

# Review of: "Citrulline supplementation attenuates the development of non-alcoholic steatohepatitis in female mice through mechanisms involving intestinal arginase"

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Dragana Rajcic *et al.* investigated the attenuated effects and underlying mechanisms of L-citrulline (L-Cit) supplementation on the development of non-alcoholic steatohepatitis in female mice. They demonstrate that the protective effects of L-Cit on the non-alcoholic steatohepatitis are associated with the alterations of intestinal arginase activity and intestinal permeability. This study is very interesting, and has a scientific contribution and significance to the related research field. Authors have done a lot of work and obtained some solid data. The structure of the paper is well organized, and the statement is clear and logical. In the whole, authors did an excellent job, and it is my best honor to review this paper. However, I have some minor suggestion for your reference. Please see below.

1. After L-Cit treatment, the activity of arginine is reduced, but no significant difference is found in the mRNA and protein expression of Arg2. If authors could give some data to explain how L-Cit affects the arginine activity, it would be very helpful to clarify the mechanism by which L-Cit attenuates the development of non-alcoholic steatohepatitis in female mice. In my opinion, the experiment of molecular docking between L-Cit and arginine can be carried out in the future.
2. Authors use the arginase inhibitor N( $\omega$ )-hydroxy-nor-L-arginine (NOHA) to treat FFC mice supplemented with L-Cit. The results show that the effect of L-Cit on the non-alcoholic steatohepatitis in FFC mice is markedly reversed after the supplement of NOHA. If authors could assay whether the expression of tight junction protein and inflammation in the small intestine tissue of FFC mice supplemented with L-Cit were altered after NOHA treatment, the relationship among the arginase activity, gut barrier function and non-alcoholic steatohepatitis would be further clarify.
3. Some researchers have reported that the disruption of gut vascular barrier plays a vital role in the development of non-alcoholic steatohepatitis. If the gut vascular barrier could be investigated in this study, it would be perfect.
4. For the animal gender, half male and half female may be more reasonable.

