Author’s response to reviews

Title: Effects of ChondroT on Potassium Oxonate-Induced Hyperuricemic Mice: Downregulation of Xanthine Oxidase and Urate Transporter 1

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Author’s response to reviews:

Editor Comments:

1. Please include the email addresses of all authors on the title page of your manuscript. The corresponding author should still be indicated.

   As you mentioned, we revised this part.

2. Please move the List of abbreviations to after the Conclusions section.

   We revised the mistakes.

3. Please clearly state in the Methods section all of the anesthetic and euthanasia methods used in this study and any concentrations and doses.

   As you mentioned, we revised this part in the Methods section.

4. We note that you have not included an acknowledgements section. If you have no acknowledgements please put ‘Not Applicable’ in this section.
We revised the mistakes. As below,

"This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI17C0911)."

Vikneswaran Murugaiyah (Reviewer 1):

1. Do include as references the other similar studies that used sample size of 5.
   → As you mentioned, we carefully added in the discussion section. As below, “Furthermore, Phellodendri Cortex has been reported to decrease serum UA and liver XOD activity in PO-induced hyperuricemic mice [29]. In addition, Phellodendri Cortex was reported to protect human osteoarthritic cartilage and chondrocytes [30]. Moreover, Lonicerae Folium and Clematidis Radix showed inhibitory effects against XOD activity in vitro, but these effects were not strong [31]. Clematidis Radix also has been reported to show anti-rheumatoic arthritis effects that are mediated through decrease PLA2 activities and PGE2 production and lipopolysaccharide-induced COX-2 protein expression [32].”

In the introduction section, our studies about ChondroT composed of 5 herbs were described with references, as below.

“We previously reported that GHJTY inhibited the inflammatory processes associated with arthritis [8]. Using bioinformatics analysis [9] and screening experiments, we selected the following five effective herbal constituents of GHJTY, Osterici Radix, Lonicerae Folium, Angelicae Gigantis Radix, Clematidis Radix, and Phellodendri Cortex and named the resulting concoction as ChondroT [10]. ChondroT showed more significant multifunctional therapeutic effects on inflammation and arthritis than GHJTY did [10].”

2. Do include the following statement in the manuscript "The in vivo enzyme inhibitory activity of Chondro T is the net inhibitory activity of both XOD and xanthine dehydrogenase (XDH)."
   → Thanks for your comments. As you suggested, we added the sentence in the discussion section.
3. the statement "However, these uricosuric agents limited to use clinical trials, which further studies will be required to determine the safety of uricosurics effects of ChondroT for antihyperuricemia." Should be replaced by "However, the uricosuric effect of Chondro T could have limited clinical use due to safety issues such as risk of uric acid stone formation".
   → As you mentioned, we revised this part in the Discussion section (page 14 line 15).

Bunleu Sunghthong (Reviewer 2):

1. Page 9 line 3: "uric acid (UA) blood levels" should be "blood uric acid levels (UA)" or "uric acid levels (UA) in blood" or "levels of uric acid (UA) in blood".
   → As you mentioned, we revised it.

2. Page 19 line 19: "Previous our results suggested..." should be "Our previous results suggested...". This sentence seems to be that it was not completed in writing.
   → We are very sorry for the mistake and thank you for the comments. We revised the sentence.

   “In our previous results, seven reference components in ChondroT, such as chlorogenic acid, berberine Cl, nodakenin, isoferulic acid, oxypeucedanin hydrate, decursin, and decursinol angelate were selected for quality control of ChondroT.”

3. Page 28 in table 1: The scientific names of the third and fourth plants are not in italics.
   Lonicera japonica => both in italics
   Ostericum koreanum => both in italics
   → We revised the mistakes.