

## Peer Review File

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### Reviewer A

Line #	Referee's Comments	Author's Responses
109	So far, has basic research been carried out to determine the role of TCM in cancer treatment? From here, readers will learn about the progress that has been made in cancer treatment through TCM	Basic researches have been carried out to determine the role of TCM in cancer treatment. We have modified our text as advised (See Page 4, line 111-114)
110-112	Traditional Chinese medicine is one of the best healing techniques in the world. The author can add specific types of treatment (e.g., acupuncture) and to treat what kind of tumor or cancer (e.g., breast or prostate cancer)	We have modified our text as advised (See Page 4, line 116-118)
Methods	Does this article use statistical analysis? If yes, how do you performed the statistical analysis on the data you have obtained? including ways to correct data errors.	This article doesn't use statistical analysis.
Conclusions	In your opinion, what type of method or herbal is appropriate for cancer treatment. More specific herbal targets will help to design future research. You can add this statement to the conclusion section.	We have modified our text as advised (See Page 12, line 400-405,407)
References	Author(s) can add other references published in Translational Cancer Research Journal	We have modified our text as advised (See Page 4, line 114)

### Reviewer B

There are several sentences needing an adequate support and explanation. See for instance the sentence: Modern research has confirmed that TCM can regulate antitumor immunity. There are no references, furthermore the authors refer about a confirmation assuming that TCM can regulate antitumor immunity. What is the meaning of can? The possibility in a pathology like cancer is not sufficient. The MN should be able to clear this key aspect.

Again in page 6: New studies have demonstrated the immune-regulating effects of some of CHM' active ingredients (e.g., polysaccharides, glycosides, and alkaloids). Which kind of studies? Why there are important and reliable? What are the studies reliable and what the others

are not reliable? Why these compounds should be more active against other ones? It is important that a review like this is able to report comments and considerations, otherwise it is list of already known and therefore without any real utility.

See the further sentence: CHM can regulate the tumor immune microenvironment (TIME) and the human body's immunity in a dual manner. Again, it is assumed the reality of his activity, but the aim of the MN should be a demonstration of the activity. The argument is in part reported in the Discussion, but the different parts of the MN should be in accordance.

A comparison between the reliability of Chinese publications and the international ones could be interesting, as well a comment about the temporality of the publications regarding experimental data.

In conclusion, the MN does not adequately debate the key arguments concerning the validation of TCM remedies, including the quality and control of the preparations and several others. Each sentence must be supported by data and nothing can be considered already demonstrated, otherwise the result is a confused reader.

**Reply 1:** The sentence: Modern research has confirmed that TCM can regulate antitumor immunity. It is a general summary. TCM can prevent and treat tumor metastasis/recurrence and enhance the body's immune response by regulating the TME and reshaping the immunosuppressive cells in the TME, which can be referred to 14. And the following references listed in the tables can support this view.

**Reply 2:** In page 6: New studies have demonstrated the immune-regulating effects of some of CHM' active ingredients (e.g., polysaccharides, glycosides, and alkaloids). You may refer to the studies in table 2 to table 5. Most of the studies we selected were animal models and in vitro cell experiments, which have explored the mechanism of action, so we believe that they are reliable. Some clinical studies were not included because they were not sufficiently rigorous in design and the mechanisms of action were not sufficiently explored. This paper only summarizes the active compounds that have been studied, which may be a limitation of this paper. Active contrast between different compounds need the help of pharmaceutical professionals, which is also lacking in our team.

**Reply 3:** The further sentence: CHM can regulate the tumor immune microenvironment (TIME) and the human body's immunity in a dual manner. Again, it is a generalization. Evidence supporting can be found in Table 2 to Table 5.

Comparing the reliability of Chinese publications and the international ones could be an interesting point, but we don't think it is the focus of this paper, so we will not make a comparison here.

**Reply 4:** We must acknowledge that not adequately debate the key arguments concerning the validation of TCM remedies, including the quality and control of the preparations and several others, is where we fall short. In the future, we may be able to conduct studies on the validation of TCM together with pharmaceutical professionals.

## Reviewer C

The paper titled “Advances in traditional Chinese herbal medicine and their pharmacodynamic mechanisms in cancer immunoregulation” is interesting. The theory of a CIC is of guiding significance to regulating tumor immunity via CHM. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) What is the indication, genotype, and immunotype of the CIC? Please discuss the importance of considering a tumor's immunological phenotype.

**Reply:** In October, Ira Mellman et al. published a paper titled “The cancer-immunity cycle: Indication, genotype, and immunotype”. This paper updates our understanding of CIC. In particular, this paper emphasizes the importance of considering a tumor's immunological phenotype (immune inflamed, immune excluded, and immune desert).

**Changes in the text:** No changes in the text.

2) The core issue of CHM anti-tumor immune research is the mechanism of action of drugs. Different CHM can act on different receptor cells, resulting in different effects. How to view the differences and targeted effects of different CHM? It is recommended to add relevant contents.

**Reply:** According to their different functions, CHM can be divided into heat-clearing and detoxifying medicine, supplementing medicine, qi-rectifying and blood-invigorating medicine and so on. Specific targeting effects of CHM and its effective components have been described in detail in the tables. For your suggestion, we make brief generalizations in the discussion section.

**Changes in the text:** See Page 11, line 361-366.

3) What is the role of CHM on patient's immune system when treating cancer patients? It is recommended to add relevant contents.

**Reply:** The effect of CHM on the immune system of cancer patients has been described in detail in the paper, and we think it is unnecessary to repeat the relevant contents.

**Changes in the text:** No changes in the text.

4) There are many databases. Why did the author only select PubMed and CNKI databases in this study for searching? Please explain the reason.

**Reply:** PubMed and CNKI are two major databases in English and Chinese respectively, they contain literatures in various fields and are widely used. We also conducted a search in other databases and found that the search results were duplicated with PubMed and CNKI. So we finally chose PubMed and CNKI databases for searching.

**Changes in the text:** No changes in the text.

5) What are the elements of the complement system that come into play in the CIC? It is recommended to add relevant contents.

**Reply:** The complement system, a central element of innate immunity, has surged as a master regulator of cancer immunity. Complement activities are mediated by more than 50 circulating, cell surface-bound and intracellular proteins. In light of the breadth and complexity of the immune response, we are unable to elaborate the role of complement in the regulation of the

CIC. This paper mainly focuses on immune cells and their related cytokines, and the relationship between the complement system and CIC may be elaborated in future articles.

**Changes in the text:** No changes in the text.

6) The research on anti-tumor immunity of CHM also includes aspects such as quality control and compatibility contraindications of CHM, and it is recommended to discuss them.

**Reply:** Your suggestion is very enlightening! However, our study on anti-tumor immunity of CHM is only a classification of anti-tumor immunity steps. Future research can focus on the quality control and compatibility contraindications of CHM.

**Changes in the text:** No changes in the text.

7) This study is based on the analysis and summary of the literatures. It is suggested to add clinical experimental research, which may be more meaningful.

**Reply:** Thank you for your valuable comments and we will conduct clinical experimental research in the future.

**Changes in the text:** No changes in the text.