Author's response to Reviewer's Comments

We appreciate thoughtful and thorough comments by the reviewers and editors. We have revised our manuscript accordingly and feel it has improved and will be acceptable for publication. Following are the author's response to reviewer's comments.

Reviewer # 1

Comment 1) "Add references to table 1"
Response: We have added the references to table 1

Comment 2) "correct the statement "butyrate-producing bacteria such as Akkermansia muciniphila""
Response: We have made the correction.

Reviewer # 2

Comment 1) "Making improvements to English language expression and syntax throughout the paper"
1) Paragraph one of introduction "unhealthy food habits" (poor-quality diet)
Response: As per suggestion, changed the wordings to poor-quality diet

2) Paragraph 3 introduction "open the gates" (way)
Response: As per suggestion, changed the wording to way

3) Para 3 gut dysbiosis section "aiding" (promoting)
Response: As per suggestion, changed the wording to promoting

4) Para 4 gut dysbiosis "negatively correlation" (decreased abundance)
Response: As per suggestion, changed the wording to decreased abundance

5) The use of plurals "inflammations"
Response: Made the correction to inflammation

6) "modulate THE insulin release" etc etc. some sentences are too long and could be more succinct eg First sentence paragraph 3.

Response: As per suggestion, we have made the sentence short and succinct.

Comment 2) "more references to some of the important statements"
1) "Over the last decade multiple studies have indicated a possible causal role of alterations in gut microbiota with development of T2DM (reference)
Response: We have included more references

2) "Various studies are exhaustively exploring the role of gut microbiota as a biomarker for T2DM and a possible therapeutic intervention to treat T2DM (reference).
Response: We have included more references

Comment 3) "Suggest adding polycystic ovary syndrome to the list of dysbiosis-related conditions throughout the paper"
Response: We have added PCOS to the list

Comment 4) This sentence does not "fit" in with the rest of the paragraph or the flow of the paper: After the invention of insulin secreting sulfonylurea drugs in the 1950s, the industrial approach of developing newer anti-diabetic medications is towards formulating agents which increase insulin release".
Response: We have deleted this statement

Comment 5) Suggest more recent reference as MB is a rapidly developing field:"Gut microbiota in obese people lack microbial diversity and specifically there is a decline in the Bacteroidetes population along with an abundance in the Firmicutes population resulting in decreased Bacteroidetes to Firmicutes ratio [49]". (49 = 2006 paper)."
Response: We have included a more recent paper

Comment 6) "I would like to see a few more concluding sentences in some of the medication sections on the IMPLICATIONS of the study findings that are relevant to the aims of the review"
Response: Edited the manuscript per reviewer's recommendation and added the following concluding sentences.

For Metformin: "Based on the large body of evidence summarized above, it is safe to say that metformin has consistently shown a beneficial effect towards improving the gut health and cardiovascular health."

For DPP-4 Inhibitors: "Based on the current evidence summarized above, not all DPP4 inhibitors seem to have a positive impact on gut microbiota. The limited studies involving Linagliptin may have shown a benefit due its combination with a PPAR- alpha agonist, which is known to play a role in intestinal cell metabolism, differentiation, and inflammation. Although, the studies involving Sitagliptin and Vildagliptin have shown a benefit, they were conducted in mice. Future studies in humans are awaited to see if the results from the current studies can be replicated or not."

For SGLT-2 Inhibitors: "Based on the literature evidence summarized above, SGLT-2 inhibitors have a positive impact on the gut microbiota. It is well known that SGLT-2 inhibitors are effective in treating DM and in providing CV protection. Future studies are awaited to understand whether these beneficial effects are in part due to their action on the gut microbiota."

For PPAR- Gamma Agonists: "As shown above, an agonistic effect on PPAR gamma receptors that are widely present throughout the colon, can have a positive impact on gut health. However, the current

evidence is limited, and it is compounded by the infrequent use of medications belonging to this class. Hence it will be interesting to see if future studies look more closely into the relationship between PPAR gamma receptor agonism and gut microbiota."

For Sulfonylureas: " The lack of an alteration in the gut microbiota by sulfonylureas may be partly due to the limited studies that have investigated its role in gut health. However, current literature has shown no organ protection action including cardiovascular protection from the use of a sulfonylurea. This poses a question about its role in gut health and future studies are needed for a better clarification."

Comment 7) Figure 1: 3. Consider "altered mucosal permeability" rather than bacterial translocation. Bacteria are not translocated but LPS induces increased permeability.
Response: We have made the change

Comment 8) Figure 1: Consider adding a fourth box: DM, MS, CVD and PCOS.
Response: We have included PCOS as a fourth box

Comment 9) "I believe the English language expression should be improved in the conclusion and a more definitive statement made linking the aims and study findings"
Response: We have improved the language and gave a more definitive statement

EDITORIAL OFFICE'S COMMENTS

Science Editor's Comments:

Comment 1) "Self-Citation Count: 3 The self-referencing rate should be less than 3%"

Response: There are only 2 self-cited articles (Ref 9 and 45) which is <3%. Author "Kant R" in reference 20 is not Dr. Ravi Kant (1st author on our article).

Comment 2) "The format of the table should be a three-line table"
Response: Done

Company Editor-In-Chief's Comments:

Comment 1) "Provide the original Figure Documents"
Response: have uploaded the original figure documents

Comment 2) "prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor"
Response: The figures have been prepared using PowerPoint.

Comment 3) “If the picture is ‘original’, the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022”
Response: All of our pictures are original, and we have attached the above copyright information.

Comment 4) “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”
Response: We do not have any re-used figure or table. All our figures and tables are original.