September 9, 2016

Dear Editors,

Thank you very much for your letter and advice.

According to your instructions and the comments of the reviewers, we have revised our paper entitled "Naringenin protects against isoniazid and rifampicin induced apoptosis in hepatic injury" (ID: 28549), and would like to submit revised article for your consideration.

The following are our responses to the reviewers' comments

Reviewer #1: The manuscript written by Wang et al. describes the protective effect of naringenin (NRG) on hepatic injury induced by isoniazid (INH) and rifampicin (RIF). The data show significant protective effect of NRG through suppression of apoptosis, which is demonstrated by serum transaminases, liver histology, immunohistochemistry and western blotting. Since liver injury induced by INH and RIF is a serious problem for the treatment of tuberculosis, the data are important and may provide a novel clue for management of tuberculosis. However, there are some concerns that need to be addressed. Major point 1. Mice were pretreated by NRG before administration of INH and RIF. However, the effect is unclear if NRG is given after administration of INH and RIF or development of liver injury. This may be more important for clinical use in the treatment of tuberculosis with INH and RIF. Minor points 1. Adverse effect of NRG should be stated, if there is. 2. It is stated that NRG was dissolved in 5% CMC. What is CMC? Although the experiment includes the control group treated with NSS alone, another control group that should be included is the mice treated with INH/RIF and the dissolved solution with CMC/NSS.

Response: Thanks a lot for your constructive and positive comments, you give us very useful sugesstions for our ongoing research. The following is a detailed explanation of some problems above.

Major point 1. Although previous research has shown that NRG has wide range of

biological and pharmacological activities, the effect was not so good in our preliminary experiments if NRG was given after administration of INH and RIF or development of liver injury. One possible reason is that the clinical application of NRG has been limited owing to its poor water solubility and oral absorption and low blood drug concentration. Because of that, our further program is to prepare NRG solid dispersion from poorly-soluble NRG so as to improve its solubility and dissolution rate, and then increase the curative effect.

Minor points 1. NRG (4,5,7-trihydroxyflavanone), a natural flavonoid compounds, is widely distributed in citrus fruits, tomatoes , cherries, grapefruit and cocoa. As a food additive, NRG is considered safe. Earlier studies have suggested that NRG shows no toxic effect on normal cells at a similar dose.

Minor points 2. We are sorry that we didn't clearly write the full name of CMC, and we have revised in the manuscript. CMC is the abbreviation of carboxyl methyl cellulose. CMC is considered to be a safe food additive, and is widely used in frozen desserts, protein food, beverages, icings, dressings, instant noodles in food industry. In pharmaceutical industry, CMC at a proper viscosity can be used as a binder and disintegrant for tablets, a suspending aid for suspension, etc. CMC as a suspending agent can prepare NRG suspensions, so as to improve its solubility. Moreover, although the experiment should set up CMC control group, researchers now believe that the influence of the content of CMC on the experimental results can be neglected, because of CMC just be a suspension agent and improve the drug solubility. So in order to highlight the key points, lots of papers in international journals only establish NSS control group and no longer establish CMC control group. We hope that you are satisfied with our explanation, once again, thank you very much for your attention and consideration.

Reviewer #2: The authors wrote this manuscript in a good way. However, In Abstract.. Results section in line 13 BCl-2 and Bax gene expression ...it should be protein not gene as they are measured by western blot. In discussion.. line 5 via INH

and RFP infusion ... it should be intragastrically not infusion. References written in an organized way.

Response: Thanks a lot for your detailed suggestions. We have revised carefully according to your advice in the manuscript. The two changes are highlighted in red in the manuscript.

Reviewer #3: Congratulations to the authors, this is a very nice experiment, the manuscript clearly explains the protective effect of naringenin against anti tuberculosis drugs induced liver injury.

Response: Thank you very much for your concern and support. We will further our research and explore in this field.

Thank you very much for your attention and consideration.

Sincerely,

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