



**Peer- review of The Effects of shokyo (*Zingiberis Rhizoma*) and kankyo (*Zingiberis Processum Rhizoma*) on prostaglandin E2 production in lipopolysaccharide-treated mouse macrophage RAW264.7 cells**

**Dear Editor and Authors,**

The manuscript “Effects of shokyo (*Zingiberis Rhizoma*) and kankyo (*Zingiberis Processum Rhizoma*) on prostaglandin E2 production in lipopolysaccharide-treated mouse macrophage RAW264.7 cells” was professionally represented in unambiguous clear English language throughout the manuscript with structure aligned with PeerJ standard.

Additionally, the raw data have been supplied with high quality relevant figures. The introduction elaborated the context with a need for further consideration of certain studies and reviews of aqueous ginger and its effect of PGE2 levels both *in-vitro* and *in-vivo* which will be thoroughly mentioned later on.

Toshiaki Ara *et al* represented a manuscript aligned with the PeerJ scope with consistently defined research questions. All the methodologies are well described and the data is analysed in a satisfactory modern manner where this robust data was well discussing the findings. Nevertheless, a metabolomic profiling of shokyo and kankyo powders is to be provided if not declared in the certificated of analysis provided by Tsumura & Co. Also the COA provided by the commercial vendor is to be added to the supplementary section.

Comments:

A) The anti-inflammatory mechanisms of the ginger armoury of phytochemicals and either aqueous or alcoholic extracts were comprehensively vetted in the recent review (Ameliorative and protective effects of ginger and its main constituents against natural, chemical and radiation-induced toxicities: A comprehensive review, Food and Chemical Toxicology, 2018 <https://doi.org/10.1016/j.fct.2018.10.048>) for both the *in-vitro* and the *in-vivo* studies. This review should have been considered and utilised in the introductory section to draw the need for more studies on the aqueous ginger extract to be discussed briefly. Furthermore, some studies elaborated in the aforementioned review are to be considered in the discussion and/or the introduction sections for examples:

- The inhibition of induced cytokines in HaCaT cells and Mice by aqueous ginger extract (*Zingiber officinale*) protects HaCaT cells and C57BL/6 mice from ultraviolet B-induced inflammation J. Med. Food, 13 (3) (2010), pp. 673-680).

- The declined expression of IFN- $\gamma$ , IL-6 and iNOS with inhibition of the NF- $\kappa$ B activation in LPS challenged mice by aqueous ginger extract (Y.Y. Choi, M.H. Kim, J. Hong, S.-H. Kim, W.M. Yang Dried ginger (*zingiber officinalis*) inhibits inflammation in a lipopolysaccharide-induced mouse model Evid. Based Complement Alternat. Med., 2013 (2013), p. 914563).

- The orally administered Cuttlebone complex (CBC) including fresh ginger roots demonstrated a protective potentiality against indomethacin-induced gastric ulcer in rats via reducing the gastric ulcerous lesions and significant increment of the indomethacin-declined PGE2 levels in the stomach in a dose dependent manner (M.-Y. Chien, Y.-T. Lin, F.-C. Peng, H.-J. Lee, J.-M. Chang, C.-M. Yang, C.-H. Chen, Gastroprotective potential against indomethacin and safety assessment of the homology of medicine and food formula cuttlebone complex Food Funct., 6 (8) (2015), pp. 2803-2812).

B) Discuss the ginger up-regulatory effect on PGE2 in the stomach and its down-regulatory effect in macrophages and inflammation site.



C) Global metabolomic profiling of shokyo and kankyo used materials for robustness and repeatability and QC purposes in any further studies.

D) A section on the limitations of the study and ideas for future research could be included.

**Note to the editor**

Metabolic profile isn't crucial and could have been only mentioned as a future work if not essentially needed by PeerJ standard like other Natural products and ethnopharmacology journals

Overall, the article should be accepted if the authors make some revisions, minor enough that I would NOT necessarily need to re-review it back.

**Regards,**

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