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Research Article

Pinocembrin alleviates ulcerative colitis in mice via regulating gut microbiota, suppressing TLR4/MD2/NF-κB pathway and promoting intestinal barrier

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Pinocembrin, a plant-derived flavonoid, has a variety of pharmacological activities, including anti-infection, anti-cancer, anti-inflammation, cardiovascular protection, etc. However, the mechanism of pinocembrin on the anti-colitis efficacy remains elusive and needs further investigation. Here, we reported that pinocembrin eased the severity of dextran sulfate sodium (DSS)-induced colitis in mice by suppressing the abnormal activation of toll-like receptor 4 (TLR4)/nuclear factor-kappa B (NF-κB) signal pathway *in vivo*. In addition, the gut microbiota was disordered in DSS colitis mice, which was associated with a significant decrease in microbiota diversity and a great shift in bacteria profiles; however, pinocembrin treatment improved the imbalance of gut microbiota and made it similar to that in normal mice. On the other hand, *in vitro*, pinocembrin down-regulated the TLR4/NF-κB signaling cascades in lipopolysaccharide (LPS)-stimulated macrophages. At the upstream level, pinocembrin competitively inhibited the binding of LPS to myeloid differentiation protein 2 (MD2), thereby blocking the formation of receptor multimer TLR4/MD2 · LPS. Furthermore, pinocembrin dose-dependently promoted the expression of tight junction proteins (ZO-1, Claudin-1, Occludin and JAM-A) in Caco-2 cells. In conclusion, our work presented evidence that pinocembrin attenuated DSS-induced colitis in mouse, at least in part, via regulating intestinal microbiota, inhibiting the over-activation of TLR4/MD2/NF-κB signaling pathway, and improving the barriers of intestine.

Introduction

Ulcerative colitis (UC) is a chronic relasping disease of the colorectum [1]. The clinical symptoms of UC include body weight loss, diarrhea, abdominal pain, hematochezia and tenesmus [2]. UC and Crohn's disease (CD) are the main types of inflammatory bowel disease (IBD), remaining incurable at present. The existing etiology studies, however, have not confirmed the exact pathogenesis of UC. Prevailing view suggests that UC is triggered by multiple factors, including inheritance, environment, intestinal microbiota, and innate or adaptive immunity. While UC is the result of multiple factors interaction [3,4], in this regard, the relationship between gut microbiota and UC pathogenesis is being studied extensively along with the development of sequencing technology [5]. On the other hand, a growing evidence indicates that gut microbiota dysbiosis is closely related to the occurrence of UC [6]. The imbalance of gut microbiota has been observed in UC patients in particular with a decrease in the proportion of *Firmicutes* and *Bacteroidetes*,

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