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Obacunone Protects Against Ulcerative Colitis in Mice by Modulating Gut Microbiota, Attenuating TLR4/NF-κB Signaling Cascades, and Improving Disrupted Epithelial Barriers

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Obacunone, a natural limonoid compound abundantly distributed in citrus fruits, possesses various biological properties, such as antitumor, antioxidant, and antiviral activities. Recent studies suggested an anti-inflammatory activity of obacunone *in vitro*, but its efficacy on intestinal inflammation remains unknown. This study was designed to evaluate the effects and mechanisms of obacunone in ameliorating intestinal inflammation in a mouse model of ulcerative colitis (UC). We found that obacunone efficiently alleviated the severity of dextran sulfate sodium (DSS)-induced mouse UC by modulating the abnormal composition of the gut microbiota and attenuating the excessive activation of toll-like receptor 4 (TLR4)/nuclear factor-kappa B (NF-κB) signaling. The intestinal epithelial barrier was disrupted in DSS colitis mice, which was associated with activation of inflammatory signaling cascades. However, obacunone promoted the expression of tight junction proteins (TJP1 and occludin) and repressed the activation of inflammatory signaling cascades. In summary, our findings demonstrated that obacunone attenuated the symptoms of experimental UC in mice through modulation of the gut microbiota, attenuation of TLR4/NF-κB signaling cascades, and restoration of intestinal epithelial barrier integrity.

Keywords: UC, gut microbiota, TLR4/NF-κB, epithelial barrier, obacunone

INTRODUCTION

Inflammatory bowel diseases (IBDs), consisting mainly of Crohn's disease and ulcerative colitis (UC), are common, chronic, and relapsing inflammatory disorders of the digestive tract (Kaplan, 2015). The clinical features of UC include recurrent, chronic, and persistent inflammation in the gastrointestinal tract. Furthermore, the symptoms of UC frequently include diarrhea, abdominal pain, weight loss, and malnutrition, which seriously affect the quality of life of UC patients (Rosen et al., 2015). The possible etiology of UC is complex and multifactorial including genetic, immune, microbiological, and environmental factors, each of which may lead to the occurrence of UC (Bernstein, 2017). Although the exact cause of UC remains unclear, accumulating evidence has