Reviewer's report

Title: Nrf2-mediated heme oxygenase-1 induction of PPI confers adaptive survival response to NSAID-induced gastric damages

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Reviewer: Tomohisa Takagi

Reviewer's report:

In this manuscript by Lee HJ and his/her co-workers, it has been demonstrated that pantoprazole prevented NSAID-induced gastric injuries through the expression of HO-1, independent of its acid suppression. This basic research has abundant persuasive data, and was very interesting for most of gastroenterologists. I hope that the authors revise this manuscript as following comments, and plan the clinical investigation in near future.

Major
1. In your paper, the mechanism that ZnPPIX inhibited the expression of HO-1 induced by pantoprazole (Figure 3.) remains unclear. The authors should discuss this issue.

2. In Figure 4B, IL-1 expression was faint in the group treated with indomethacin (500µM) plus pantoprazole (100µM) plus ZnPPIX (50µM). The author should discuss the reason why.

3. In Figure 4B, NOX-1 expression was inhibited by treatment with pantoprazole. Why?

4. Figure 4D is absent (p. 10).

Minor
1. This paper has many wrong spells. The authors should revise more carefully.

   p1, 300 M >>>>> 300 µM
   p2, 500 M >>>>> 500 µM
   TNF- >>>>> TNF-# ........

2. p8 Figure 2B >>>>> Figure 2E?
   Figure 2A >>>>>>> Figure 3A?

Level of interest: An article of importance in its field

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:**

I declare that I have no competing interests.