The authors thank the editor and the reviewers for their useful comments. The manuscript has been amended accordingly.

Reviewer 1

Specific Comments to Authors: Thank you so much for this review. I find the aim of the review appealing and attractive, however, I believe that the authors did not comprehensively delve into the correlation between their three genes of interest and the pathological and molecular characteristics of HCC. Some key etiological factors contribute to HCC, and the authors mention them, however, they do not achieve to classify the frequency of TERT, CTNNB1, and TP53 mutations in these etiological factors. For example, they mention the frequency of TERT mutations in patients with cirrhosis, but they do not mention and delve into the frequency of these mutations in people with fatty liver, diabetes, genetic diseases such as hemochromatosis, or Wilson's disease. I believe that this might be compensated with better figures: some correlate the molecular characteristics to the etiological factors (e.g. DOI: 10.1158/0008-5472.CAN-09-1089, https://doi.org/10.1073/pnas.1807305115).

Regarding the frequency of TERT, CTNNB1, and TP53 mutations in relation to risk factors, we have schematized these data in Table 1. More references have been cited accordingly.

I recommend redesigning the figures, trying to prioritize and graph what is discussed in the section "MOLECULAR HCC SUBTYPE CLASSIFICATION" and "MOLECULAR HCC SUBTYPES AND PATHOLOGICAL FEATURES", instead of illustrating the activation mechanism of the three molecules, since that is something that readers can find in other reviews.

To graph what is discussed in the "Molecular HCC subtypes and pathological features" section, we added Figures 4 and 5 in which we highlighted correlations between molecular features and histological types of HCC mentioned in the main manuscript.

The authors explain nicely the canonical Wnt/β-catenin pathway however, this activation mechanism is not present in every HCC, since (DOI: 10.1158/0008-5472.CAN-09-1089) The activation of the Wnt/β-catenin pathway by the means of TGF-beta have been tightly related to HCC. It would be appreciated if the authors add this to the CTNNB1 section.

Regarding the activation of the Wnt/β-catenin pathway, we have added in the CTNNB1-section the activation by TGF-beta. The authors thank the reviewer for this important comment.

About Hepatocellular Adenoma (HCA) Authors provide very interesting data, maybe authors could provide the mutation frequency of the mutations in HCA, as well as the frequency of HCA that transform into HCC.

In the HCA paragraph, we have added more information about mutations frequency and frequency of HCAs that transform into HCC.

It would be interesting if the authors could classify their findings in the etiological/ molecular classification and show it in an integrative figure.

Unfortunately, our data are only a few because they are preliminary results. We commit to performing this type of correlation when a huge number of samples will be tested.

Mind the font size in the images, the actual it is hard to read, especially in the last image. In summary, I suggest redesigning the figures and showing the aim of the review which is to show the "Correlation of molecular alterations with pathological features in hepatocellular carcinoma:" and not showing the activation pathways that can be found in any other review.

The images of the activation pathways of TERT, CTNNB1, and TP53 have been redesigned with larger font. In order to show the correlation between molecular alterations and pathological features we have designed figures 4 and 5.

Reviewer #2

Specific Comments to Authors: I have carefully read your manuscript entitled "Correlation of molecular alterations with pathological features in hepatocellular carcinoma: literature review and experience of an Italian center". This is a good review pointing out the utility of molecular characterization of HCC. Some minor revisions in language and references are needed. For example, ref. 59 is incomplete; ref 64 is a review evaluating the geographical differential distribution of TERT mutations in HCC, but is inserted in page 10, in the paragraph summarizing the relationship of HBV and aflatoxin B1 exposure with TP53 mutations. Please revise.

We have made the corrections about language and references, as suggested.

Reviewer #3

Specific Comments to Authors: Generally, this paper was written well, but the language need to be polished. there were some apparent grammar errors such as: 1.The reactivation of TERT can be explained not also by the aforementioned 2.β-catenin the protein is translocated into the nucleus. 3.most significant in commonest human cancers, 4.that TERT more frequent mutations fall in a promoter region usually not covered by the exome sequencing studies. 5.correlated high alpha-feto protein (AFP) serum levels.

We have polished the language of the article considering the revisions.

Science editor:

Re-do figure 1 and 2 to summarize the main points of this review.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)
Instead of re-doing figures 1 and 2, also according to reviewer's comments, we have had two more figures (4 and 5) to summarize the main points of this review

Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

We added copyright to the bottom right-hand side of the picture as suggested.
We revised our reference list to have no more than three references from the same journal, as required.