RESPONSE TO REVIEWERS

On behalf of the authors of this manuscript, I would like to extend my sincere thanks to the editorial team and the reviewers for spending their valuable time to review this manuscript. In spite of the hectic research activities, the reviewers have found time to read our manuscript and gave an elaborate account of the strength and limitations of this manuscript. The suggestions of the reviewers are genuine and we have incorporated necessary changes in the revised manuscript. We believe, this revised version of the manuscript will meet the requirements of the journal. The responses to the individual reviewers are as follows:

S.No	Reviewer No.1	Response
	This review well summarizes the role of key molecular targets and signaling pathways of ferroptosis in gastrointestinal caners. This manuscript will be useful to readers interested in relevant fields. I have some comments about improving the manuscript before it is officially published.	We thank this reviewer for the comments. This review was prepared based on our own experimental observations involving ferroptosis in colorectal cancer and liver cancer research.
1	The introduction section is too long and boring to read. I recommend subdividing this paragraph. Additionally it may be better to put the incidence and mortality of gastrointestinal tumors together in the introduction of gastrointestinal tumors at the beginning of the article.	We regret for the lengthy content of the introduction. In order to give descriptive view about gastrointestinal tumors, the introduction part is a bit lengthy. In this revised manuscript, the sections are subdivided for ease of reading. The incidence and mortality of gastrointestinal tumors are better described as a separate Table-1 Please find the corrections in page no. 4 of the revised manuscript. We have reduced the lengthy introduction.
2	In the part of distinctive features of ferroptosis authors should reorder the paragraphs. Iron metabolism, role of ferritin in Fe transport, lipid metabolism and transcription factors should be placed before the section of ferroptosis inducers.	We thank the reviewer for this concern. We tried changing the format by bringing the regulation part in front of the manuscript. However, some of the context need some introduction in the beginning. Therefore, we have re-organized the structure of the section.
3	In the part of ferroptosis as a novel target for GI cancer research, authors should add the role of epigenetic alterations and ferroptosis in GI cancer. The exact mechanisms and signaling pathways of DNA methylation, histone modifications, non-coding transcripts and non-coding RNAs	The manuscript is a bit lengthy and hence we couldn't describe the mechanistic insights of the pathways. However, we have re-organized the section for better reading. If the reviewer, still insist to shorten the epigenetic alterations and provide more detail under the sub topic GI cancer research, we will do so.

	transcripts and non-coding RNAs in different cancers should be discussed and more examples should be provided.	
4	Please indicate the literature source of MiR-214-3p, miR-101-3p and miR 324-3p on page 8	We apologize for not quoting literature source for micro RNAs. In this revised manuscript, we have incorporated the appropriate references (Please refer to Page no.7, in the revised manuscript. Reference No.44)
	Minor revisions	
1	Please define the "GI" "ROS" that first appears	The error was rectified in the revised mansucript
2	Some key words such as gastrointestinal (GI), long non-coding RNAs (lncRNAs) Nuclear receptor coactivator 4 (NCOA4), Hepatocellular carcinoma, Epithelial-mesenchymal transition, micro RNAs (miRNAs), circular RNAs (circRNAs) and so on are defined more than once.	We apologize for the error. For all the listed key words, in this revised manuscript, we have carefully incorporated the abbreviations. Through the manuscript, you can find the errors were rectified.
3	The paragraph "The leading cause of cancer deaths…….such as colorectal cancer, liver cancer, pancreatic cancer, gastric cancer and esophageal cancer is repeated twice in pages 17 and 18.	That was an error. We apologize for the same. In the revised content, we have removed the repeating sentences. Please refer to page no.18, first paragraph
4	Please standardize the definition of abbreviations.	As suggested by this reviewer, the abbreviations were organized throughout the manscript. Please refer to page no.11
5	On page 16, line 39, glutmate cysteine cigase catalytic mighe be glutamate-cysteine ligase	On behalf of the authors, I extend my apologies for this typographical error. The same has been corrected as glutamate cysteine ligase (Refer page no.16)
6	On page 20, line 2 malonidialdehyde (MDA) might be malondialdehyde (MDA) and defined twice on pages 8 and 20.	That was a typographical error. We sincerely apologize and the same has been corrected in this revised manuscript
7	On page 20, line 44, AMPK/Mtor/p70S6K signaling pathways might be AMPK/mTOR/p70s6K signaling pathway	We sincerely apologize for erroneously describing the pathways. The same has been corrected in this revised manuscript.
8	On page 21, line 18, cyctathione β synthase (CBS) might be cystathione β synthase	In this revised manuscript, we have incorporated the correct enzyme cystathionine β synthase. We regret for the error in the previously submitted

		manuscript.
9	On page 21, CDGSH iron sulphur domain should be changed to CDGSH iron sulfur domain.	The same was changed in the revised manuscript. Please refer to page no 19
10	On page 24, line 50 lysosomal associated membrane protein (LAMP 1) might be lysosomal associated membrane protein 1 (LAMP 1)	We thank this reviewer for pointing this critical typographical error. Such careless mistakes will be avoided in all our future submissions. In this revision, we have incorporated the change.
	Overall, we thank this reviewer for the critical comments. The comments addressed by this reviewer certainly helped us to improve the manuscript. We sincerely hope our response and the changes in this revision will suffice this reviewer. Should this reviewer have any further queries or changes to be incorporated, we will be glad to do so.	
	Reviewer No.2	**Response**
	The reviewers described that the manuscript was systematically summarized. The potential mechanism and role of ferroptosis in regulating gastrointestinal tumor and summarized potential therapeutic drugs. This work is exciting, and the authors work is commendable. However, I have several questions about this manuscript. The following are the concerns	We thank this reviewer for the comments.
	The manuscript is rich in content, but the main and secondary content of the article are vague and some contents are miscellaneous. The introduction to the mechanism of ferroptosis and related signaling pathways is relatively clear which is commendable, but takes up too much space.	We thank this reviewer for critically examining this manuscript. The concern that the introduction is a bit lengthy has been criticized by other reviewer also. In view of this, we have substantially revised the manuscript to concise the introduction. The introduction part is organized as subdivisions for better clarity. New Table was included for clarity.
	Minor revision	
1	There are too many key words	The keywords were reduced in the revised manuscript.
2	The references do not seem to be correctly linked. Please check	As advised by this reviewer, all the quoted references have been scrutinized with the text. All the authors have thoroughly checked the linked references. The uniform reference style were maintained
3	The content of the introduction is superfluous and it is recommended to cut it down	This concern was rectified in the revised manuscript. Please check the revision.

4	It is recommended to use the first, second and third level title formats to standardize the paragraph level of the article.	As suggested by this reviewer, appropriate changes were incorporated in this revision. The suggestion of this reviewer helped us to reorganize the manuscript structure.
5	It is recommended to integrate the treatment part of the full text. Infact, the treatment part of this manuscript only describes the potential botanical therapeutic drugs rather than the potential therapeutic characteristics. In addition it is recommended to use table in the drug treatment section to explain the current clinical use of related drugs.	The authors express their sincere thanks for this valuable suggestion. In fact, we thought of including a table or pictorial representation of the conventional regulators of ferroptosis and its possible clinical interventions. However, in search of the literature some of the emerging drugs require a detailed evaluation and since there are limited drug regimens involved in the regulation of ferroptosis we could not highlight it. Our existing research demonstrates the role of certain plant based flavanoids such as eupatlin, celastrol and Caffeic acid phenethyl ester in mitigating colon and liver cancer through regulation of ferroptosis. In this view, the content was prepared. However, as pointed out by this reviewer, there are standard drugs that could regulate ferroptosis. In this context, in this revision we have reduced the content related to plant-based compounds as regulators of ferroptosis and incorporated conventional drugs that target ferroptopsis. Please find the Table 2 (Page no. 23)
6	It seems that the article picture is not quoted in the manuscript. Please add	Both the pictures were drawn. However, Picture 2 was adapted from previous work and the same was quoted.
	Alltogether, we thank this reviewer for the valuable comments especially to restructure the introduction part and for the suggestions to strengthen the content related to ferroptosis regulators & as potential drug targets. We hope our responses will convince this reviewer. We will be willing to include any additional points to strengthen this manuscript.	
	Reviewer No.3	**Response**
1	Based on the current understanding, under what circumstances do you think short strand RNA, non-coding RNA and circrnas are generally used to regulate iron sagging and then treat gastrointestinal cancer diseases?	Several studies reported microRNA-214-3p upregulates the iron concentration by increasing MDA and ROS levels, to induce ferroptosis with erastin and circular RNAs, like cIARS induce ferroptosis by negatively regulating *ALKBH5* to induce ferritinophagy in HCC, suggesting the involvement of non-

		coding RNAs in the treatment of GI cancers by regulating iron sagging and ferroptosis. (*Li L et., 2022)*
2	The article mentioned that it is an effective method to control and adjust iron sagging by changing the availability of iron through ways related to iron metabolism. Could you please expand on the aspects in which the availability of the iron can be changed?	The availability of the iron can be changed through altering the expression of proteins such as Tf (Transferrin), DMT1, Ferritin etc., involved in iron metabolism. For e.g., the Tf is highly dependent on the change in pH, thus altering the pH will affect the availability (*Chen X et al., 2020*).
3	Compared with traditional methods, what are the advantages of finding natural plant active ingredients control iron sagging?	Natural products are focus of research because of their novel toxicity profile for eg., Studies reported that natural products like Formosanin C regulates iron metabolism by downregulating FTH1 thereby effectively mediated ferroptotic cell death (*Lin PL et al., 2020*). Observations from our laboratory demonstrate that flavonoids regulate ferroptosis in experimental colon cancer and liver cancer.
4	The format of references is not uniform. Some references have DOI numbers while other do not. The format of references in articles 23,35,43,44 and 160 is irregular with large spaces and underscores	We profusely thank this reviewer for scrutinizing the references content. We, the authors regret for the careless mistakes. We should have paid attention to look into the minute details. The references in the revision have been aligned and all the errors were rectified.
5	Transcription factor parts and iron sagging parts in different cancers can be numbered.	These errors were rectified in the revised manuscript
6	Please explain in detail how STEAP1 and STEAP2 are associated with human malignancies?	STEAP family proteins have been reported to affect both intracellular oxidative stress and inflammation as well as other cellular biological processes. STEAP1 silencing suppresses ROS levels and oxidative stress through Nrf2 mediation in CRC cells. Conversely in gastric cancer STEAP1 upregulation promotes cancer proliferation, migration and invasion. In prostate cancer STEAP2 was induced by activation of ERK and its overexpression results in causing metastasis. Thus STEAP1 and STEAP 2 associated with human malignancies (*Chen WJ et al., 2021*)
7	What is the basic principle of synergistic treatment of FC and	A recent study on breast cancer TNBC MDA-MB-231 cells by Chen and group

	cisplatin and enhancing the therapeutic potential of cisplatin?	revealed that cisplatin and FC, modulate the expression of gene (FTH1) involved in the iron metabolism, similarly genes involved in electron transport chain (MT-CO3) were reported to be differently expressed which co treated with FC, apart from that structural component of ribosomal gene (RPS2) is also expressed different that cisplatin treatment alone. These genetic tweaks could be potential mechanism for synergism. (*Chen HC et al.,2022*).

Over all response to the Reviewers

This manuscript was originally prepared to give a comprehensive idea about ferroptosis and its mechanistic insights in regulating key signaling pathways of gastro intestinal cancers. However, it was observed by the reviewers that the introduction is very descriptive and some additional points could have been represented in a presentable manner. Therefore, as advised by the reviewers, in the revised manuscript, the introduction part is modified and the additional contents that are out of context, were removed. Some sections were re-structured to fit in the relevant sub topic. Additional content about GPX4 regulation and ferroptosis were incorporated to illustrate the figure. To further strengthen this manuscript, explanation about the connections of ferroptosis and cell death modalities were included. The individual sections involving gastrointestinal cancers were carefully revised to make it concise with more relevant points. New tables were added as advised by the reviewers. As advised by the reviewer, the therapeutic aspects of ferroptosis were restructured to include additional conventional drugs apart from natural compounds. The references were carefully linked with the text. In this revised manuscript body, the characters stained in red are the corrections/changes. I sincerely hope that the revised manuscript will suffice the authors for accepting this manuscript. If there are any corrections to be incorporated, we will be glad to initiate those changes. On behalf of the authors, I once again thank the Editorial team and Reviewers for their time and effort to improve this manuscript.