

27<sup>th</sup> May 2021

Manuscript ID 64970

Title: "**Liver and inflammatory bowel disease: a review**"

Dear Editor

Thank you for giving us the opportunity to resubmit a new revised version of the above manuscript.

We found the comments very helpful and we addressed all points raised (see below).

In the manuscript the revisions are highlighted in red font.

We hope that the manuscript is now acceptable for publication.

Looking forward to hearing from you

Yours sincerely,

Rui Gaspar

Guilherme Macedo

Reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** In this review article on "Liver and inflammatory bowel disease: a review" authors nicely reviewed the hepatobiliary manifestations of IBD. This review will enhance the knowledge on liver manifestation of IBD. This manuscript needs some minor spelling and grammatical corrections.

**We thank the Reviewer for the comments.**

**As suggested, we reviewed and corrected some minor spelling and grammatical correction**

Reviewer #2:

**Scientific Quality:** Grade A (Excellent)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** Inflammatory bowel disease (IBD) is a term for two conditions (Crohn's disease and ulcerative colitis) that are characterized by chronic inflammation of the gastrointestinal (GI) tract. Prolonged inflammation results in damage to the GI tract. IBD arises due to a defective immune system, and in IBD, the immune system reacts incorrectly to the environmental triggers which causes inflammation in the GI tract. IBD patients exhibit several hepatic abnormalities, this includes liver and biliary track diseases. Common manifestations include fatty liver, and sclerosing cholangitis, however, IBD is also associated with cholelithiasis, granulomatous hepatitis, portal vein thrombosis, IgG4-related cholangiopathy, pyogenic liver abscess, hepatic amyloidosis and primary biliary cirrhosis. In this review paper, the authors have comprehensively reviewed the literature on IBD, symptoms of IBD, drugs that are used in the treatment of IBD and associated liver dysfunctions because of the drug toxicity. The sections on drugs used in IBD medications are extensively covered. Overall, this a very nicely written review paper. Comments: The quality of review will be significantly improved if the authors include a section on naturally available anti-inflammatory compounds with minimal side effects that have been suggested to improve the conditions of IBD in patients in-light of recent reports. In this context Kesharwani *et.al* demonstrated that curcumin local delivery to GI tract has the potential to treat IBD ( Site-directed non-covalent polymer-drug complexes for inflammatory bowel disease (IBD): Formulation development, characterization and pharmacological evaluation, J Control Release, 2018 Nov 28;290:165-179). The link to the paper is provided. <https://pubmed.ncbi.nlm.nih.gov/30142410/>. This reference along with other reports if available should be cited.

**We thank the Reviewer for the comments. We had now this section:**

**Naturally available anti-inflammatory compounds:**

Although less studied, there are several natural compounds that are tested for the treatment of inflammatory bowel disease.

Curcumin, the main active compound of the plant *Curcuma longa*, has been shown to have anti-inflammatory, anti-oxidant and antibacterial activity. [68] Kesharwani et al shown that curcumin might have an important role inhibiting IBD severity and colitis associated cancer. [69] In addition, it has a good safety profile and is extremely well tolerated, besides some reports of its hepatoprotective effect. [68, 70-72]

**The changes have been made accordingly.**