

# Trilobatin targets Nrf2 to ameliorate lipopolysaccharide-induced depressive-like behavior: Involvement of microbiota-gut-brain axis

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## Abstract

**Abstract Background and Purpose:** Activation of Nrf2 holds great promise for treating major depressive disorder (MDD). Trilobatin (TLB) is a naturally occurring food additive conferring robust neuroprotection with Nrf2 activation potency. This study was designed to explore whether TLB is able to overcome MDD, and the role of Nrf2 in the antidepressant effect of TLB. **Experimental Approach:** Mice and primary hippocampal astrocytes challenged with lipopolysaccharide (LPS) were used to decipher the effects of TLB on MDD. Nrf2-deficient mice were treated with TLB and fecal microbiota transplantation (FMT) to validate the potential targets of ICS II on ALI. **Key results:** TLB ameliorated depressive-like behavior in LPS-induced MDD mouse model. Single-cell RNA sequencing analysis of the hippocampus revealed that astrocytes exhibited distinct MDD-related clustering with increased Nrf2 in the antidepressant effect of TLB. TLB directly bound to Nrf2 and increased Nrf2-antioxidant response element (ARE) binding activity, which ultimately restored mitochondrial function, reduced oxidative stress and neuroinflammation. TLB improved intestinal microbiota dysbiosis and attenuated intestinal barrier through increasing expressions of the tight junction proteins. Fecal microbiota transplantation from TLB-treated mice also ameliorated depression-like behavior after LPS insult. Furthermore, by using genetically modified Nrf2-knockout mice, we validated that the antidepressant effect of TLB were Nrf2/ARE signaling dependent, suppressing astrocytes activation and gut microbiota dysbiosis. These favorable effects of TLB were abrogated in Nrf2 deficiency mice. **Conclusions and implications:** Our results reveal a new-found pharmacological property of TLB: serves as a novel and naturally-occurring Nrf2 activator to conquer MDD through modulating microbiota-gut-brain axis.

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