

Peer Review File

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Reviewer A

The article 'Integrated UPLC-MS, Network Pharmacology and Gut Flora Analysis to Determine the Effect of Qiangzhi Decoction Treatment on Comorbid Tourette Syndrome and RRTI' shows an attractive approach for the possible treatment of Tourette syndrome and recurrent urinary tract infection respiratory. Although well-written and organized, the article needs to address the issue of the synergy of the Qiangzhi decoction and associate the chemical composition with the biological effects presented.

Reply: Thank you for your comments. We think this is an excellent suggestion. First of all, we would like to answer your question about the issue of the synergy of the Qiangzhi decoction. We analyzed this issue from two perspectives and added relevant contents to the manuscript:
① Multi-ingredient synergistic effect. We have revised our text on page 13, line 13.
② Synergistic summation of multiple targets in a complex biological process. We have revised our text on page 15, line 1.

Then, we explored the relationship between the main chemical composition and the biological effects on page 13, line 3.

Changes in the text: We have added the relevant content as advised (see page 13, line 3; page 13, line 13; page 15, line 1).

Reviewer B

Comment 1: Figure 1

Please explain RT, NL, FTMS, and pESI in the legend if applicable.

Reply: Thanks for your reminder, we have added the note about "RT, NL, FTMS, ESI" to the legend as requested: "RT, Retention Time; NL, nominal level; FTMS, Fourier transform mass spectrometry; ESI, electrospray ionization."

Changes in the text: We have modified our text as advised (see Page 21, line 10).

Comment 2: Figure 2

a) Please provide 2A with a clearer version, the current version cannot be seen clearly.

b) Please explain PPI in the legend.

Reply: a) As you suggested, we have replaced the image of Figure 2A with a clearer one.

b) We apologize for not explaining PPI and have now added an explanation of PPI: "PPI, protein protein interaction"

Changes in the text: We have modified our text as advised (see Page 22, Figure 2; Page 22, line 10).

Comment 3: Figure 4 and 5

Please explain QZD and CON in the legend.

Reply: We have added explanations about QZD and CON as advised.

“...QZD, Qiangzhi decoction; CON, control group; MODEL, model group; THT-FFS, tiapride hydrochloride and bacterial lysate capsules group; QZD-L, QZD low-dose group; QZD-M, QZD moderate-dose group; QZD-H, QZD high-dose group.”

Changes in the text: We have modified our text as advised (see Page 24, line 6; Page 25, line 5).

Comment 4: Figure 6

Please explain QZD, CON, and LDA in the legend.

Reply: We have added explanations about QZD and CON as advised.

“...QZD, Qiangzhi decoction; CON, control group; MODEL, model group; THT-FFS, tiapride hydrochloride and bacterial lysate capsules group; QZD-L, QZD low-dose group; QZD-M, QZD moderate-dose group; QZD-H, QZD high-dose group... LDA, Linear Discriminant Analysis.”

Changes in the text: We have modified our text as advised (see Page 26, line 4).

Comment 5: Table 2

Please check if the number is correct here. And please also provide the unit for the time.

Table 2 Chromatographic gradient

Time (9)	Water phase rat
1	98

Reply: We appreciate the editor’s careful review of our manuscript have removed the "(9)" here (see Page 27, Table 2).

Changes in the text: We have modified our text as advised (see Page 27, Table 2).

Comment 6: Table 3

Please explain all the abbreviations in the table footnote.

Reply: We have added explanations the abbreviations in the table 3 footnote.

“*RT: Retention Time; ESI, electrospray ionization.”

Changes in the text: We have modified our text as advised (see Page 34, line 11).

Comment 7: References/Citations

Please double-check if more studies should be cited as you mentioned “studies”.

and the incidence shows an increasing tendency (14). Previous studies have found that the immune function of children with RRTI was generally weaker than that of normal children, suggesting that abnormal immune function was an important cause of RRTI in children (15). Some studies have demonstrated increased frequency of respiratory infections in TS patients (16). A retrospective analysis of 273 children with tics showed

Zhi (wisdom). Previous studies and clinical observations have shown that QZD can significantly reduce tic disorders while also reducing RRTI episodes (18).↵

secretion in cerebrospinal fluid, peripheral blood, and 24-hour urine (45). Recent studies showed that 5-HT regulates DA neurons through several 5-HT receptors in the brain. Most of the effects of 5-HT on dopamine neurons are indirect, rather than direct effects on DA nerve terminals (46). Peripheral serotonin has been shown to have critical roles in the regulation of both innate and adaptive immune responses (47,48). Recent studies found serum serotonin levels might be considered a predictor of outcome in SARS-CoV-2 infection (49).↵

disease. Recent studies have found that children with RRTI have significantly fewer numbers of *Bifidobacteria* and *Lactobacilli* and more *Escherichia* in their intestines compared to healthy children (55).↵

Reply: Thank you for pointing this out, we have modified our text as advised (see Page 4, line 1; Page 4, line 5; Page 12, line 32; Page 14, line 29; Page 14, line 23; Page 15, line 26).
Changes in the text: We have modified our text as advised (see Page 4, line 1; Page 4, line 5; Page 12, line 32; Page 14, line 29; Page 14, line 23; Page 15, line 26).