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September 16, 2013

Dear Director:

Thank you very much indeed for your kind letter concerning our manuscript entitled "**Anti-cancer potential of litchi seed extract.**" The constructive suggestions from yours are greatly appreciated. We really appreciate that you would consider our revised version. Enclosed please find the revised manuscript as attached file, which has been re-edited entirely according to the comments and suggestions from reviewers as follows:

1. Comment 1: In this manuscript the authors have dealt with the anticancer properties exhibited by litchi seed extract towards different cancer cell lines. The manuscript is well written and summarized the most relevant and recent aspects of the topic. However, before full acceptance, the authors should considered making some minor modifications. Particularly, I believe that at least one figure summarizing the main findings described in the review is necessary to strengthen the quality of the manuscript and improve its comprehension.

Our answer: We summarize the pharmacologic effects of litchi seed extract in figure 1. Thanks a lot to reviewer 1.

2. Comment 2: This manuscript reviews the recent findings regarding the benefits of the litchi seed extract in the treatment of human cancer and the possible cellular and molecular mechanisms. The title is interesting and suitable for the Journal.

Our answer: Thanks a lot to reviewer 2.

3. Comment 3: The review of Chih-Cheng and colleagues discusses the potential of litchi seed extract as anti-cancer treatment. This is a comprehensive editorial of the properties of this Traditional Chinese Medicine compound in which the authors linked the ancient knowledge of Chinese Medicine with the recent findings regarding the possible cellular and molecular mechanisms of the compounds from litchi seed as anti-tumoral agents. I would recommend increasing the number of references since for a reader not familiar with this topic, it would be interesting to know the work done in this field. If that were at all possible, it would improve the editorial. Moreover, there are some typos throughout the text that should be corrected.

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Our answer: We have additionally signed reports in references from no. 58 to 64 and the typos have been corrected. Thanks for the kind suggestion of reviewer 3.

4. Comment 4: The review described by Lin et al. summarizes well the current situation of researches on anti-cancer potential of litchi seed extract and is well written. However, it would be too early to make mention of the benefits of the seed extract for the treatment of human cancer, because only a few paper have so far reported the in vivo anti-tumor effect of the seed extract. To improve this review, it is necessary to add a little more emphasis on the in vivo anti-tumor activity. If available, add more information about the anti-tumor activity of the litchi seed extract in animal experiments. Minor comments: 1) Page 6. It is better to divide the section "Anti-tumor activity and possible mechanisms of the litchi seed" into two sections "Anti-tumor activity of the litchi seed" and "Possible mechanisms of the litchi seed", and put the literatures (refs. 29 ,30, 32) describing the anti-tumor activity of the litchi seed together in the former section. 2) Provide the reference number to the following sentences. Page 6, line 7 " Some of these compounds appear to exhibit anti-neoplasm activities...". Page 6, line 11 " In our report...". Page 6, line 17. "Xu and colleagues isolated...".

Our answer: We have reviewed and signed some reports that showed litchi seed extract exhibited in vivo anti-tumor activity and described from line 24 of page 7 to line 1 of page 8. The section "Anti-tumor activity and possible mechanisms of the litchi seed" has been divided into two sections "Anti-tumor activity of the litchi seed" and "Possible mechanisms of the litchi seed". The reference number has also been added. Thanks for the kind suggestion of reviewer 4.

5. Comment 5: In this paper, the author reviewed the recent findings regarding the pharmacologic effects and benefits in the treatment of human cancer and the possible cellular and molecular mechanisms of the litchi seed. But importantly, chronic infection and the ensuing inflammation are the most important environmental factors that contribute to tumourigenesis and the progression of established cancerous lesions. The extracts obtained from litchi seeds exhibit a wide range of biological effects, including antibacterial, antiviral, anti-inflammatory and antioxidant activity. So the author should

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discuss the biological effects such as inflammatory status influenced by litchi seeds. In addition, as a potent anti-tumor agent, its advantages and disadvantages should be discussed compared with synthesized anti-cancer drugs and other Chinese *Herbal Medicines*. Furthermore, the possible side effects and the limitations of litchi seed extract should be *indicated* in the manuscript.

Our answer:

- 1) we discuss the protective effect of litchi seed to livers in nonalcoholic steatohepatitis rat at line 10 of page 6 to line 12 of page 6.
- 2) We discussed more efficient anti-cancer effect of some components of litchi seed than anti-cancer drug adriamycin and other TCM at line 9 of page 8 to line 14 of page 8.
- 3) We discussed the possible side effect and the limitation of litchi seed extract at line 7 of page 11 to line 14 of page 11.

Thanks a lot for the kind suggestion of reviewer 5.

Thank you for kindly assistance,

Your Sincerely,

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