



### PEER-REVIEW REPORT

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

**Manuscript NO:** 61152

**Title:** Huanglian decoction suppresses the growth of hepatocellular carcinoma cells by reducing CCNB1 expression

**Reviewer's code:** 02468318

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Professor, Research Fellow

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

**Author's Country/Territory:** New Zealand

**Manuscript submission date:** 2020-11-26

**Reviewer chosen by:** Pan Huang (Quit in 2020)

**Reviewer accepted review:** 2020-11-29 20:44

**Reviewer performed review:** 2020-12-01 19:43

**Review time:** 1 Day and 22 Hours

<b>Scientific quality</b>	<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 Grade E: Do not publish
<b>Language quality</b>	<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
<b>Conclusion</b>	<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
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input 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



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

1. The quality control of Huanglian Decoction and its drug-containing serum should be provided. 2. To collecting compounds of Huanglian Decoction, only using TCMSP database is insufficient, it should be multiple databases such as OMIM and GeneCards etc. 3. To identify the DEGs, not only TCGA and GEO datasets, but also more datasets such as HIT, TCMgeneDIT, TCMID, and ETCM etc. could be used. 4. Authors should provide the experimental evidences of Huanglian Decoction regulated cell cycle through CCNB1. 5. The main apoptosis-related pathways should be validated by the experiments. 6. Authors should discuss how the compounds in Huanglian Decoction could activate what signal pathways to inhibit cancer cell apoptosis, cell cycle, cell migration and invasion, and descript multi-compounts, multi-tardets and multi-effects feature of Huanglian Decoction in HCC treatments. 7. GOs and pathways enrichment analysis could be changed to a bubble diagram.



### PEER-REVIEW REPORT

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

**Manuscript NO:** 61152

**Title:** Huanglian decoction suppresses the growth of hepatocellular carcinoma cells by reducing CCNB1 expression

**Reviewer's code:** 03738365

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

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

**Author's Country/Territory:** New Zealand

**Manuscript submission date:** 2020-11-26

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2020-11-27 08:41

**Reviewer performed review:** 2020-12-01 21:52

**Review time:** 4 Days and 13 Hours

<b>Scientific quality</b>	<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
<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 type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <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 checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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

Major: 1. In the section 3.7, only 3 groups in the experiments shown in Figure C/D/E/F were insufficient, the effect of Huanglian Decoction on CCNB1 cannot be demonstrated clearly. It is recommended to increase to 4 groups like the experiment shown in Figure A/B (add a Huanglian Decoction without si-CCNB1 group). Minor: 1.

The "Conclusion" was absent in the ABSTRACT, please add it. 2. In the INTRODUCTION, the authors did not provide reference about the utility of Huanglian Decoction in the treatment of liver cancer, please complement related reference. 3. In the Figure1, the meaning of "Patients" and "Samples" is unclear for the readers. Please modified as "tumor samples" and "non-cancerous samples" as in the article. 4. In the last sentence of the figure legends of Fig2, "Downregulated genes are marked in light blue". It seems like green according to the picture. Please check again. 5. In the section 3.5 line 12, authors wrote that "we noticed that CCNB1 promotes tumor development". The "promote" was not suitable here, please modified into "associate".



## PEER-REVIEW REPORT

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

**Manuscript NO:** 61152

**Title:** Huanglian decoction suppresses the growth of hepatocellular carcinoma cells by reducing CCNB1 expression

**Reviewer's code:** 01799205

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Professor

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

**Author's Country/Territory:** New Zealand

**Manuscript submission date:** 2020-11-26

**Reviewer chosen by:** Pan Huang (Quit in 2020)

**Reviewer accepted review:** 2020-11-30 01:57

**Reviewer performed review:** 2020-12-17 01:48

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



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## **SPECIFIC COMMENTS TO AUTHORS**

Huanglian Decoction suppresses the growth of hepatocellular carcinoma cells by reducing CCNB1 expression. The authors utilized several databases to find the main DEGs in HCC and Huanglian Decoction inhibits the growth, migration and invasion via CCNB1. There are some questions are not clear. **Majors** 1. The authors only did the in vitro experiment to verify that Huanglian Decoction suppressed HCC growth, migration and invasion via CCNB1. As they mentioned in the discussion, the major limitation is the absence of in vivo work. There are lot of TCM or single compound worked well in vitro, but failed in vivo. If they can verify its effect in vivo that would be more convincing. 2. The authors only used one concentration of Huanglian Decoction to treat each cells, please state why choose this concentration? There was no minimal effective dose to the HCC cell lines and the toxic dose to the normal hepatocyte was absent, which should be clearly detected and essential for the potential therapeutic treatment. 3. The authors found 5 bioactive compounds in Huanglian Decoction to target CCNB1. Why didn't do the further investigation on each compound or their synergistic effect additionally? This will be helpful to understand the mechanism of Huanglian Decoction to inhibit the expression of CCNB1. 4. For the preparation of Huanglian Decoction aqueous extract, the authors should provide more details, like soaking time, which equipment and temperature were used for the concentration, please provide the gravity not the rpm. Before the in vitro and in vivo studies, a chromatography and mass spectrometry should be done to authentic the bioactive compounds are constantly presented in the extract. **Minors:** 1. Please check the typos, like 3.2 line 1 "Huang Ren Tang" change to "Huang Lian Tang"; 3.7 line 5 "Si-CCNB1" to "si-CCNB1"; discussion paragraph 3 "CCNB2", the refs 36-42 studied CCNB1 not CCNB2. 2. The full name of TRT? 3. WB method didn't state the gravity of centrifugation nor which



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membrane was used for transfer, PVDF or NC or others?