Author's response to reviews

Title: Sho-saiko-to, a traditional herbal medicine, regulates gene expression and biological function by way of microRNAs in primary mouse hepatocytes

Authors:

Kwang Hoon Song (ksong@kiom.re.kr)
Yun Hee Kim (ddyunee@kiom.re.kr)
Bu-Yeo Kim (buykim@kiom.re.kr)

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We thank the reviewer for their helpful comments and advice. We have made responses and revised the manuscript in accordance with the comments from the reviewers. Revised-or related-sentences were highlighted in yellow.

Reviewer: Chang-Gue Son

Comment: This revised manuscript has been improved. However, I suggest that this manuscript needs to be revised more, especially regarding making a concise and clear answer for their original question (explanation of SST pharmacological mechanisms of SST). In conclusion section, authors described that "cell cycle pathways", "metabolism-related pathways" and "immune-related pathways" are involved in the SST actions. However, it is too broad to explain the mechanisms of SST' pharmacological actions because those pathways would be always appeared no matter any drug is used. Please extract and interpret the most meaningful data, and then provide your readers a clear and interesting conclusion.

Response: We appreciate the important suggestion that biologically meaningful mechanism should be provided for explanation of SST pharmacological effect. We completely agree with the reviewer’s comment, but the main purpose of the present study was to identify genome-wide changes occurring in primary mouse hepatocytes by SST treatment. We have also focused on the elucidation of gene regulatory mechanism controlled by microRNAs by treatment with SST. Therefore, our result could only provide general molecular targets possibly regulated by SST and it would be hard to demonstrate that our result can explain the exact pharmacological mechanism of SST. Even we did not use disease-related model or -cell type for elucidation of specific pharmacological activity of SST. Considering the diverse clinical activities of SST, the pharmacological mechanism of SST would be complex and different depending on each pathological condition of experimental subjects.

Therefore we have aimed to provide novel approach that can be applied to various types of experimental conditions to delineate molecular events induced by SST by using genomic network composed of multiple genes and microRNAs.
But we have also tried to interpret widely-known pharmacological activity of SST based on our results. For example, genes (CCNA2, CCL7, CDC25B, CDK1, CYP2F2, CYP3A11, and CYP2C50) and pathways (especially “cell cycle pathway”, “cytochrome metabolism pathways”, and “immune-related pathways”) identified in present study were previously reported to be involved in the liver regeneration process by SST. Because liver regeneration is one of the main pharmacological activities of SST against diverse liver diseases, we expect that our result could contribute to the elucidation of molecular mechanism of liver regenerative process by SST.

We have clarified that biological roles of pathways and genes can give clue to the elucidation of molecular mechanism of liver regenerative activity of SST in Abstract, Discussion, and Conclusion section. We have also avoid the excessive use of “pharmacological mechanism of SST” to indicate the limit of our result.