Author’s response to reviews

Title: The modified Si-Jun-Zi decoction attenuates colon cancer liver metastasis by increasing macrophage cells

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The modified Si-Jun-Zi decoction attenuates colon cancer liver metastasis by increasing macrophage cells

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BMC Complementary and Alternative Medicine

Editor Comments:

1. At present we feel your manuscript contains comments which are not suitably justified. These comments diverge from what we would expect from a scientific manuscript and read more as uncritical opinions. We would ask you to remove or amend the following sentences:

1.1 "In China, the modified Si-Jun-Zi Decoction (SJZ) is a famous traditional Chinese medicine (TCM) used to replenish Qi and invigorate spleen functions and it has been widely used against cancers including CRC in clinical treatment" (Background, lines 13-15).

1.2 "In TCM, spleen deficiency [22-25] and Qi deficiency [26-32] are common symptoms in cancer patients, including CRC patients [20, 24]. Modified SJZ has been used in clinic in Jiangsu Province Hospital of Traditional Chinese Medicine as a remedy for cancer patients with "Qi deficiency", which is closely associated with cancer relapse and metastasis. However, the possible underlying mechanism is poorly understood. Here, we used the nude mouse model to identify the possible mechanism." (Discussion, lines 6-11)
Please only use statements which are supported by previously published (and peer-reviewed) scientific work (for instance in vitro, animal studies, clinical studies or observational studies). You are welcome to state that traditional medicine is utilised by a large number of individuals, properly referenced.

Answer:
1.1. We change it as following according to editor’s comments:
"In China, the modified Si-Jun-Zi Decoction (SJZ) is a famous traditional Chinese medicine (TCM) used against cancers including CRC in clinical treatment"

1.2. We remove this part and corresponding references as following according to editor’s comments.

2. At present, we do not feel that there is sufficient evidence presented in your Background section to justify the testing of Si-Jun-Zi Decoction in an animal model. We would therefore ask you to expand this section to include as much referenced evidence as possible to explain why you would expect this treatment to have an effect in this model. This evidence should come from previous in vitro or animal work. Please note that we are unable to accept traditional medical use as sufficient justification for animal studies.

Answer:
We appreciate the constructive feedback from the editor on this point. In the manuscript, we have included ample introduction and discussion on the clinical and experimental rationale for testing this drug in animal models. Specifically, in introduction part, we cited previous clinical literature to show the effect of modified si-jun-zi decoction on patients with colorectal cancer[6], with gastric cancer[7], on human peripheral blood mononuclear cells[8] and in post-operational patients of gastrointestinal tumor[9,10]. In animal experiments, there are some papers investigating the effect of modified si-jun-zi decoction on immune function of whole body irradiated mice[11], on the proliferation of lymphocyte in spleen cells in hydrocortisone treated C57BL/6J mice in vitro[12], on immunoregulation of peritoneal macrophage cytotoxic activity in normal mice[13]. All these references are related with gastrointestinal tumor or body's immune function, which are what we are focused on in our manuscript.

3. In your methods section, please clarify how the mice were saturated with CO2 and if any anesthetic was used.

Answer:
We change it as following:
Briefly, at the day of sacrifice, animals were euthanized according to NIH ARAC guidelines for euthanasia of rodents using carbon dioxide. Mice were euthanized by trained personnel via source of compressed gas in their home cage. After checking each mouse for lack of respiration and faded eye color, we confirmed their death. CO2 flow was maintained for a minute after respiration ceases. No anesthesia was used during the euthanasia.

4. The Availability of data and materials section refers to the raw data used in your study and presenting tables and figures is not sufficient to state that all data is contained within the manuscript and additional files. Please only use this statement if you have indeed provided
all raw data on which your study is based.

Answer:
We have changed it as following:

Availability of data and materials

All the data obtained and materials analyzed in this research are available with the corresponding author upon reasonable request.

5. In the Funding section, please also describe the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Answer:
We have changed it as following:

Funding

This work was funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), by Clinical Medical Research Center of Digestive Diseases on Chinese Medicine of Jiangsu Province (No. BL2014100), by peak academic talents plan in Jiangsu Province Hospital of Chinese Medicine (No. k2014yrc20 and No. k2018yrc25), by Six Talent Peaks Project in Jiangsu Province (No. LGY2018062) and by State Administration of Traditional Chinese Medicine of the People's Republic of China (National Famous Chinese Medicine Doctor Studio NO. 2018-119) and National Natural Science Foundation of China (Grant No. 81603566). The funding bodies provided financial support, and the awardees performed the research. The founding sponsor had no role in the study design, performance, data collection and analysis, decision to publish, or preparation/writing of the manuscript.

6. Please remove the response to the reviewers comments file from the file inventory as it is no longer needed at this stage of the editorial process.

Answer:
We change it according to comments.

7. At this stage, please upload your manuscript as a single, final, clean version that does not contain any tracked changes, comments, highlights, strikethroughs or text in different colours. All relevant tables/figures/additional files should also be clean versions. Additional files should remain uploaded as separate files. Please ensure that all figures, tables and additional-supplementary files are cited within the text.

Answer:
We change it according to comments.

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Reviewer reports:
Kottayath Govindan Nevin (Reviewer 2): Authors have satisfactorily addressed the suggestions
Answer:
Thanks!

Chakrabhavi Dhananjaya Mohan (Reviewer 3): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.
Answer:
We change it according to comments.