

### 3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review report. Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** The article summarizes the advantages and disadvantages of G-quadruplexes by describing its characteristics and different sites and functions in various gastrointestinal tracts, and provides research ideas for future research. Excellent manuscript. Fluent and logic.

**Response:** Thank you very much for your approval.

Reviewer #2:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:**

The authors reported a comprehensive review the application of G-quadruplex targets in gastrointestinal cancers. The recent advancements, challenges and prospects of targeting G-quadruplex for using as a therapeutic meaning against gastrointestinal cancers has been thoroughly analyzed by the authors. Detailed references are cited and largely covered the area of interested. The information presented could be useful and attractive a broad readership. The manuscript is thus suggested for publication in World Journal of Gastrointestinal Oncology.

**Response:** Thank you very much for your approval.

However, the authors are strongly recommended for addressing some minor points to further improve the quality and the attractiveness of the review. Details are listed as follows:

1. Introduction: the authors should mention a time frame of the literatures that have been intensively discussed in the manuscript. G-quadruplexes are also drug targets of other cancers but not only gastrointestinal cancers. The authors should briefly mention about this fact.

**Response:** Thank you very much for your suggestion. The time frame of the literatures that have been intensively discussed in the manuscript has been supplemented, and the manuscript has been revised as follows:

“In this review, we summarize the literature on G-quadruplexes and their ligands from 1962 to 2023 and describe G-quadruplex characteristics, including the existing sites, structural details, and physiological functions, and their potential applications in gastrointestinal cancer therapy. ”

G-quadruplexes are also drug targets of other cancers but not only gastrointestinal cancers. This fact has briefly been mentioned about in the introduction, and the manuscript has been revised as follows:

“The crystal or solution structures of various DNA or RNA G-quadruplexes have been increasingly resolved, with their physiological functions gradually clarified, especially their roles in various forms of cancers, such as breast cancer, osteosarcoma, and cervical carcinoma [3,15-19].”

2. Prospect: The authors should briefly describe wider on the use of G-quadruplexes as the drug targets against human diseases, such as antiviral, antibacterial, etc..., and citing the most recent review articles such as Viral G-quadruplexes: New frontiers in virus pathogenesis and antiviral therapy, Annu Rep Med Chem. 2020; 54: 101-131; Structurally diverse G-quadruplexes

as the noncanonical nucleic acid drug target for live cell imaging and antibacterial study, Chem. Commun., 2023, 59, 1415-1433; etc...

**Response:** Thank you very much for your suggestion. The use of G-quadruplexes as the drug targets against human diseases has been briefly described wider, such as antiviral, antibacterial, etc..., and the most recent relevant articles such as Viral G-quadruplexes: New frontiers in virus pathogenesis and antiviral therapy, Annu Rep Med Chem. 2020; 54: 101-131; Structurally diverse G-quadruplexes as the noncanonical nucleic acid drug target for live cell imaging and antibacterial study, Chem. Commun., 2023, 59, 1415-1433; etc. have been cited. The manuscript has been revised as follows:

"Therefore, G-quadruplexes can be the drug targets against multiple human diseases, such as viral infection [222], bacterial infection [223], muscular atrophy [60] and cancer, especially gastrointestinal cancers."

3. The conclusion: The conclusion in its current form is not sound. It could be presented better. Authors at least conclude why G-quadruplexes are better and promising drug target than other target against gastrointestinal cancers.

**Response:** Thank you very much for your suggestion. The conclusion has been revised as follows:

"In addition to telomeres, G-quadruplexes are widely present in the promoter regions of oncogenes as well as cancerous genes, and can regulate various biological processes, especially gene transcription and translation, laying a good foundation for G-quadruplexes to become anticancer targets from the perspective of gene regulation. Multiple genes regulating EC, PC, HCC, GC, CRC and GIST have been found to contain G-quadruplex structures, including the key regulatory gene KRAS for PC and CRC, and c-kit for GC and GIST. Many small molecular ligands or biomolecules based on the G-quadruplex of these genes have been designed, synthesized, or discovered, and preclinical studies have shown that these molecules have good anticancer effects. Therefore, G-quadruplexes as targets against gastrointestinal cancers

have broad application prospects. However, due to the diversity of G-quadruplex functions and the complexity of the biological internal environment, the application of G-quadruplex as a target of anticancer drugs still faces some challenges, which requires further exploration and research. We hope this work will provide references for anticancer strategies based on G-quadruplex targets in gastrointestinal cancers.”

4. Some grammatical errors found. The authors please check carefully again before publishing the review. - Line 543: “have been focus of” - Line 632: “evidence has shows”

**Response:** Thank you very much for your suggestion. The grammatical errors have been corrected. For example: “have been focus of” has been modified as “have been shown on”, “evidence has shows” has been modified as “evidence has shown”. The manuscript has been reedited in language and has obtained an editing certificate.

Reviewer #3:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** The paper gives an overview of application of G-quadruplex targets in gastrointestinal cancers. With over 200 references, comprehensive research with highly topical articles on this topic has been compiled here. The latest results show the current state of research. The article is well prepared and understandable for the reader.

**Response:** Thank you very much for your approval.