simply describing details without providing much meaning.

Response: The part of the discussion has been revised based on the helpful comments from the reviewer. We adjusted the discussion sections according to the order of the research results to make it easier for reviewers to read. We expand the analysis and discussion of each result, and strengthen the relationship between results. In addition, it is further discussed by combining with literature reports. Please see the detailed modification content marked in yellow in the manuscript.

6. Comment: Spacing, punctuation marks, grammar, and spelling errors should be reviewed thoroughly. I found so many typos throughout the manuscript.

Response: We thank the reviewer for pointing out this issue. We worked on the manuscript for a long time and the repeated addition and removal of sentences and sections obviously led to poor readability. We have now worked on corrections for writing errors. We really hope that the fluency of the manuscript has been substantially improved.

7. Comment: English is modest. Therefore, the authors need to improve their writing style. In addition, the whole manuscript needs to be checked by native English speakers.

Response: We apologize for the poor language of our manuscript. The revised manuscript has now been carefully proofread and polished by an English-editing professional service.

Special thanks to the reviewer for the helpful comments.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in yellow in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Thank you and best regards.

Yours sincerely,

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Round 2

Dear Editors and Reviewers:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editors and reviewers very much for their positive and constructive comments and suggestions on our manuscript (Manuscript NO.: 89639, Basic Study).

We have studied reviewer's comments carefully and have made revision which marked in red in the revised manuscript. We have tried our best to revise our manuscript according to the comments which we hope meet with approval. The main corrections in the manuscript and the responds to the reviewer's comments are as following:

Responds to the reviewer's comments:

Comment: The discussion should be rather organized around arguments avoiding simply describing details without providing much meaning. A real discussion should also link the findings of the study to theory and/or literature.

Response: We are very sorry for our negligence of discussion writing and we have expanded the content of the discussion section according the suggestions. In the revised discussion section, we mainly discussed the important pathways and targets screened by network pharmacology and bioinformatics. The key roles of these pathways and targets in this study were further discussed in combination with literature research, and connected with the subsequent analysis of experimental results. Please see the detailed modification content marked in red in the manuscript.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the revision will meet with your approval.

Thank you and best regards.

Yours sincerely,

Ying-Qian Ma