Below we have responded point-by-point to the reviewer's comments.

3 Peer-review reports

Reviewer #1:

A plethora of excellent dedicated and very detailed reviews about probiotics, prebiotics (and synbiotics, which these authors did not present), and fecal microbial transplantation (FMT) in IBD has been published. In order for a new review to be published, it should bring some new data, ideas, figures, interpretation of studies etc. Unfortunately, this manuscript does not bring anything new (but a lot of pages) and just gives some examples of each therapy, in a very superficial manner.

The authors do not present the real emerging therapies, which include new human-derived oral biotherapeutic products (composed of mixtures of protective commensal bacterial strains, like strains of Clostridium cocktail and other well-defined strains), substrates from microbiota (PolyP, from path E. coli), editing pathobionts and inhibiting binding (Tungstate), bacteriophages (AIEC-specific), protective yeasts (Candida glabrata), engineered bacteria (producing IL-10, IL-35, Elafin, Trefoil), while all these new possibilities were recently published in an excellent review by "Oka A, Sartor RB. Microbial-Based and Microbial-Targeted Therapies for Inflammatory Bowel Diseases. Dig Dis Sci. 2020 Mar;65(3):757-788 Published 31 January 2020 ".

There is very scarce useful data in the manuscript, and nothing about concrete "Personalized therapy based on microbiota profiles", while the review by Oka and Sartor emphasized this. Therefore, in any way I would suggest a major revision, this would not be possible, as all the useful information has been already published, in excellent reviews. One thing that I would mention: maybe the authors could write about herbal medicine in IBD and expand that paragraph to write a very useful review, which would benefit doctors and their patients.

Comments:

A. TITLE: Regulation of the intestinal microbiota: an emerging therapeutic strategy for IBD" – it may be an emerging strategy, but the authors did not present anything

new. Besides, as I mentioned previously, they did not present the real emerging strategies.

Response: Your comments are crucial and help us extend the cognition of intestinal microbiota. The theme of the article is to review the most recent evidence for direct or indirect interventions that targeting to intestinal microbiota for the treatment of IBD, to understand the current limitations of IBD therapies, and to shed light on personalized treatment options.

B. ABSTRACT: The authors wrote "We review the most recent evidence for direct or indirect interventions targeting intestinal microbiota for treatment of IBD in order to overcome the current limitations of IBD therapies and shed light on personalized treatment options". First, they did not write a proper review of existing studies in the literature. Second, they did not shed any light on personalized treatment options.

Response: Thanks for your comments. We admit there still some deficiency in this review. In our review, we explore therapies targeting intestinal microbiota, such as FMT, pro/prebiotics, and herbal medicinal products, that represent effective therapeutic options to control and slow the progression of IBD. We additionally discuss some clinical applications and where to put more focus in relation to these emerging therapeutic strategies. It has direct inspiration on researchers to overcome the current limitations of IBD therapies and shed light on personalized treatment options.

C. CORE TIP:

1. The authors wrote: In this review, we explore therapies targeting intestinal microbiota, such as FMT, pro/prebiotics, and herbal medicinal products, that represent effective therapeutic options to control and slow the progression of IBD". Which are these effective therapeutic options to control and slow the progression? There are some Probiotics useful only in UC and pouchitis (and the authors did not even

mention all of them), for Prebiotics – there is a very scarce evidence, and for FMT the efficacy is not clear yet, especially in CD and not without side effects.

Response: Thanks for your suggestion. As for the effective therapeutic options, such as FMT, pro/prebiotics and herbal medicinal products, we listed the corresponding descriptions in each section, from line 96 to line 300. We also inserted more evidence (red highlighted) to strengthen this section.

2. The authors wrote: We additionally discuss some challenges and controversies in relation to these emerging therapeutic strategies." What are these challenges and controversies? Besides, these are not emerging therapeutic strategies.

Response: Thank you. We deleted the original sentence-"We additionally discuss some challenges and controversies in relation to these emerging therapeutic strategies", and inserted the description "We additionally discuss some clinical applications and where to put more focus on these emerging therapeutic strategies." in line 92-93.

3. The authors wrote: „It has direct inspiration on researchers to overcome the current limitations of IBD therapies and shed light on personalized treatment options." What inspiration on researchers was given? How come these therapies shed light on personalized therapy? Please explain.

Response: Thank you. We described the inspiration on researchers in CONCLUSION AND FUTURE PERSPECTIVES section, in line 471-476. The last paragraph from line 479 to 483 is regarding the prospect on personalized therapy

D. INTRODUCTION:

1. "Although genetic, immunological, microbial, and environmental factors are involved in the etiology of IBD, none have been identified as the explicit and direct cause of IBD[2, 3]" please insert „epigenetics".

Response: Thank you. We have inserted "epigenetics" in line 52.

2. Page 3: paragraph starting with „It has been verified"…instead writing about microbiota in general, the authors could write a smart table, summarizing the scientific evidence of dysbiosis in IBD (UC and CD). In any case, the sentence „It has been verified that the intestine has rich microbial abundance, and includes enteric bacteria (>99% of the gut microflora), fungi (about 0.1%), and viruses." is not correct. The authors wrote this info also in their paper from 2019, "Yue B, Luo X, Yu Z, Mani S, Wang Z, Dou W. Inflammatory Bowel Disease: A Potential Result from the Collusion between Gut Microbiota and Mucosal Immune System. Microorganisms 2019, 7" however the reference they used was old.

Response: Thank you. Actually more evidence supports the sentence-"It has been verified that the intestine has rich microbial abundance, and includes enteric bacteria (>99% of the gut microflora), fungi (about 0.1%), and viruses.", in reference 9. and it is really the latest report.

3. Page 4 – the authors wrote about postbiotics as novel therapeutic strategies for IBD, however they did not approach this topic in the manuscript. It can be found in the above mentioned review by Oka and Sartor.

Response: Thank you. We carefully checked the article you mentioned by Oka and Sartor, but we didn't find the relevant descriptiont about postbiotics. We found the descriptions regarding postbiotics in another review paper (PMID: 31586663), which mentioned "Postbiotics refer to cell-wall components and/or metabolic byproducts, which are secreted by live bacteria or released following bacterial lysis that could contribute to health improvement of the host. Postbiotics may stimulate anti-inflammatory immune responses and act as immunomodulators". According to the precise definition of postbiotics, we found that postbiotics can directly beneficial to the host instead of via direct or indirect regulating intestinal microbiota. So finally we deleted the word "postbiotics" in the manuscript.

4. Page 4: As I mentioned in the Abstract, the aim of this review was not fulfilled: "Aim: we explore therapies targeting intestinal microbiota, such as FMT, pro/prebiotics, and herbal medicinal products, that represent effective therapeutic options to control and slow the progression of IBD. We additionally discuss some challenges and controversies in relation to these emerging therapeutic strategies."

Response: Thank you. We changed the sentence to "We additionally discuss some clinical applications and where to put more focus on relating to these emerging therapeutic strategies." in line 92-93.

5. Figure 1: a. Please correct dysbacteriosis with dysbiosis (as everywhere in the text).

Response: Thank you. We have modified "dysbacteriosis" to "dysbiosis" throughout the manuscript.

b. There are probiotics used also in enema (like Lactobacillus reuteri ATCC 55730) – reference: Oliva S, et al. Randomised clinical trial: the effectiveness of Lactobacillus reuteri ATCC 55730 rectal enema in children with active distal ulcerative colitis. Aliment Pharmacol Ther. 2012 Feb;35(3):327-34. doi: 10.1111/j.1365-2036.2011.04939.x.

Response: Thank you. Yes, you are right. We inserted the description regarding enema in figure 1.

c. Figure 1 mentions synbiotics (combination of probiotics and prebiotics in a form of SYNERGISM), but there is no paragraph in the text.

Response: Thank you. As we all know, synbiotics are the products that combine probiotics and prebiotics in a synergistic form. So the action mechanisms of synbiotics are similar to that of probiotics and/or prebiotics, in a way of regulating intestinal microbiota. We discussed synbiotics in line 404.

D. FMT is given not only by "coloclysis". Please correct.

Response: Thank you. Yes, you are correct. What the figure shows is the general administration approaches.

E. There is no mention in the figure about probiotics in pouchitis (mentioning only alleviating active ulcerative colitis).

Response: Thank you. We have added the content regarding probiotics in pouchitis in figure 1 and line 124.

f. Title of the figure – again, these are not emerging therapies….

Response: Thank you. We have modified figure title to "Regulation of intestinal microbiota as a therapeutic strategy for IBD." in line 997.

• Why the role of symbiotics in IBD have not been addressed in this review?

Response: Thank you. As aforementioned, we discussed synbiotics in line 404.

E. THERAPEUTIC STRATEGIES TARGETING INSTESTINAL MICROBIOTA

1. Probiotics:

a. There is no need to mention their history.

Response: Thank you. In this section, we briefly summarized the historical origin of probiotics, which may help to seek next-generation probiotic strains.

b. Sentence :" Probiotic strains discovered to date mostly belong to the phylum Firmicutes and include the genera Aerococcis, Enterococcus, Lactobacillus, Lactococcus, Leuconostoc, Oenococcus, Pediococcus, Streptococcus, Carnobacterium, Tetragenococcus, Vagococcus, and Weissella" is not correct and the reference is obviously wrong (16 - Roberfroid M. Prebiotics: the concept revisited. J Nutr 2007).

Response: Thank you. We have replaced the original reference (Roberfroid M. Prebiotics: the concept revisited. J Nutr 2007) with a new reference paper (ref. 21,

Stiles ME, Holzapfel WH. Lactic acid bacteria of foods and their current taxonomy. Int J Food Microbiol. 1997, 36: 1-29 [PMID: 9168311 DOI: 10.1093/jn/137.3.830S])

c. In this paragraph, the authors wrote about efficacy of VSL#3 (described wrongly as VSL#L) in UC. However, later on, there is another Paragraph titled „,

Response: Thank you. We have corrected all the typos about VSL#3.

CLINICAL APPLICATIONS OF PROBIOTICS AND PREBIOTICS IN IBD TREATMENT”, in which they wrote again about probiotics. It should be synthetized better. In any case, either they decide to write a review of published studies on probiotics in IBD (which would not be the best idea, since many wonderful reviews on this topic were previously published” or they present just the studies with proven efficacy.

These studies should include populations, type of disease and activity, type of probiotic, doses, duration, effects and other medication used. About VSL#3, I particularly advise the authors to read the new scientific news on this probiotic, as nowadays it is called ”De Simone Formulation”, since this is the original formula that was invented by Claudio de Simone.

d. Reference 22 refers to a Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease, not a recent study, as the authors wrote.

Response: Thank you. We have inserted reference 35 regarding VSL#3 (Claudio de Simone….). Plus, we have rectified the sentence to “in a recent systematic meta-analysis” in line 123.

e. At the end of this paragraph, just mentioning some potential effects of probiotics in IBD has no point here, since the one of the next paragraphs presents the potential therapeutic mechanisms

Response: Thank you. We made a brief summary with respect to the potential effects of probiotics in IBD at the end of this paragraph in line 123-127. Subsequently, we

described the potential therapeutic mechanisms.

(POTENTIAL THERAPEUTIC MECHANISMS BY WHICH INTESTINAL MICROBIOTA ARE TARGETED).

Please revise. f. Also (page 5) lactocepin is not "a novel antimicrobial protease encoded by Lactobacillus paracasei part P", as it was discovered in 2012.

Response: Thank you. We have corrected it to "An antimicrobial protease encoded by Lactobacillus paracasei part P." in line 143.

g. In a whole, this paragraph about "Probiotics" does not show any new data.

Response: Thank you. This is a comprehensive and in-depth review of the current data regarding probiotics in IBD therapy.

2. Prebiotics:

a. Again, there is no point in writing about history of definitions; we have the new one from 2017 and that is enough. This manuscript should focus on therapies in IBD. Enumerating the types of prebiotics and their effects in general has no relevance here. There are thousands of published papers about prebiotics, types and their effects, which mention in detail all their effects, not only some. Please remove everything that is not related to IBD (from pages 6 and 7).

Response: Thank you. As aforementioned, in this section, we briefly summarized the historical origin of probiotics. All the content in this paragraph is relevant to IBD.

b. To note here, references 29 and 39 are the same – new definition of prebiotics.

Response: Thank you. We have corrected this.

c. Starting with "Studies evaluating the potential" refers to IBD. However, there are only some studies mentioned, not all studies that used prebiotics in IBD. How were these particular studies selected and why? Same comments as for probiotics.

Response: Thank you. We have corrected it to "Several studies evaluating the potential…" in line 186.

d. The authors wrote "Studies evaluating the potential therapeutic effects of prebiotics on animal colitis models and IBD patients have demonstrated beneficial effects" [43, 44] – however, references 43 and 44 are reviews of the available scientific literature on IBD, not studies. Reference 43 presents the available scientific evidence about probiotics, prebiotics, vitamin D and caloric restriction and 44 about applicable (antibiotics, prebiotics, probiotics, synbiotics) and emerging microbiota treatment modalities (postbiotics, and fecal microbiota transplantation). They represent excellent reviews and contain more scientific data than this manuscript, with available studies in Tables etc, as it should be.

Response: Thank you. We replaced references 43 and 44 with references 49-53 (PMID: 27931127; 30395776; 30589960; 27658624; 20848469) in line 641-656.

e. Reference 45 is just one study in rats. Then the authors presented results of a systematic review and meta-analysis, but performed in "preclinical trials". And, then suddenly, without presenting any study in humans they conclude that "In comparison with animal studies of prebiotic applications, studies of prebiotics in IBD are very limited and remain controversial [43]. In brief, based on the current results for prebiotic interventions, we cannot conclude that prebiotics ameliorate IBD symptoms [49]." Therefore, what would really interest the physicians treating people with IBD is limited to 4 lines (beginning of page 8). There are many studies in people with IBD, however there is not enough evidence. But, the authors did not mention any study. Many other reviews mentioned all the available studies on prebiotics (the two mentioned above, as well as the one by Oka and Sartor). Therefore, what is the novelty brought by this review?

Response: Thank you. We have modified the description to "Moreover, a recent

experiment study of prebiotics in IBD models demonstrated that these agents play a strong beneficial role in relieving TNBS-induced colitis." in line 192-194.

3. Fecal microbiota transplantation:

a. There is no point in having the history of FMT, these facts have already been described in countless papers. Please just to the point. The authors wrote "Several clinical investigations have demonstrated promising treatment outcomes for patients in the mild or moderate active period of the disease." And they cited only a systematic review from 2012 (Anderson et al, ref. 57) and a systematic review and meta-analysis from 2017 (Paramsothy et al, ref. 58). However, the above mentioned reference – 44 – contains even a Table of the 8 (EIGHT) existing meta-anayses in IBD, with precise details of intervention, country, type of disease, number of studies, number of patients, clinical results and study heterogeneity. Therefore, the reference 44 has complete data. Moreover, the excellent review by Oka A and Sartor RB, that I mentioned all the time and published in 2020, has a detailed summary of all studies with FMT performed in UC, CD and pouchitis. In fact, Table 6 of this excellent review mentions in detail also all the ongoing RCTs registered on ClinicalTrials.gov on probiotics, prebiotics, synbiotics, FMT, but also emerging therapies (bacteriophage and LBP). The reference 44 also mentioned the major limitations of FMT, regarding safety issues and long-term side consequences in treating IBD, citing a systematic review (Wang S, et al. PLoS One 2016) and other new excellent manuscripts (Sunkara, T, et al, J. Inflamm. Res. 2018; Basso PJ, et al, Front. Pharmacol. 2019; Imdad A, et al. Cochrane Database Syst. Rev. 2018).

Response: Thank you. The overall theme of this review is to summarize the research concerning regulating intestinal microbiota for the treatment of IBD. We admit there still some aspects to improve our manuscript. As you will find, we have considerably revised our manuscript using the helpful comments to guide us.

F. POTENTIAL THERAPEUTIC MECHANISMS BY WHICH INTESTINAL

MICROBIOTA ARE TARGETED These mechanisms have already been detailed in dedicated reviews, like Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A1. Mechanisms of Action of Probiotics. Adv Nutr. 2019 Jan 1;10(suppl_1):S49-S66. doi: 10.1093/advances/nmy063, with detailed and amazing figures for each mechanisms. Thus, this paragraph is not useful, as it is not complete.

Response: Thank you. We have reviewed all relevant publications in recent years concerning intestinal microbiota in the treatment of IBD, which include the reference article by Plaza-Diaz J. We would like to carry out more in-depth analysis in the future.

G. CLINICAL APPLICATIONS OF PROBIOTICS AND PREBIOTICS IN IBD TREATMENT Now, we are back to IBD therapy. Could this structure be improved and this material be organized? Not to have so many redundant paragraphs? In any case, there are just words, without any precise data on what, when and how to use.

Response: Thank you. We added description in line 418-419 and 428-433 to strengthen our manuscript. We admit there still some aspects to improve our work in the future. This is a comprehensive and in-depth report of gut microbiota and IBD treatment. On the other hand, the content the review is new and timely.

H. CONCLUSION AND FUTURE PERSPECTIVES This paragraph could be divided in a proper „Conclusion" – which, in fact, shows nothing new and „Future perspectives". The latter paragraph could be inserted in the text, as this one represents the REAL EMERGING THERAPIES"…However, as said, this topic was already detailed in the excellent review by Oka and Sartor (2020)

Response: Thank you. In CONCLUSION AND FUTURE PERSPECTIVES section, we summarized the whole paper and gave perspectives for the future IBD treatment. We inserted the description "Remarkably, Oka A and Sartor RB proposed that concomitant companion diagnostic tests to profile individual's microbiota for guiding optimal personalized microbial therapies." in line 457-459.

I. Figure 2 is very incomplete. Minor observation: The manuscript is not prepared according to the WJG requirements. No ORCHID number of authors, no required format, etc.

Response: Thank you. We have modified Figure 2. The revised manuscript has complied with the requirement of the journal.

Reviewer #2:

The review submitted by Yue and cols., aims to summarize and discuss the modulation of intestinal microbiota as an alternative to treat IBD. However, there is a lack of novelty regarding the use of these molecules to treat IBD and the mechanism behind their functionality. Furthermore, some aspects need further clarification:

Response: Thank you for your comments. The overall theme of this review is to summarize the research concerning regulating intestinal microbiota for the treatment of IBD. This is a comprehensive and in-depth report, which may provide insight into the further evaluation of the therapeutic strategies for IBD. We admit there still some aspects to improve our manuscript. As you will find, we have considerably revised our manuscript using the helpful comments to guide us.

• So far, regarding the role of microbiota disturbances in IBD onset/outcome, some hypothesis have been proposed: 1- environmental factors influencing gut microbiota composition; 2 – different patterns of colonization in early life and, 3 – genetic-related immune disturbances leading to the lack of tolerance to indigenous microbial components. Because authors have described the first two, the third must be added to the manuscript.

Response: Thank you for your very helpful suggestion. We inserted description "In addition, the defects of several pattern recognition receptors (PRRs) genes, such as toll-like receptors (TLRs) and nod like receptors (NLRs), lead to the disturbances of innate immunity, which can ultimately reduce the host tolerance against intestinal

microorganisms.” in line 60-63.

• Authors have stated that gut microbiota composition is represented by 99% of bacteria and a minor population of fungi and viruses. However, it is believed that bacterial population represents 96-98%, further, besides the role of fungi and viruses in gut microbiota, some studies have been addressing the role of archaea in such composition. Thus, this information must be added to the review.

Response: Thank you. We inserted description “It has been verified that the intestine has rich microbial abundance, and includes enteric bacteria (99.1 % of the gut microflora), archaea (the majority of the rest), as well as only 0.1% of fungi and viruses.” in line 76-66, which can be found in reference 8 (PMID: 20203603) by of Qin J, et al. Nature. 2010; 464(7285):59-65.

• Authors must add a short description regarding the meaning of the word “virome”.

Response: Thank you. We added the description “The enteric vitrome includes all nucleic acids (DNA and/or RNA) that mapped to viral genomes are from fecal samples or virus-like particles rooted in fecal samples” in line 71-73.

• In several parts of the text there is a lack of reference. e.g: “However, in recent years, increasing evidence suggests that the intestinal microbial composition is significantly altered in IBD patients compared with that in health subjects”, suggestion: Microbial-Based Therapies in the Treatment of Inflammatory Bowel Disease - An Overview of Human Studies. Basso PJ, Câmara NOS, Sales-Campos H. Front Pharmacol. 2019 Jan 10;9:1571. doi: 10.3389/fphar.2018.01571. Authors must verify the entire review concerning the lack of references in parts of the text.

Response: Thank you. We have checked throughout the manuscript and inserted the corresponding references.

• Despite the lack of consistent data *regarding the effects of probiotics in intestinal

tract, several mechanisms have been proposed. Thus, authors must add an in-depth description of proposed mechanisms of action of probiotics. The mechanisms of action of probiotics in IBD are not limited to three, as described in the text. Suggested references:

o An introduction of the role of probiotics in human infections and autoimmune diseases. Sales-Campos H, Soares SC, Oliveira CJF. Crit Rev Microbiol. 2019 Aug;45(4):413-432. doi: 10.1080/1040841X.2019.1621261

o Sonnenburg JL, Chen CT, Gordon JI. 2006. Genomic and metabolic studies of the impact of probiotics on a model gut symbiont and host. PLoS Biol. 4:e413.

o Vitali B, Ndagijimana M, Maccaferri S, Biagi E, Guerzoni ME, Brigidi P. 2012. An in vitro evaluation of the effect of pro- biotics and prebiotics on the metabolic profile of human microbiota. Anaerobe. 18:386–391.

o Urdaci MC, Bressollier P, Pinchuk I. 2004. Bacillus clausii pro- biotic strains: antimicrobialand immunomodulatory activ- ities. J Clin Gastroenterol. 38:S86–S90.

o Madsen K, Cornish A, Soper P, McKaigney C, Jijon H, Yachimec C, Doyle J, Jewell L, De Simone C. 2001. Probiotic bacteria enhance murine and human intestinal epithelial barrier function. Gastroenterology. 121:580–591.

Response: Thank you very much for the information you provided. We have read these references carefully and added the description “4) Probiotics can directly impact the metabolic profile of intestinal microbiota and host, thus promoting the regulation of colonic cell proliferation and the clearance of hazardous substances in intestinal tract” in line 137-139.

• The authors stated that prebiotics selectively stimulate and increase the abundance of solely Lactobacillus and/or Bifidobacterium. However, due to the complexity and composition of gut microbiota it is almost impossible to ensure that prebiotics stimulate only two different populations. Thus, authors must rephrase and adequate this part of the text.

Response: Thank you. We have modified the sentence to “The effect of prebiotics is

to stimulate several microbial groups, and to increase not only the abundance of commensal *Lactobacillus* and/or *Bifidobacterium*, but also other beneficial taxa, such as *Roseburia*, *Eubacterium* and *Faecalibacterium* spp" in line 165-167.

• Because of the recent events regarding the use of FMT as a therapeutic tool, authors must highlight the detrimental outcome recently described by FDA (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse) and discuss how this observation may impact the further use of FMT in clinical practice.

Response: Thank you. We have carefully read the content from the link, and added description "And recently, the U.S. Food and Drug Administration (FDA) notified the potential risk of serious or life-threatening infections with the use of fecal microbiota for FMT, and claimed that bacterial infections are caused by multi-drug resistant organisms (MDROs) [U.S. Food & Drug Administration]. So potential risk of FMT reminds researchers again to focus more on how to increase the stability and security of FMT." in line 428-433.

• In page 11, authors stated: "The above mentioned novel treatment strategies…" However, none of the strategies addressed represent a "novel" therapeutic approach to treat IBD, rather, they have already been used either in experimental models or in clinical trials – this observation is also applied to the conclusion section. Thus, authors must rephrase this sentence. Further, the approaches described in the text may impact not only bacteria but the entire gut microbiota community.

Response: Thank you. We have rectified the word "novel" to "emerging" in the corresponding sentence in line 299. In addition, we added the description "including the inhibition of pathogenic microorganism and promoting the entire gut microbiota community" in the line 306-307.

• Starting at page 11, authors refer to microbiota disturbance as “dysbacteriosis”, however, because gut microbiota is composed by other microorganisms the correct term is gut dysbiosis or solely dysbiosis.

Response: Thank you. We have rectified “dysbacteriosis” to “dysbiosis” throughout the manuscript.

• The word “metabonomics” must be replaced by “metabolomics”

Response: Thank you. We have replaced the word “metabonomics” by “metabolomics” throughout the manuscript.

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• Why the role of symbiotics in IBD have not been addressed in this review?

Response: Thank you. As we know, synbiotics are the products that combine probiotics and prebiotics in a synergistic form. So the action mechanisms of synbiotics are similar to that of probiotics and/or prebiotics, in a way of regulating intestinal microbiota. We discussed synbiotics in line 404.

• In page 15, the word “synbiotics” must be replaced by “symbiotics”

Response: Thank you. We have replaced the word “synbiotics” by “symbiotics”.

Reviewer #3:

The authors have completed a narrative review on the use of manipulation of the intestinal microbiota in the treatment of inflammatory bowel disease, including probiotics, prebiotics, FMT and herbal supplements. it also discusses how these therapies may work which provides an interesting article for treating clinician. It is a well written and interesting article that is supplemented with good diagrams that aid the overall message of the article. The main issue that needs to be defined in such a review is the scope of the review and what questions the authors intend to answer as the current description is quite general. The method of identifying relevant papers for the review should be discussed either in the main paper or as supplemental material.

Minor points:

• The term VSL#L is used a few times – is this VSL#3 or something else? Please explain it further.

Response: Thank you. We have corrected all the typos for VSL#3.

• In the FMT section the line "complicated with intraabdominal inflammatory mass" can be changed to "complicated by an intraabdominal inflammatory mass" or "complicated by an intraabdominal inflammatory phlegmon"

Response: Thank you. We have changed the description"complicated with intraabdominal inflammatory mass" to "complicated by an intraabdominal inflammatory mass" in line 247-248.

• First sentence in "Herbal compounds and prescriptions" section is difficult to understand, consider changing this to "There are some safety concerns with the long-term use of conventional medications which has increased interest in traditional medicines for the treatment of IBD"

Response: Thank you. We have changed the description to "There are some safety concerns with the long-term use of conventional medications (e.g., anti-inflammatory, immunosuppressive, and biologic therapies), which has increased interest in traditional medicines for the treatment of IBD." in line 259-261.

• Treatment section – the use of probiotics and prebiotics in the treatment should be explained to be in conjunction with conventional medications given the limited evidence

Response: Thank you. We added the description "Moreover, the use of probiotics and prebiotics in the treatment of IBD usually in conjunction with conventional medications gives the limited evidence." in line 418-419.

• The sentence “The empirical evidences for prebiotics is relatively scarce” should be changed to “The evidence for probiotics are relatively scarce”

Response: Thank you. The sentence “The empirical evidences for prebiotics is relatively scarce” has been changed to “The evidence for probiotics is relatively scarce” in line 412-413.