

Reviewer #1:

Q.1 “the specific mechanism of beneficial gut microbiota in improving metabolic syndrome has not been explained in detail. It would be better if we could elaborate on the mechanism in detail.”

Author Response: Thank you for this recommendation. Beneficial gut microbiota produce short-chain fatty acids (SCFAs), which have an effect through tissue-specific mechanisms that are protective against metabolic syndrome by improving insulin sensitivity, such as the SCFA propionate promoting the release of glucagon like peptide-1. Additionally, metabolic syndrome is associated with inflammation, and maintenance of the gut barrier is important for preventing pro-inflammatory bacterial products from crossing into the systemic circulation. Beneficial gut microbiota promote the gut barrier through SCFA production.

Reviewer #2:

Q.1. “reduction in the Firmicutes to Bacteroidetes ratio, what would be the effect”?

Author Response: *Firmicutes* to *Bacteroidetes* ratio has been considered the hallmark of obesity and the reduction in the ratio is associated with improvement in obesity. We have added references to the article.

References:

- Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006 Dec 21;444(7122):1022-3. doi: 10.1038/4441022a. PMID: 17183309.
- De Filippo, Carlotta, et al. "Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa." *Proceedings of the National Academy of Sciences* 107.33 (2010): 14691-14696.

Q.2. “decrease in Enterococci and Enterobacteriaceae”?

Author Response: A decrease in Enterococci and Enterobacteriaceae has been shown to decrease the risk for inflammatory bowel disease. We have added the reference to the article.

Reference:

- Baldelli V, Scaldaferri F, Putignani L, Del Chierico F. The Role of Enterobacteriaceae in Gut Microbiota Dysbiosis in Inflammatory Bowel Diseases. *Microorganisms*. 2021 Mar 27;9(4):697. doi: 10.3390/microorganisms9040697. PMID: 33801755; PMCID: PMC8066304.

“Increase in *Faecalibacterium prausnitzii*”?

Author Response: Increase in *Faecalibacterium prausnitzii* has anti-inflammatory properties. We have added the reference to the article.

Reference:

- Maioli TU, Borrás-Nogues E, Torres L, Barbosa SC, Martins VD, Langella P, Azevedo VA, Chatel JM. Possible Benefits of *Faecalibacterium prausnitzii* for Obesity-Associated Gut Disorders. *Front Pharmacol*. 2021 Dec 2;12:740636. doi: 10.3389/fphar.2021.740636. PMID: 34925006; PMCID: PMC8677946.

“Increase in Bifidobacteria”?

Author Response: Increase in *Bifidobacteria*, which is one of the most commonly used probiotic promotes gut health, decrease expression of inflammatory cytokines and improve insulin sensitivity. We have added the reference to the article.

Reference:

- Amar, J. et al. Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment. *EMBO Mol Med* 3, 559–572 (2011).

“with a decrease in Bacteroides”?

Author Response: Decrease in Bacteroides is beneficial to humans since it is a pathogen commonly found anerobic infection and causes significant antibiotic resistance. We have added the reference to the article.

Reference:

- Wexler HM. Bacteroides: the good, the bad, and the nitty-gritty. *Clin Microbiol Rev.* 2007 Oct;20(4):593-621. doi: 10.1128/CMR.00008-07. PMID: 17934076; PMCID: PMC2176045.

Q.3. “This statement needs reference: It is known that obesity, T2DM and CVD are caused or worsened by multiple factors like genetic predisposition, environmental factors, unhealthy high calorie diet, and sedentary lifestyle”

Author Response: Thank you for this recommendation. We have added the reference to the article.

References:

- Groop, Leif. "Genetics of the metabolic syndrome." *British Journal of Nutrition* 83.S1 (2000): S39-S48.
- Gluckman, Peter D., and Mark A. Hanson. "The developmental origins of the metabolic syndrome." *Trends in Endocrinology & Metabolism* 15.4 (2004): 183-187.
- Edwardson, Charlotte L., et al. "Association of sedentary behaviour with metabolic syndrome: a meta-analysis." *PloS one* 7.4 (2012): e34916.

Q.4. “An increased production of SCFA has been found in obesity and decreased production of butyrate and propionate is seen in T2DM. In mice studies, butyrate was shown to be associated with increased production of Lachnospiraceae and Proteobacteria and decreased production of Clostridiaceae. SCFA can reduce obesity, so why is it contrary to the results of the latter experiment.”?

Author Response: Thank you for pointing out the discrepancy. There is typo in the first sentence, and we have rectified it to say, “Increased production of acetate has been found in obesity.....”

“And butyrate and propionate are produced by Postbiotics”?

Author response: The SCFA's, butyrate and propionate are among the metabolites that are produced from the inactive microbe aka postbiotic.

Q.5. This statement needs reference: Various studies in animals have shown their benefits in improving gut microbiome composition.

Author Response: Thank you for this recommendation. The below references have been included.

Ref:

- Cao L, Yang X.J, Li Z.J, Sun F.F, Wu X.H, Yao J.H. Reduced lesions in chickens with *Clostridium perfringens*-induced necrotic enteritis by *Lactobacillus fermentum* 1. 20291. *Poult. Sci.* 2012;91(12):3065–3071.
- Chaves B.D, Brashears M.M, Nightingale K.K. Applications and safety considerations of *Lactobacillus salivarius* as a probiotic in animal and human health. *J. Appl. Microbiol.* 2017;123(1):18–28.

Q.7. “Another study with 40 participants with insulin resistance were placed in a double-blind trial and given either Akkermansia muciniphila or a placebo, and the study showed reduction in inflammatory markers and improved insulin sensitivity in the Akkermansia muciniphila group. What is this sentence trying to say at the end? I think it is not a summary of this article and should be placed at the front”.

Author Response: Thank you for pointing this out. We have made the necessary change by moving the sentence to the appropriate place in the article.

Q.8. “The table can be further refined, for example, what are the effects and what can be done through what mechanism”.

Author Response: Thank you for this recommendation. We have edited Table 2 to include the above recommendations.

Q.9. “Figure2, 3, 4 in The beneficial effects of prebiotics , postbiotics , probiotics on the gut microbiome consistent, what are the different differences in their effects, compared to the common use or which one is the best, in order to be more intuitive, and then have a I think it is necessary to have a longitudinal comparison of the figure”.

Author Response: Thank you for this recommendation. We have included the differences in their effects and have included a longitudinal comparison of the figure.

EDITORIAL OFFICE’S COMMENTS

“The author(s) must include the keyword “Diabetes” in the keywords list”

Author Response: Thank you for this recommendation. We have included the keyword “Diabetes” in the keyword list.

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“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”.

Author Response: Yes, we have followed the above suggestions.

“Please check and confirm whether the figures are original”

Author Response: We have added the required information on the bottom right-hand side of the picture in PowerPoint.