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# Comment on: Oleanolic acid co-administration alleviates ethanol-induced hepatic injury via Nrf-2 and ethanol-metabolizing modulation (sic) in rats

Danielle Camer
*University of Wollongong*, dc608@uowmail.edu.au

Xu-Feng Huang
*University of Wollongong*, xhuang@uow.edu.au

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**Abstract**
To the Editor: Alcohol induced hepatic oxidative stress and inflammation is known to cause liver injury. An increase in reactive oxidative species (ROS) from alcohol consumption leads to oxidative stress [1]. This can activate the inflammatory cytokines, IL-6 and TNF-α which promote liver injury. Both IL-6 and TNF-α are activated and transcribed by the inflammatory molecule, NFκB [2]. We read the interesting paper by Liu et al., entitled, "Oleanolic acid co-administration alleviates ethanol-induced hepatic injury via Nrf-2 and ethanol-metabolizing modulating in rats", published in your journal recently [3]. The authors demonstrated that oleanolic acid can reduce hepatic injury by elevating Nrf-2 related antioxidants, reduce inflammation, and increase ethanol metabolism. We believe that the mechanism of modulating these signalling pathways could be important for understanding the protective effects of oleanolic acid.

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**Authors:** Danielle Camer[1] and Xu-Feng Huang[1*]

**Affiliation:** [1]School of Medicine and Illawarra Health and Medical Research Institute, University of Wollongong, NSW, 2522, Australia.

***Corresponding author:**

Professor Xu-Feng Huang, MD, PhD, DSc
Illawarra Health and Medical Research Institute,
School of Medicine,
University of Wollongong,
Northfields Avenue, NSW, 2522, Australia
Tel.: 61-02-42214300
Fax: 61-02-42214096
*E-mail address:* xhuang@uow.edu.au

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**To the Editor:** Alcohol induced hepatic oxidative stress and inflammation is known to cause liver injury. An increase in reactive oxidative species (ROS) from alcohol consumption leads to oxidative stress[1]. This can activate the inflammatory cytokines, IL-6 and TNF-α which promote liver injury. Both IL-6 and TNF-α are activated and transcribed by the inflammatory molecule, NFκB[2]. We read the interesting paper by Liu et al., entitled, "Oleanolic acid co-administration alleviates ethanol-induced hepatic injury via Nrf-2 and ethanol-metabolizing modulating in rats", published in your journal recently [3]. The authors demonstrated that oleanolic acid can reduce hepatic injury by elevating Nrf-2 related antioxidants, reduce inflammation, and increase ethanol metabolism. We believe that the mechanism of modulating these signalling pathways could be important for understanding the protective effects of oleanolic acid.

Firstly, the reduction of oxidative stress and inflammatory signalling pathways by oleanolic acid may contribute to decreased liver injury as shown by the authors. In this study, it has been shown that IL-6 and TNF-α elevation was attenuated by oleanolic acid administration, however, NFκB was not examined. Oleanolic acid has been found to reduce NFκB signaling by inhibiting LPS-induced phosphorylation of IkB, and subsequently the expression of the cytokines TNF-α and IL-1[4]. Thus, a reduction in NFκB signalling by oleanolic acid may cause the reduced expression of the cytokines IL-6 and TNF-α found in this study. However, whether oleanolic acid directly targets NFκB in alcohol induced liver injury remains unknown. Therefore, whether oleanolic acid can directly inhibit NFκB leading to a subsequent reduction in activation and transcription of inflammatory cytokines may also be important in the attenuation of alcohol induced liver injury. Oleanolic acid has been shown to directly inhibit intracellular signalling molecules including PTP1B, a molecule that can be activated by NFκB[5]. This interaction occurs by oleanolic acid binding directly to site B of PTP1B, leading to its inhibition.

In addition, it has been found that Nrf2 and NFκB signalling pathways cross-talk[6]. Nrf2 has been found to be activated as a result of NFκB induced inflammation and ROS production as a defensive response. Nrf2 activation also causes reduced hepatic inflammatory genes including IL-6, and TNF-α. Therefore, it would be interesting to compare the effects of oleanolic acid on the activity of both Nrf-2 and NFκB signalling pathways in order to determine their role in alcohol induced liver injury.

In conclusion, the ability of oleanolic acid to influence the activity of Nrf2 and NFκB signalling suggests potential targets of this compound in these molecular signalling pathways. Further studies are required to elucidate the exact mechanisms linking Nrf2 and NFκB to induce the therapeutic benefits of oleanolic acid in alcoholic induced liver disease.

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