Revision changes:

Reviewer 1:

I have just a couple of minor suggestions: a) I understand Cannabis use is commonly not reported associated with constipation. However, opioid induced constipation is a common side effects of opids and even negative findings about Cannabis are welcomed in a review MS, b) the Authors use Rome Foundation classification for cannabis related hyperemesis and same attitude should be applied to IBS classification is Literature consent it. No additional points on this side

- *Added constipation section with GI motility*
  The foreseen physiologic effect of marijuana in gut motility contrasts with its apparent effect on constipation. An animal study found cannabis improved loperamide-induced constipation in mice likely due to gut microbiota changes [38]. Interestingly, a national cohort study in the United States demonstrated a 30% decrease in constipation with recent marijuana use compared to past or nonusers but lacked any association with diarrhea. This paradoxical effect may be explained by different cannabis compositions and presence of counteracting cannabinoids of the CB1 receptor [39].

- *Added IBS definition using Rome IV*
  Irritable bowel syndrome is defined by Rome IV criteria as a functional disorder in which changes in bowel habits or defecation is associated with recurrent abdominal pain experienced at least once a week for the past 3 months [41].

Reviewer 2: Shorten and add more IBD scientific evidence

Abstract section needs shortage and language correction as shown. Introduction needs shortage, and language correction. What is it?: Needs more arrangement. THE ENDOCANNABINOID SYSTEM: needs more arrangement and shortage. IBD section needs more scientific support, arrangement, and more shortage. GI motility section: needs shortage. Irritable Bowel Syndrome section: needs shortage. Abdominal pain/Visceral pain section: needs correction as shown. Nausea and Vomiting section needs shortage. Obesity section needs shortage and language correction as shown. GI Malignancies section needs shortage. RISKS AND ADVERSE SIDE EFFECTS section needs shortage, and arrangement. Conclusion needs more and more shortage. The paper needs more scientific support, and the topic needs more strong evidence based medicine to support the use of cannabis in GIT diseases.

- Language corrected per reviewer changes

- Abstract shortened from 203 to 167 words

- Introduction section shortened from 160 to 142 words. *What is it* section rearranged and shortened from 111 to 74 words

- The Endocannabinoid system section rearranged and shortened from 382 to 208 words

- IBD section shortened from 584 to 519 words with addition of more recent evidence based studies and additional facts/numbers from previous studies including Cochrane review. All of Naftali's studies are included in this section as well. Additional studies

also mentioned in Table 1 ***(figures and tables in the second document attached** – had to designate as video file, would not let me update the designation as table file)*

e.g. In a small prospective placebo-controlled study, the authors found 90% of CD individuals using THC-rich cannabis had a greater than 100 point reduction in Crohn's Disease Activity Index. Quality of life, appetite, pain scores and satisfaction also improved [28].

A nationwide study on inpatient outcomes found that although cannabis users with CD required less parenteral nutrition needs than nonusers (3% vs 4.7%) and had shorter hospital stays due to potential symptomatic improvement, there were higher complications of active fistulas or intraabdominal abscesses compared to nonusers (8.6% vs 5.9%) [30]

Ref 22- Dalavaye N, Erridge S, Nicholas M, Pillai M, Bapir L, Holvey C, Coomber R, Rucker JJ, Hoare J, Sodergren MH. The effect of medical cannabis in inflammatory bowel disease: analysis from the UK Medical Cannabis Registry. *Expert Rev Gastroenterol Hepatol*. 2023;**17**(1):85-98. [PMID: 36562418 doi:10.1080/17474124.2022.2161046].

Ref 27- Kerlin AM, Long M, Kappelman M, Martin C, Sandler RS. Profiles of Patients Who Use Marijuana for Inflammatory Bowel Disease. *Dig Dis Sci*. 2018;**63**(6):1600-4. [PMID: 29594968 doi:10.1007/s10620-018-5040-5].

Ref 30- Desai R, Patel U, Goyal H, Rimu AH, Zalavadia D, Bansal P, Shah N. In-hospital outcomes of inflammatory bowel disease in cannabis users: a nationwide propensity-matched analysis in the United States. *Ann Transl Med*. 2019;**7**(12):252. [PMID: 31355219 doi:10.21037/atm.2019.04.63].

Ref 33- Kafil TS, Nguyen TM, MacDonald JK, Chande N. Cannabis for the Treatment of Crohn's Disease and Ulcerative Colitis: Evidence From Cochrane Reviews. *Inflamm Bowel Dis*. 2020;**26**(4):502-9. [PMID: 31613959 doi:10.1093/ibd/izz233].

- IBS section shortened from 353 to 294 words

- Abdominal pain/visceral pain corrected

Added additional study of chronic abdominal pain. "Conversely a small phase 2 clinical trial demonstrated THC was not superior to placebo in patients with chronic abdominal pain [49]."

Ref 49- de Vries M, van Rijckevorsel DCM, Vissers KCP, Wilder-Smith OHG, van Goor H, Pain, Nociception Neuroscience Research G. Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled

Study. *Clin Gastroenterol Hepatol*. 2017;**15**(7):1079-86 e4. [PMID: 27720917 doi:10.1016/j.cgh.2016.09.147].

- Nausea and vomiting section shortened from 490 to 326 words
- Obesity section shortened from 453 to 307 words
- GI malignancies section shortened from 345 to 283 words
- Risks and adverse effects section rearranged paragraphs. Shortened from 1311 to 1064 words.
- Conclusion section shortened from 124 to 98 words

Editor:

Thank you for your time to review my paper. 6 additional references added to the revision with a total of 151 references to increase evidence of the paper