

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 81978

**Title:** Ferroptosis regulates key signalling pathways in gastrointestinal tumors:  
Underlying mechanisms and therapeutic strategies

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 06412958

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** India

**Manuscript submission date:** 2022-12-11

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-12-16 00:52

**Reviewer performed review:** 2022-12-21 08:36

**Review time:** 5 Days and 7 Hours

|                    |   |
|--------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| Language quality   | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion         | <input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection             |
| Re-review          | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |

|                                     |   |
|-------------------------------------|---|
| <b>Peer-reviewer<br/>statements</b> | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous |
|                                     | Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  |

## SPECIFIC COMMENTS TO AUTHORS

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? 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 iron can be changed? 3. Compared with traditional methods, what are the advantages of finding natural plant active ingredients control iron sagging? 4. The format of references is not uniform. Some references have DOI numbers, while others do not. The format of references in articles 23, 35, 43, 44 and 160 is irregular, with large Spaces and underscores. 5. Transcription factor parts and iron sagging parts in different cancers can be numbered. 6. Please explain in detail. How STEAP1 and STEAP2 are associated with human malignancies? 7. What is the basic principle of synergistic treatment of FC and cisplatin and enhancing the therapeutic potential of cisplatin?

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**Peer-review model:** Single blind

**Reviewer's code:** 06479106

**Position:** Peer Reviewer

**Academic degree:** MBChB

**Professional title:** Doctor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** India

**Manuscript submission date:** 2022-12-11

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-12-29 06:39

**Reviewer performed review:** 2022-12-31 15:36

**Review time:** 2 Days and 8 Hours

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|---|--|
| Scientific quality                          | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Novelty of this manuscript                  | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair<br><input type="checkbox"/> Grade D: No novelty   |
| Creativity or innovation of this manuscript | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair<br><input type="checkbox"/> Grade D: No creativity or innovation                                |

|   |  |
|---|--|
| <b>Scientific significance of the conclusion in this manuscript</b> | <input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair<br><input type="checkbox"/> Grade D: No scientific significance   |
| <b>Language quality</b>   | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>   | <input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection          |
| <b>Re-review</b>  | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No  |
| <b>Peer-reviewer statements</b>                                     | Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous  |
|   | Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |

## SPECIFIC COMMENTS TO AUTHORS

Sudhandiran Ganapaam et al. systematically summarized the potential mechanism and role of ferroptosis in regulating gastrointestinal tumors, and summarized potential therapeutic drugs. This work is exciting, and the authors' work is commendable. However, I have several questions about this manuscript:    Main problems: This manuscript is rich in content, but the main and secondary contents of the article are vague, and some contents are miscellaneous. The author's introduction to the mechanism of ferroptosis and related signaling pathways is relatively clear, which is commendable, but takes up too much space. The introduction to the mechanism and role of ferroptosis in gastrointestinal tumors is relatively brief, so I hope to increase the description of gastrointestinal tumors and reasonably adjust the content and structure of the article.    Minor Tip: 1. There are too many keywords. It is recommended to control within 6 keywords. 2. The reference does not seem to be correctly linked, please check 3. The content of the introduction is superfluous, and it is recommended to cut it down (L 105-113) 4. It is recommended to use the first, second and third level title formats to standardize the paragraph level of the article 5. It is recommended to

integrate the treatment part of the full text. In fact, 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 6. It seems that the article picture is not quoted in the manuscript, please add

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**Peer-review model:** Single blind

**Reviewer's code:** 05296794

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** India

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**Reviewer chosen by:** AI Technique

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**Reviewer performed review:** 2023-01-06 05:56

**Review time:** 7 Days and 22 Hours

|   |  |
|---|--|
| Scientific quality                          | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Novelty of this manuscript                  | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair<br><input type="checkbox"/> Grade D: No novelty   |
| Creativity or innovation of this manuscript | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair<br><input type="checkbox"/> Grade D: No creativity or innovation                                |

|   |  |
|---|--|
| <b>Scientific significance of the conclusion in this manuscript</b> | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair<br><input type="checkbox"/> Grade D: No scientific significance   |
| <b>Language quality</b>   | <input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>   | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection          |
| <b>Re-review</b>  | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No  |
| <b>Peer-reviewer statements</b>                                     | Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous  |
|   | Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |

## SPECIFIC COMMENTS TO AUTHORS

This review well summarizes the role of key molecular targets and signaling pathways of ferroptosis in gastrointestinal cancers. This manuscript will be useful to readers interested in relevant fields. I have some comments about improving the manuscript before it is officially published. 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 this article. 2. In the part of distinctive features of ferroptosis, authors should reordered the paragraphs. Iron metabolism, role of ferritin in Fe transport, lipid metabolism and transcription factors should be placed before the section of ferroptosis inducers. 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 in different GI 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. Some

minor revisions: 1. Please define the “GI”, “ROS” that first appears. 2. Some key words, such as, Gastrointestinal (GI), Long non-coding RNAs (lncRNAs), Nuclear receptor coactivator 4 (NCOA4), Hepatocellular carcinoma (HCC), Epithelial-mesenchymal transition (EMT), microRNAs (miRNAs), circular RNAs (circRNAs) and so on, are defined more than once. 3. The paragraph “The leading cause for cancer deaths ...such as colorectal cancer, liver cancer, pancreas cancer, gastric cancer and esophageal cancer” is repeated on pages 17 and 18. 4. Please standardize the definition of abbreviations, for example, long-chain fatty acid protein 5 (ELOVL5) and FADS1 (fatty acid desaturase 1) on page 13. 5. On page 16, line 39, glutamate- cysteine ligase catalytic might be glutamate-cysteine ligase catalytic. 6. On page 20, line 2, malondialdehyde (MDA) might be malondialdehyde (MDA). 11. are defined twice on pages 8 and 20. 7. On page 20, line 44, AMPK/Mtor/p70S6K signalling pathway might be AMPK/mTOR/p70S6K signaling pathway. 8. On page 21, line 18, cystathione  $\beta$  synthase (CBS) might be cystathionine- $\beta$ -synthase (CBS). 9. On page 21, CDGSH iron sulphur domain 1 (CISD1) might be CDGSH iron sulfur domain 1 (CISD1). 10. On page 24, line 50, lysosomal associated membrane protein (LAMP1) might be lysosomal associated membrane protein 1 (LAMP1).



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** India

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**Reviewer chosen by:** Li Li

**Reviewer accepted review:** 2023-02-24 14:19

**Reviewer performed review:** 2023-02-24 14:25

**Review time:** 1 Hour

|                           |   |
|---------------------------|---|
| <b>Scientific quality</b> | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| <b>Language quality</b>   | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>         | <input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection             |
| <b>Peer-reviewer</b>      | Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous   |



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statements

Conflicts-of-Interest: [ ☒ ] Yes [ ☐ ] No

#### **SPECIFIC COMMENTS TO AUTHORS**

No further questions.