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Neorogioltriol and related diterpenes from the red alga *Laurencia* inhibit inflammatory bowel disease in mice by suppressing M1 and promoting M2-like macrophage responses

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Macrophages, central mediators of inflammation, obtain pro inflammatory (M1) and anti-inflammatory (M2) phenotypes, which can be modulated by soluble factors, including natural products. Despite the crucial protective role of inflammation, chronic or deregulated inflammation can lead to pathological states, such as autoimmune diseases, metabolic disorders, cardiovascular diseases and cancer. In the present study we evaluated in depth the anti-inflammatory activity of the brominated diterpene neorogioltriol and identified two structurally related diterpenes, neorogioldiol and *O*[11],15-cyclo-14-bromo-14,15-dihydrorogiol-3,11-diol, with equally potent activity. We investigated the mechanism of action of the three metabolites and found that all three suppressed macrophage activation and promoted an M2-like anti-inflammatory phenotype by inducing expression of Arginase1, MRC1, IRAK-M, the transcription factor C/EBPβ and the miRNA miR-146a. In addition, they suppressed iNOS induction and nitric oxide production. Importantly, treatment of mice with the bioactive compounds suppressed DSS-induced colitis by reducing tissue damage and pro-inflammatory cytokine production. Thus, all these three diterpenes are promising lead molecules for the development of anti-inflammatory agents targeting macrophage polarization mechanisms.

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