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Response to Reviewers' Comments:

Reviewer #1

The authors submit their original work of a mini review regarding pathogenesis of IBD. I would like to thank the authors for their hard work on submitting this manuscript and I enjoyed reading their outcomes. Their hard work is admirable. While I do think the current work may be worthy of publication as this type of comparison has rarely been done before, I would recommend the authors address the minor issues listed below before further consideration. Abstract: No additional recommendations. Manuscript: -Would recommend including a paragraph in the intestinal microbes disorder section detailed if fecal microbiota transplantation is beneficial. Other minor edits: Can the authors check that the entire manuscript be written in the past tense? Again, I applaud the authors for their hard work. I look forward to reading the revised manuscript.
Question 1: Would recommend including a paragraph in the intestinal microbes disorder section detailed if fecal microbiota transplantation is beneficial. **Response 1**: Thanks for the reviewer's advice. FMT was being explored for conditions like inflammatory bowel

disease, though evidence remains mixed. The gut microbiome is complex, and outcomes can vary based on donor microbiota, patient factors, etc. Risks include transient gastrointestinal symptoms, rare serious adverse events, and lone-term safety uncertainties. The main contents of this paper aim to the development of comprehensive interventions that reduce harmful influences, enhance protective factors and use an integrative approach to address the diseases for the benefit of the human being.
Question 2: Can the authors check that the entire manuscript be written in the past tense? **Response 2**: Thanks for the reviewer's advice. We carefully proofread the main text.

Reviewer #2

The article provides a comprehensive overview of the pathophysiological differences between Crohn's disease and ulcerative colitis. A detailed discussion on recent specific molecular pathways involved in each condition, also, advancements in genetic and microbiome research included. However, I recommend further clarification on the comparison of current therapeutic approaches tailored to each disease's pathogenesis would provide valuable insights for clinicians. The organization of the manuscript is commendable, as it presents the information in a logical and coherent manner. Each section flows smoothly into the next, making it easy for readers to follow the comparative analysis of Crohn's disease and ulcerative colitis. The title accurately and concisely reflects the core focus of the manuscript. The abstract effectively summarizes the key findings and objectives of the review, providing a clear overview of the comparative aspects of Crohn's disease and ulcerative colitis. However, it could benefit from a more concise statement of the main conclusions drawn from the analysis. Including specific insights or implications for clinical practice would enhance its impact and relevance to the reader. The keywords selected for the manuscript are relevant and effectively capture the main themes of the review. However, it may be beneficial to include additional keywords that reflect specific aspects of the pathogenesis discussed in the article, such

as "immune response," "microbiome," or "genetic factors." This would enhance the manuscript's discoverability and ensure it reaches a broader audience interested in these specific areas of research. The introduction provides a solid foundation for the review, clearly outlining the significance of studying the pathogenesis of Crohn's disease and ulcerative colitis. It effectively sets the stage for the comparative analysis that follows. The conclusion succinctly reiterates the main points discussed in the manuscript and emphasizes the importance of understanding the distinct pathophysiological mechanisms of Crohn's disease and ulcerative colitis. To strengthen this section, consider adding recommendations for future research directions or clinical applications based on the findings presented. This would provide a forward-looking perspective that could inspire further investigation in the field. The references cited in the manuscript are relevant and up-to-date, reflecting a comprehensive review of the current literature on Crohn's disease and ulcerative colitis. The manuscript would benefit from the inclusion of an abbreviations section, as the absence of this section may hinder readability, especially for readers who may not be familiar with all the terms used. A dedicated list of abbreviations and their corresponding meanings would enhance clarity and allow for quicker comprehension of the text. This is particularly important given the complex terminology associated with Crohn's disease and ulcerative colitis. Including this

section will improve the overall accessibility of the manuscript for a wider audience. The figures and tables included in the manuscript are exceptionally well-designed and serve to enhance the overall presentation of the data. Each figure is clear and visually appealing, effectively illustrating key concepts and findings related to Crohn's disease and ulcerative colitis. The table is well-organized, providing concise summaries that facilitate quick reference and comparison. Together, these visual elements significantly enrich the reader's understanding of the content and contribute to the manuscript's overall clarity and impact. Great job in utilizing visuals to support the narrative. I appreciate the effort you put into it. I wanted to point out a small spelling mistake I noticed: [21st century]. I hope this helps in refining your work further.
Question 1: I recommend further clarification on the comparison of current therapeutic approaches tailored to each disease's pathogenesis would provide valuable insights for clinicians. **Response 1**: Thanks for the reviewer’s advice. As the reviewer advised, further clarification on the comparison of current therapeutic approaches tailored to each disease's pathogenesis provide valuable insights for clinicians. We have been writing new articles, hoping to contribute to this journal after writing.

Question 2: However, it could benefit from a more concise statement of the main conclusions drawn from the analysis. Including specific insights or implications for clinical practice.

Response 2: Thanks for the reviewer's advice. Six common and fourteen unique aspects of the pathogenesis of inflammatory bowel disease, primarily Crohn's disease and ulcerative colitis, illustrate the causes and beneficial factors of resistance to inflammatory bowel disease, providing critical insights for targeted treatment of Crohn's disease and ulcerative colitis. Based on the research trend of IBD pathogenesis, interdisciplinary innovation is needed. We give the latest insights into the pathogenesis of inflammatory bowel disease research at each end, which would enhance its impact and relevance to the reader.

For example, in the section of ***Intestinal microbes disorder and imbalance.***

"Studying changes in the composition and function of gut microbiota in IBD patients not only advances our understanding of the disease's pathogenesis but also broadens the potential for future research directions. Therapeutic approaches could include promoting ecological agents to correct intestinal flora imbalance, such as interleukin-13 (IL-13)[44]. From a nutritional and health perspective, interventions like yogurt consumption can help reduce inflammation by enhancing the integrity of the intestinal lining[45]. Improved intestinal integrity can

prevent pro-inflammatory molecules produced by intestinal microorganisms from entering the blood[46]. Further treatments for IBD are likely to focus on microbiota-based interventions. Moreover, the development of probe technologies targeting specific intestinal microorganisms could enable accurate identification and differentiation of IBD subtypes. This approach could allow for the precise distinction between Crohn's disease and ulcerative colitis by targeting key bacterial species within the gut. Additionally, there is a need to develop immuno-regulatory therapeutic agents that can promote immune system activation and inhibit inflammatory response by bypassing cellular transport mechanisms, making them suitable for direct ingestion by IBD patients. Furthermore, there is an urgent need to establish a comprehensive and sophisticated treatment system for IBD that utilizes one or more intestinal flora as bio-markers. Such a system could not only deliver therapeutic agents but also facilitate accurate diagnosis and simultaneous treatment of IBD."

Question 3: However, it may be beneficial to include additional keywords that reflect specific aspects of the pathogenesis discussed in the article, such as "immune response," "microbiome," or "genetic factors."

Response 3:

Thanks for the reviewer's advice. Additional keywords that reflect

specific aspects of the pathogenesis discussed in the article were added.

Key Words: Immune responses; Gene function; Microbes

Question 4:

To strengthen this section, consider adding recommendations for future research directions or clinical applications based on the findings presented.

Response 4:

Thanks for the reviewer's advice. Six common and fourteen unique aspects of the pathogenesis of inflammatory bowel disease, primarily Crohn's disease and ulcerative colitis, illustrate the causes and beneficial factors of resistance to inflammatory bowel disease, providing critical insights for targeted treatment of Crohn's disease and ulcerative colitis. We give the latest insights into the pathogenesis of inflammatory bowel disease research at each end, which would provide a forward-looking perspective that could inspire further investigation in the field.

For example, in the section of ***Dysregulated immune responses..***

The pathogenesis of immune responses to IBD offers new insight into pharmacological therapies, such as inhibiting inflammatory signaling. It also reveals that clinical parameters alone cannot sensitively stratify IBD patients, highlighting the need for more accurate analytical methods. High-resolution analytical technologies for delivering

precision agents and predicting responses to specific IBD therapies can facilitate more effective and personalized treatment[19]. Promising analytical methods include immune response profiling, germline genetics, *in vivo* real-time molecular endoscopy, gut micro-biome analysis, and tissue transcriptomics.
Question 5: The manuscript would benefit from the inclusion of an abbreviations section, as the absence of this section may hinder readability, especially for readers who may not be familiar with all the terms used. **Response 5:** Thanks for the reviewer's suggestion. As the reviewer advised, abbreviations and their corresponding meanings were carefully checked.
Question 6: I wanted to point out a small spelling mistake I noticed: [21st century]. **Response 6:** Thanks for the reviewer’s advice. We've done spell check.