Response to Reviewer 3 Comments

The authors found the kazal-type elastase inhibitor ShSPI from centipede venom. Using chemically synthesized ShSPI, they examined the inhibitory activity of ShSPI, identified amino acid residues essential for activity, and determined its three-dimensional structure.

Major points
-1. How did the authors find ShSPI cDNA? Was ShSPI cDNA the main component of centipede venom cDNA, or was one of the sequenced cDNAs happened to be ShSPI?

<Response: Thank you for your suggestion. The section of the construction of cDNA library has been rewritten in the revised manuscript (line 272-276, highlighted by bright green). Briefly, we selected the cDNA clones (>350bp) and sequenced. Protein or peptide that belongs to serine proteinase inhibitor was chosen according to the results of blast. Consequently, ShSPI was one of the sequenced cDNA clones.

-2. It has not been confirmed that ShSPI is actually present in centipede venom. It is better to examine elastase inhibitory activity in centipede venom.

<Response: Thank you for your comment. We have exhausted our effort. Unfortunately, we could not be able to collect enough crude venom of Scolopendra hainanum to examine the protease activity. Our research will focus on the purification of the crude venom in the future study.

-3. The authors must explain why ShSPI does not include an N-terminal QRNRR.

<Response: We appreciate your comment. As illustrated in figure 1, the sequence without signal peptide has been boxed. Within the boxed sequence, the N-terminal part of QRNRR is thought to be pro-peptide according to our experience. The synthesized sequence belongs to the domain of the kazal family according to the blast results. Accordingly, the mature form of ShSPI has been identified as CPQVCPAIYQPVFDEFGRMYSNCEMQRARCLRG.

Minor points
-1. line 94, 50 nM → 500 nM

<Response: Thank you for the comment. The concentration of ShSPI/Sivelestat in figure 3C was marked incorrectly. We have revised the figure 3, in which the X axis of figure 3B and 3C has been corrected.

-2. line 203, physical → physiological?

<Response: Thank you for the comment. In the revised manuscript, “physical” in line 203 has been replaced by “physiological” (line 214, highlighted by bright green).