Peer Review File

Reviewer A

Comment 1: The atrial fibrillation (AF) and type 2 diabetes were the crucial topic in the paper. How about the incidence of AF in T2DM patients? Please state in the introduction.

Reply: We are grateful for the suggestion. As suggested by the reviewer, we have added more details of the incidence of AF in T2DM patients (see Page 4, line 95-97).

Changes in the text: Page 4, line 95-97

Comment 2: It was better to add related reference (DOI: 10.21037/atm.2019.09.03) about the applications of SGLT2i.

Reply: We deeply appreciate the reviewer's suggestion. According to the reviewer's comment, we have added related reference (DOI: 10.21037/atm.2019.09.03) about the applications of SGLT2i. (see Page 13, line 406-408).

Changes in the text: Page 13, line 406-408

Comment 3: In the part of methods, please state clearly the dose of used SGLT2i.

Reply: We are grateful for the suggestion. According to the reviewer's comment, we have added the dose of used SGLT2i. (see Page 8, line 235).

Changes in the text: Page 8, line 235

Comment 4: How about the effects of SGLT2i on the expression of SGLT2? So, firstly, it was better to test the expression of SGLT2 by Western blot.

Reply: We are appreciative of the reviewer's suggestion. Indeed, it will be more profound if we test the expression of SGLT2 by Western blot. However, due to the time of molding, we could not finish it in time. We will study it in the future work.

Changes in the text: None.

Comment 5: In the paper, there were top 10 hub genes identified in the PPI network. It was better to validate representative hub genes by experiments.

Reply: We appreciate the reviewer for the effort to review our manuscript. Indeed, it will be more profound if we validate representative hub genes by experiments. However, due to the time of molding, we could not finish it in time. We will study it in the future work.

Changes in the text: None.

Comment 6: In the paper, the diet induced obese (DIO) mice were used. It was suggested to further test the effects of SGLT2i on type 2 diabetes by B6.BKS(D)-Leprdb/J or B6.Cg-Lepob/J mice.

Reply: We are appreciative of the reviewer's suggestion. Indeed, it will be more profound if we further test the effects of SGLT2i on type 2 diabetes by B6.BKS(D)-Leprdb/J or B6. Cg-Lepob/J mice. We will study it in the future work.

Changes in the text: None.

Comment 7: In the figure 12, the inflammatory reaction was showed. How about the effects of SGLT2i on cytokines? Please supplement in the discussion.

Reply: We are grateful for the suggestion. According to the reviewer's comment, we have added the effects of SGLT2i on cytokines. (see Page 15, line 469-470).

Changes in the text: Page 15, line 469-470

Comment 8: What were the roles of AGE and RAGE in AF? Please state in the discussion.

Reply: We are appreciative of the reviewer's suggestion. According to the reviewer's comment, we have added the roles of AGE and RAGE in AF in the discussion. (see Page 15, line 451-455).

Changes in the text: Page 15, line 451-455

Reviewer B

Comment 1: First, in the title, please indicate that this is a network pharmacology study.

Reply: We are appreciative of the reviewer's suggestion. We have indicated that this is a network pharmacology study in the title. (see Page 1, line 3-5).

Changes in the text: Page 1, line 3-5

Comment 2: Second, the abstract needs further revisions. The background needs to indicate the clinical needs for this research focus and why SGLT2i is potentially effective for obesity-related AF. The methods need to describe more details of the animal experimental procedures. The results need to quantify the findings by reporting AF rates and other outcomes in the two groups and accurate P values for the statistical comparisons. The conclusion needs more detailed comments for the clinical implications of the findings.

Reply: We are grateful for the suggestion. According to the reviewer's comment, we have added more details in our revised manuscript. (see Page 2, line 37-43, line 46, line 62; Page 8, line 235-243; Page 12, line 371; Page 13, line 406-408; Page 15, line 451-455; Page 15, line 469-470).

Changes in the text: Page 2, line 37-43, line 46, line 62; Page 8, line 235-243; Page 12, line 371; Page 13, line 406-408; Page 15, line 451-455; Page 15, line 469-470

Comment 3: Third, in the introduction of the main text, please review what has been known on the physiological and pharmacological mechanisms and the effectiveness of SGLTi2 for AF including the effect size and whether its effectiveness of SGLTi2 is convincing in the level of clinical evidence. Please also clearly indicate the potential clinical significance of this research focus.

Reply: We are grateful for the suggestion. According to the reviewer's comment, we have added more details in our revised manuscript. (see Page 4, line 105-108).

Changes in the text: Page 4, line 105-108

Comment 4: Fourth, in the methodology of the main text, please briefly review the experimental procedures of this research and the questions to be answered by these procedures. In statistics, please ensure P<0.05 is two-sided.

Reply: We are appreciative of the reviewer's suggestion. According to the reviewer's comment, we have added more details in our revised manuscript. (see Page 10, line 281-287).

Changes in the text: Page 10, line 281-287.

Reviewer C

1. Your abstract is too long. The abstract should be 200-350 words, but you have 378. Please revise.

Reply: We are grateful for the suggestion. and we have revised the abstract.

2. References:
1) Reference 6 and 31 are duplicate references in your Reference list. Please check and revise.
2) There are two reference lists in your manuscript. Please remove the first one.

Reply: We are grateful for the suggestion. and we have checked and revised.

3. Please check if any more references need to be added in the below sentence since you mentioned "Studies", but only one reference was cited. If not, "studies" should be changed to "a study/a previous study".

471   persistent AF could be prevented (55). In addition, studies have shown that elevated
472   levels of MMP-9 lead to excessive degradation of the extracellular matrix and increased
473   tissue remodeling, which can cause myocardial fibrosis and micro-reentrants,
474   ultimately leading to AF (56). A meta-analysis showed that compared to those without

Reply: We are grateful for the suggestion. and we have changed "studies" to "a previous study".

4. Figure 1:

1) Figure 1 is not clear enough. Please provide it in higher resolution.

2) Please indicate the full name of "SGLT2i", "PPI", "GO", "KEGG" in the legend.

Reply: We are appreciative of the suggestion. According to the comment, we have done them.

5. Figure 3:

Figure 3A is vague. Please provide Figure 3 in higher resolution.

Reply: We are appreciative of the suggestion. According to the comment, we have provided Figure 3 in higher resolution
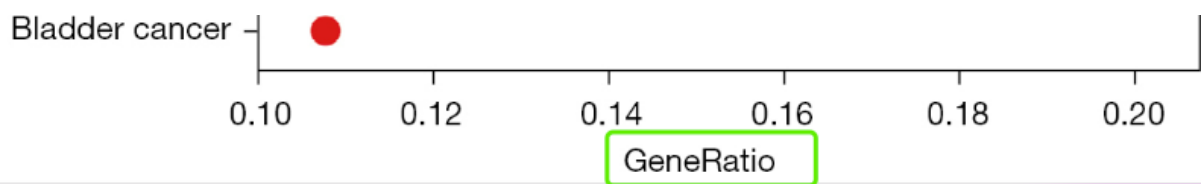
6. Figure 5:

Please indicate the full name of "BP", "CC", "MF" in the legend.

Reply: We are appreciative of the suggestion. We have indicated the full name of "BP", "CC", "MF" in the legend.
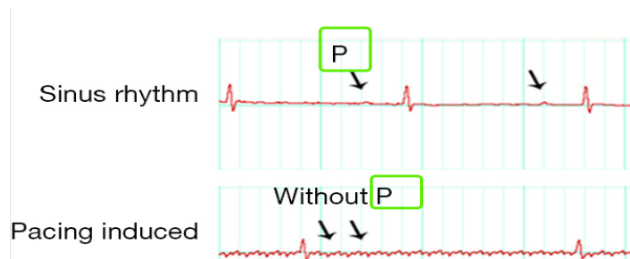
7. Figure 6:

Please revise "GeneRatio" to "Gene Ratio".

Reply: We are appreciative of the suggestion. We have revised "GeneRatio" to "Gene Ratio".

8. Figure 9:

What is the meaning of "P"? Please indicate it in the legend.

Reply: We are appreciative of the suggestion. We have indicated it in the legend.

9. Please indicate the full name of "SGLT2i" in Figures 1-3, 7-12 legends.

Reply: We are appreciative of the suggestion. We have indicated the full name of "SGLT2i" in Figures 1-3, 7-12 legends.