

## PEER-REVIEW REPORT

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

**Manuscript NO:** 76258

**Title:** Novel therapeutic Diiminoquinone exhibits anticancer effects on human colorectal cancer cells in 2D and 3D in vitro models

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

**Peer-review model:** Single blind

**Reviewer's code:** 03737417

**Position:** Peer Reviewer

**Academic degree:** BMed, MPhil, PhD

**Professional title:** Doctor, Surgeon

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

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

**Manuscript submission date:** 2022-03-18

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-03-23 08:43

**Reviewer performed review:** 2022-04-04 08:20

**Review time:** 11 Days and 23 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <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 Grade E: Do not publish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 <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 type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<b>Peer-reviewer 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

The authors should be commended on taking on a project which aims to advance our understanding of chemoresistance. The manuscript is however, far too long. The abstract is almost double the length of a standard abstract, and the methods section is hard to understand. My feeling is that this manuscript would best be published in a journal with more focus on pre-clinical/laboratory findings. Further comments see below:

Title. Does the title reflect the main subject/hypothesis of the manuscript? Title is ok.

2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? Abstract is too wordy - 460 words. Standard length is between 200-300 words. Moreover, I cannot really agree with claims such as "Chemotherapy for colorectal cancer (CRC), the second leading disease of cancer-related mortality, has so far revealed partial success." Firstly, it depends on which stage of CRC is in question. But it appears that the authors refer to stage 4 disease, that is patients with metastases. Although there are no studies so far that can show prolonged OS with oncological treatment, it shows increases PFS. Furthermore, with triple agents, up to 70% of patients will respond to treatment, and can be candidates for curative surgery. The conclusion "This study is the first documentation of the molecular mechanism of the novel anticancer therapeutic DIQ via targeting CSC, findings that will certainly have therapeutic implications for colon cancer patients. " is not warranted by the findings.

3 Key words. Do the key words reflect the focus of the manuscript? ok

4 Background. Does the manuscript adequately describe the background, present status and significance of the study? The authors should be commended for trying to advance our understanding of chemoresistance. Though the background fails to communicate the



**Baishideng  
Publishing  
Group**

7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
**https://**[www.wjgnet.com](http://www.wjgnet.com)

oncological treatment regimens that are available – they mention 5FU, which is one of the oldest treatment agents, which is often used in combination with other drugs. Moreover the treatment entails the use of several drugs, not just one. There are several strong statements such as the following, which lack proper underpinning: “The presence of chemoresistant CSCs has been determined to be one of the most significant causes of tumor recurrence.” Moreover, the sentence reads in a peculiar way – how can chemoresistant CSC be the cause of tumor recurrence? If they are resistant, and not dead, if they appear in a manifest form (say CT) they have not properly recurred, but have been there all the time.

5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? The methods section is very extensive, and hard to follow. The authors need condense it, and seek out to describe the key methods. The remaining can be attached as supplementary.

6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? The authors need to be more specific about what their findings have contributed to the field, this is something which should be explained in the discussion. The results section reads as a combination of intro with sentences about the characteristics of cancer (say invasions), and results.

7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper’s scientific significance and/or relevance to clinical practice sufficiently? The authors fail to put the findings in context – what has been shown before, and why this study is unique.

8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? The



**Baishideng  
Publishing  
Group**

7041 Koll Center Parkway, Suite  
160, Pleasanton, CA 94566, USA  
**Telephone:** +1-925-399-1568  
**E-mail:** [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
<https://www.wjgnet.com>

illustrations are generally of good quality. 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? The statistics section is extremely brief, and the quality of the English is poor. It is hard to understand exactly which test that used when. 10 Units. Does the manuscript meet the requirements of use of SI units? Yes 11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? There are several strange references - specifically ref 2 and 3. 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? The manuscript is on the whole far too wordy. It needs to be condensed and better organized. Language is ok, though there are several grammatical errors, and choice of words are at times a bit odd. 13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? Yes, 14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? Yes

## PEER-REVIEW REPORT

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

**Manuscript NO:** 76258

**Title:** Novel therapeutic Diiminoquinone exhibits anticancer effects on human colorectal cancer cells in 2D and 3D in vitro models

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

**Peer-review model:** Single blind

**Reviewer's code:** 06266798

**Position:** Peer Reviewer

**Academic degree:** PhD

**Professional title:** Professor

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

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

**Manuscript submission date:** 2022-03-18

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-03-21 14:57

**Reviewer performed review:** 2022-04-06 07:05

**Review time:** 15 Days and 16 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <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 <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 type="checkbox"/> Accept (General priority) <input checked="" 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 statements</b>	Peer-Review: [ <input checked="" type="radio"/> ] Anonymous [ <input type="radio"/> ] Onymous
	Conflicts-of-Interest: [ <input type="radio"/> ] Yes [ <input checked="" type="radio"/> ] No

## SPECIFIC COMMENTS TO AUTHORS

Authors investigated the anticancer activity of DIQ against CRC cell lines and primary CRC stem cells. They showed that DIQ targets CSCs, reducing their tumorigenic potential by downregulating the  $\beta$ -catenin, AKT and ERK oncogenic signaling pathways.

Q1 The authors refer to their previous study on the characterization of the antitumor activity of DIQ (Monzer, 2019), but in that paper a number of compounds was investigated. The author should clearly specify in materials and methods or results which of those compounds they are investigating, showing structure and IUPAC name.

The presence of such (partial) information in the abstract alone is not, in my opinion, sufficient. Q2 Pag 17 .. Following 72 h, the inhibitory effect of DIQ was accompanied

with considerable changes in cell morphology and confluency.... I expect that, since cells viability is reduced upon DIQ treatment, cell morphology and confluency change. I

suggest to remove this sentence Q3 MTT allows to assess cell viability, as a surrogate for cell counts. Reduced viability could be ascribed to cell death and / or reduced cell proliferation. To assess cell proliferation a CFSE or BRdU assay should be performed.

Please modify figures and text accordingly.

Minor point

Pag 17. ...HCT116 and HT29 human CRC cells micromolar concentrations... è HCT116 and HT29 human

CRC cells at micromolar concentrations