Dear Professor Luo

Your letter of 14th of Aug 2019, together with the comments of reviewers to our manuscript (Manuscript ID: molecules-574039) entitled “Unraveling The Molecular Mechanism of Traditional Chinese Medicine Against Acute Viral Infections of Airway”, was received. Thank you very much. We are very grateful and thank reviewers for these kind corrections and suggestions. We have revised our manuscript according to these comments point by point. We have also asked a native English speaker to check the grammar and font of text thoroughly. Now, we are glad to send the revision of our manuscript to you.

*Molecules* is the leading international peer-reviewed open access journal of chemistry. We supposed that our work could improve the understanding of the mechanisms of herbal medicine and TCM. We hope that our answers are satisfactory. We would be most grateful if our manuscript could be considered for publication in the *Molecules*. Thank you very much.

Sincerely Yours,

Jung San Chang

Aug 26th, 2019
Response to the reviewer 1:

1. It looks like a chapter in a thesis rather than a paper. It has too much information and does not have a stand-out story.

   **Ans:** We would like to thank reviewer for this kind reminding. We completely agree that this review provide much information and does not have a stand-out story. However, the purpose of this review is to summarize the current knowledge and shortage of molecular mechanisms of traditional Chinese medicine (TCM) using TCM formulas against airway viral infection for examples. Therefore, we slightly modified the title into “Unraveling The Molecular Mechanism of Traditional Chinese Medicine: Formulas Against Acute Airway Viral Infections as Examples”. We suppose that our work will contribute to the aim of this supplement. Thank you very much.

2. Introduction of TCM is too long, section 1-3 is not directly linked to management of viral infections! Therefore, your content does not fully reflect the title but more like an overview of complex molecular mechanisms and possible interactions of TCM. Section 5 discusses the limitation of TCM, however, how does that link with the title - mechanistic studies?

   **Ans:** We would like to thank reviewer for this kind suggestion and reminding. We completely agree that section 1-3 are not directly linked to the management of viral infections that does not fully reflect the title. We also agree that section 5 cannot link with the title - mechanistic studies. To make the content fully reflecting the title, we slightly modified the title into “Unraveling The Molecular Mechanism of Traditional Chinese Medicine: Formulas Against Acute Airway Viral Infections as Examples”. We hope that our revision is satisfactory. Thank you very much.

3. Please check the grammar and font of text thoroughly

   **Ans:** Thank you very much for this kind suggestion. We have asked a native English speaker to check the grammar and font of text thoroughly. We are glad to provide you the revision and hope that our revision is satisfactory. Thank you very much.

4. It would be good to add a column of associated pathways to table 1-5, or even have a signalling pathway maps (similar to Figure 1). Then it is very clear of how those compounds interact with each other or with their targeted receptors.
Ans: We would like to thank reviewer for this kind suggestions. We have supplemented figure of signaling pathway to each TCM formula to make it clearer for readers to understand their mechanisms. Thank you very much.

5. Most of the bioactive compounds in the herb have very low amount in the herb and formula. Therefore, the likelihood of interaction is even lower if it is administered as in a decoction or formula. You may discuss a bit more of the clinical significance.

Ans: We would like to thank reviewer for this kind correction and comment. We completely agree that most of the bioactive compounds in the herb and formulas have very low amount. However, with a little amount of bioactive compounds, herbs and TCM formulas actually have bioactivities, including clinical effects and side effects. This is why we need to unravel their molecular mechanisms. We have supplemented the discussion in section 3 for overview, in section 5.2 for effectiveness, and in section 5.4 for interactions as follows:

In the second paragraph of section 3: Someone might questions that most of the amount of bioactive compounds in the herbs is very low. Combination of herbs to form TCM formula can further decrease the amounts of bioactive molecules. Is it possible that herbs and TCM formulas can be effective with so little amount of bioactive compounds? Is it possible that little amount of bioactive molecules can cause interactions? In orthodox western medicine, little amount of vitamins can show their clinical effects. Therefore, the amount of bioactive molecules is not the point. Instead, their molecular mechanisms are the key. In real world practice, herbs and TCM formulas actually have bioactivities. Besides, several side effects of TCM formulas have been reported which raises the safety issue of TCM formula. With only little amount of bioactive molecules, natural products and TCM formulas can cause effects and side effects…..

In section 5.2: …..ginkgo for dementia or mild cognitive impairment [125]. Amount of the most bioactive compounds in herbs and TCM formulas are very little. This also raises questions on their effectiveness. One study discussed the clinical effect of Ma-Huang-Tang (MHT) against seasonal influenza [126]. MHT shows equivalent clinical effect to neuraminidase inhibitors. However, not every TCM formula can provide the evidence. Several TCM formulas, such as Ma-Xing-Gan-Shi-Tang (MXGST), Ge-Gen-Tang (GGT), and Xiao-Qing-Long-Tang (XQLT), are among the top ten commonly used TCM prescriptions for patients with upper respiratory tract infections (URTIs) in Taiwan [127]. However, there are not enough clinical trials to support their uses.
Therefore, more studies are required to provide the evidence and the mechanisms.

In section 5.4: TCM formulas have numerous bioactive compounds to form a kind of cocktail therapy. However, the amount of each bioactive compound in TCM formulas can be very few. This raises a question about the likelihood of their interactions with other molecules during administration in a decoction. Ginseng, a natural product commonly used among adults [4], has about thirty ginsenosides as its bioactive compounds [138]. The amount of each ginsenoside is very few. After oral administration, ginsenosides are metabolized and transformed by intestinal microbiota. Diet can markedly influence the transformation of ginsenosides. They exert pharmacologic effects in animals and show various clinical effects in randomized controlled trials [138]. Also, several side effects and drug interactions have been reported [138]. Therefore, little amount of bioactive compounds do have clinical effects and side effects. The effects may come from individual pharmacological activity of bioactive compounds or their synergism. The side effects may also come from individual unfavorable bioactivity or from interactions. Besides, herbal medicine and TCM therapy is commonly used in combination with orthodox medicine by the patients.

We would like to thank reviewer gratefully for these kind reminding and suggestions. We hope that our answers are satisfactory. Thank you very much.