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From

Dr Lekshmi R Nath,
Asst. Professor,
Department of Pharmacognosy
Amrita School of Pharmacy,
Amrita Institute of Medical Sciences,
Amrita Vishwa Vidyapeetham
Kochi, Kerala, India-682041

Subject: **Letter to the Editor** for *World Journal of Gastrointestinal Oncology* Manuscript
Revision-*Manuscript No: 68634* reg

Dear Editor,

Please find our enclosed revised draft entitled” **Critical biomarkers of Hepatocellular carcinoma in body fluids and gut microbiota**” which we would like to submit for publication as a letter to the Editor in " *World Journal of Gastrointestinal Oncology*".

The reviewer comments are as follows

Reviewer #1

This article reviews various biomarkers in body fluids and faeces of patients that have contributed to the prediction of prognosis or recurrence, which is essential for selecting appropriate treatment measures and developing new treatment methods.

Comment 1: Molecular biomarkers in body fluids and faeces of HCC patients, like proteins, metabolites, circulating nucleic acids, circulating tumor cells, extracellular vesicles, and gut microbiota from blood, urine and faeces are useful in early diagnosis, prognosis before or after therapy. But how much do they have to reach in order to play these roles?

Answer: We have included the suggested modification in the manuscript as a **yellow highlight**.

Comment 2: The description of biomarkers of hepatocellular carcinoma in intestinal microbiota is not enough, please add.

Answer: As per your suggestion, we have made the modification and highlighted in **green**.

Comment 3: Add diagrams to illustrate related markers is more clearly.

Answer: Thank you for the valuable comment. The diagram is included in the manuscript as graphical abstract .

Reviewer #2

Comment 1: The manuscript is a synopsis of the content of the review by Guan MC (2021) [doi: 10.4251/wjgo.v13.i5.351]. The previously published review professionally summarized advanced developments for HCC in biomarkers derived from body fluids and faeces, including proteins, metabolites, circulating nucleic acids, CTCs, EVs, and gut micro biota. These biomarkers have the potential in diagnosis, therapy monitoring, recurrence prediction, and prognosis of HCC. Therefore, the publication of the submitted review on the review in the format of a letter to the editor is not reasonable, since it basically duplicate the original (for example, the bibliography completely duplicates 12 literary sources from the original review), without providing any new scientific information.

Answer: Thank you for your valuable comments. We have modified the manuscript completely with new additions from other literature evidence and highlighted the content with yellow, ash and green as well as the new references in in pink colour

Reviewer #3

The review summarizes novel biomarkers for the diagnosis and management of hepatocellular carcinoma in blood urine and faeces. As introduced these promising biomarkers may help in early detection of HCC in a non-invasive and accurate manner. The well-organized manuscript provides a full discussion of the review reported by Guan MC et al and provides important new insight. However, the following contents of this paper require further modification or supplementation:

Comment 1: The content about biomarkers from faeces requires enrichment and extension.

Answer: We have made modifications as suggested and highlighted in yellow.

Comment 2: Relevant references of “Diagnosis of HCC at advanced stages is one of the prime reason for the resistance offered to most HCC therapies” at the end of the article should be provided.

Answer: The suggested modification has been included and highlighted the same in grey colour

Comment 3: "... For the early detection of Hepatocellular carcinoma (HCC) in normal and recurrence cases" should be modified to "... for the early detection of primary and recurrent hepatocellular carcinoma".

Answer: As per your comment, we have modified the sentence and the corresponding changes are highlighted in blue colour

Comment 4: There are still some grammatical mistakes in this manuscript, such as "recurrence cases" and "one of the prime reason". Therefore, the language also needs further polishing.

Answer: Thank you for the valuable comment. The grammatical mistakes in the manuscript have been corrected and rectified using Grammarly software.

Reviewer #4

Comment 1: I personally think that the author's manuscript states what we all know, and there is no up-to-date information in it.

Answer: We have added a few more recent information regarding biomarkers in hepatocellular carcinoma and the corresponding changes are highlighted in red.

Thank you for your kind consideration.

Sincerely,



Lekshmi R Nath, PhD