Reviewer #1:

1. "The principal drawback of the main topic discussed in the paper, is that it can be hardly supported directly at the current stage of technology. However, this point is partially mentioned by the authors in the Biomarkers for assessing response of dietary therapy section."

Reply: We acknowledge the limitations with the current technologies available for assessment of H_2S and nitric oxide to progress research in the area *(see the end section of 'role as luminal toxins in the pathogenesis of UC' and also in 'biomarkers for assessing response of dietary therapy')*. However, we believe that it is precisely for this reason that the concepts proposed in the manuscript are needed to stimulate interest in the area to develop more reliable technical assessments. Therefore, to take into account the reviewers' comment, we have expanded the section of 'Biomarkers for assessing response' (p. 12) to highlight the gap in the current technology, suggested future techniques to overcome this gap as well as additional text in 'Summary' (p. 13) to emphasize the importance of addressing this need.

2. "In the abstract, the role of H2S (only is discussed). I would suggest to revise the abstract in accordance to what is discussed in the paper. Please, pay attention to the keywords as well."

Reply: Thank you for your suggestion. We have revised the abstract and keywords to include both H_2S and nitric oxide as is discussed in the paper.

3. "The role of dysbiosis in pathogenesis of ulcerative colitis is not commonly accepted. Please, revise the statement of the paragraph 1 on page 6, accordingly."

Reply: Thank you for highlighting this. We have revised the statement accordingly:

"Gut dysbiosis may be the main pathogenic factors of UC, and the higher dominance of sulphate-reducing microbes may potentially contribute to the dysbiosis hypothesised in the pathogenesis of UC."

4. In table 1, please use the other markers to refer the footnotes, as superscripted 1-3 seems weird (ml^2 or kg^3). Here, references [32] and [34] seem inappropriate. Please, provide the table's title before the table.

Reply: Thank you for the important comment. The table was changed as suggested and we have double checked the references. The references are correct.

5. Figure 1 is not clear. Could you explain what is shown in the main part of the picture (not in the text boxes)? The text labels don't match the figure itself.

Reply: We have re-drawn Figure 1 and added potential other mechanisms for which H2S and nitric oxide may play a role in the pathogenesis of UC to address the comment (comment #1) of reviewer #3.

5. Minor language polishing is required.

Reply: We have checked the manuscript for spelling and grammatical errors and have made edits to the language.

Reviewer   #2:
1. Throughout the manuscript there is lack of bibliographic references. - Core tip doesn't include in the Word document.

Reply: Thank you for pointing this out. We have gone through the manuscript and inserted references as needed. We have also added the core tip.

2. "Under DIET AS PRIMARY STRATEGY FOR COLONIC H2S & NITRIC OXIDE MANIPULATION I would add some literature notes to better contextualize the impact of probiotics and prebiotics."

Reply: Thank you for suggesting that we add a section to better contextualize the impact of probiotics and prebiotics. The ability of fructo-oligosaccharide, a well-established prebiotic and resistant starch, a candidate prebiotic, to suppress H_2S production have already been elucidated in the second paragraph (page 8) of the section. We have thus expanded the discussion regarding the effects of prebiotics, essentially fermentable fibres, on modulating H2S and added brief text on probiotics on pages 8-9.

3. "Additianally, BIOMARKERS FOR ASSESSING RESPONSE OF DIETARY THERAPY other self-reported questionaries (abdominal pain frequency with visual analog scale, food frequency questionnaire, Food-related quality of life (FRQoL), health-related quality of life (HRQOL)) could mentioned under this topic to evaluate adherence/response of diet interventions."

Reply: Thank you for this comment. <u>The following sentences have been added to this section (p. 12):</u>

"Therefore, as in most studies, assessment of dietary response is primarily assessed by different questionnaires such as dietary intake questionnaires, food-related quality of life or health-related quality of life questionnaire. Combined biomarker measurements with assessment by questionnaires can be the ideal tool for estimating the effect of specific dietary exposure."

Reviewer #3:
1. The relationship between gas metabolites and the pathogenesis of UC needs to be explored in more detail, and it is better to summarize the possible mechanisms in the form of pictures.

Reply: We have added a new Figure 1 to include possible pathogenic mechanisms that H2S and nitric oxide are involved in UC.

2. "It is better to list the results of clinical studies on targeted reduction of gas metabolites through dietary regimen as a treatment strategy for UC in the form of tables, and put forward constructive suggestions for subsequent clinical studies combined with the existing research conclusions."

Reply: Thank you for this suggestion. We have now added Table 2 summarising existing dietary interventions studies in the treatment of ulcerative colitis (UC) as a possible strategy to modify H_2S production. Each study characteristics of diet intervention, design, results of main outcomes and limitations are detailed in the table, and we have added the following sentence to the "Translating proposed dietary strategy into clinical application" section:

"Moreover, the limitations of the available reported clinical trials targeting reduction of H_2S production as a strategy treatment for UC (Table 2) suggest the need for larger quality designed

studies incorporating gut microbiome composition and function assessment including changes in microbial H$_2$S metabolism."