Comments and Suggestions for Authors are in *italics*.

**Reviewer 2:**

- In general, the manuscript is clear and well written, but its main weakness point is the lack of integration/relationship between endocannabinoid and apelin system. How do the authors justify the decision to compare endocannabinoid and apelin systems? What is their relationship, if any?

  We chose endocannabinoid and apelin systems as two promising signalling pathways with an extraordinary potential to be used to reduce hepatic stellate cell activity and for the treatment of liver fibrosis, as reflected in the literature. We did not try to compare or integrate both signalling pathways since they do not have a direct relationship. However, we had to mention one paper (Reichenbach V J Pharmacol Exp Ther. 2012) in which fibrotic rats treated with either AM1241 or F13A (CB2 agonist and APJ antagonist) displayed similar anti-fibrotic outcomes. This does not mean that both signalling pathways are closely related but the outcomes of both therapies ameliorated the same parameters in fibrotic rats. We agree with the reviewer that this differentiation was not clear enough, and therefore we have clarified this point in the new version of the manuscript (*lines 294* - 295 and *471* - 474).

Additional points:

- The section on endocannabinoids has been mainly focused on CB1/CB2 than on the system as a whole. Endocannabinoid activity strongly depends on endocannabinoid tone which is deeply modulated by FAAH hydrolase. In this respect, FAAH is an additional possible therapeutic/diagnostic biomarker. In spite literature in the field, this point has never been discussed in the manuscript. Thus the article is focused on the activity of cannabinoid receptor in the liver and not on hepatic endocannabinoid system.

  We thank the reviewer for this insightful comment. Since the endocannabinoid system comprises endogenous cannabinoids, their receptors and the enzymes responsible for their synthesis and degradation (including FAAH), we have added some discussion about the major synthesis and degradation pathways of anandamide and 2-AG in the new version of the manuscript (*lines 89* - 105). We agree that we missed the role of FAAH hydrolase. Thus, we have added an example of a possible therapeutic approach targeting this enzyme in the section health and disease (*lines 186* – 187, and the new reference 72) and clarified its role in obesity (*lines 196* – 198). As suggested by the reviewer, we have now focused on the hepatic endocannabinoid system as a whole and not only on canonical cannabinoid receptors. We have given more emphasis to EC and we have included more discussion and literature on the role of FAAH modulating the endocannabinoid activity (*lines 213* - 230).

  The paragraphs focused on endocannabinoid/apelin system in health and disease have a general title but are mainly focused on cardiovascular disorders/angiogenesis.

  We beg the reviewer to understand that we could not expand further the roles of endocannabinoid/apelin system in health and disease due to the limitations of space (avoiding a too long review), and we focused on the main section and topic for the journal issue: liver fibrosis.
The use of abbreviations is not consistent all over the main text and figures (as for instance see anandamide AEA or rimonabant SR141716). Not all abbreviations have been defined at the first appearance in the main text.

We have now defined all abbreviations and checked for consistence over the main text and figures in the new version of the manuscript, as requested by the reviewer.

88 “EC receptors (Structure and location)”: This paragraph lists the canonical and not canonical EC receptors, focuses on CB1/CB2 and summarizes their tissue expression, thus (structure and location) is not suitable.

We have deleted (structure and location) according to the reviewer’s request.

90-91 “Both CB are seven transmembrane class A metabotropic G-protein-coupled receptors (GPCRs) but differ in the amino acid sequence (48% homology)”: specify the specie in which such an homology has been detected.

We have specified the specie for such homology as humans (line 113).

98-99 “The CNR1 gene encodes for CB1 in humans, and consists of 472 amino acids”: this sentence requires changes in that the gene does not consist of 472 amino acids.

As requested by the reviewer, we have corrected this mistake in the new version of the manuscript (line 121).

101-103: among peripheral tissues expressing CB1, the authors forget female reproductive tissues The authors generally use “inverse agonists”; due to the large number of synthetic agonists/antagonists-all exhibiting specific properties with respect to cannabinoid receptors- they have to specify what agonist are talking about. Figure 3: see the previous comment.

We thank the reviewer for these comments. We have now mentioned the female reproductive tissues (line 127) and we have added the nomenclature of main agonists in the new Figure 3 in the new version of the manuscript.