Reviewer's report

Title: Toona Sinensis Leaf Extract Has Anti-nociceptive Effect Comparable to Non-steroid anti-inflammatory Agents in Mouse Writhing Test

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Reviewer: Hong-Won Suh

Reviewer's report:

In the present manuscript, the authors showed the antinociceptive effect of aqueous extract from the leaves of Toona sinensis (TS) in a visceral pain model, a writhing test.

The authors have demonstrated that one of fraction of TS was effective in relieving the pain response and further characterized TSL1 fraction shows a significant reduction in writhing response when compared to control. Furthermore, in a time-course study, TSL1 fraction exerted its antinociceptive effect up to 6 hr. The authors suggest that the antivisceral pain properties of TS is comparable to those of cyclooxygenase-2 (COX-2) inhibitor and diclofenac, implicating that TS might be a good candidate for treating intractable visceral pain in human. However, to improve the manuscript, the authors are advised to revise several points in response to the following comments.

Major Comments:

1. What is the mechanism of the TS or TSL1 in the production of antinociception?

2. The authors have demonstrated that TS extract at mg/kg dose range has antinociceptive effect in a writhing test. However, TSL1 fraction exerted an antinociceptive effect at a dose of g/kg range, which is much higher compared to TS crude extracts. The authors should clarify why more dose was needed in more purified fraction (TSL1) than in crude extract (TS).

3. Furthermore, TSL1 produced analgesic effects dose-independently. The authors should explain more thoroughly, with expand and logical speculation.

4. In addition, they compared antinociceptive effects of TS or TSL with COX2 inhibitor in addition to one of NSAID compound. When authors compare two drugs, both efficacy as well as potency should be compared. They should perform the additional experiments related to this issue.

5. The additional experiment such as rotarod test should be performed. The antinociceptive behavior induced by TS or TSL might be due to the abnormal behavior related to motor coordination.

6. The authors are emphasizing the visceral pain in cancer patients. The writhing test does not represent the whole visceral pain. If authors really suggests that TS or TSL1 are good candidate against the visceral pain, the antinociceptive ability of TS or TSL1 should be demonstrated by performing another visceral pain
model using 2,4,6-trinitrobenzenesulfonic acid (TNBS).

Minor Comments:
1. Throughout the whole manuscript, there are some English grammatical errors. The manuscript should be edited by a skillful native English editor.
2. In introduction part, one of pharmacological effect of TS is known to produce apotosis. Are there any side effects or behavioral changes of TS or TSL1 at doses used in the present study. The authors should discuss these issues in Discussion Section.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No