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Regulatory activity of nobiletin on MAPK/NF-κB signaling pathway in indomethacin-induced gastric damage

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Nobiletin (NOB) is an important flavonoid obtained from citrus fruits such as *Citrus depressa, Citrus reticulata, Citrus sinensis* and *Citrus limon*. Studies have demonstrated that effects are anti-inflammatory, antioxidant, immunomodulatory, anticancer, neuroprotective, anti-atherosclerosis, antiapoptotic, and antidiabetic. There are still limited studies on the efficacy of nobiletin on the pathways underlying gastric damage. Therefore, in the present study, we investigated both the effects of nobiletin on the mitogen-activated protein kinase (MAPK)/nuclear factor kappa B (NF-κB) signaling pathway, one of the pathways in indomethacin (IND)-induced inflammation and whether it has gastroprotective activity. NOB+IND and PAN+IND groups were treated with substances for 7 days (10 mg/kg NOB, 5 mg/kg PAN). On the 8th day, gastric damage model was created with a single dose of 100 mg/kg indomethacin. In indomethacin-induced gastric injury, nobiletin significantly decreased NF-κB-p65, MAPK levels and significantly increased prostaglandin E2 (PGE2) production in the stomach. In addition, nobiletin administration caused a decrease in interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) and interleukin 1α (IL-1α) levels and an increase in interleukin 10 (IL-10) levels against indomethacin-induced inflammation. When the ulcerative areas were evaluated, it was found that ulcerative areas were significantly reduced in the nobiletin group compared to the indomethacin only group, and when the ulcer inhibition levels of nobiletin and pantoprazole administration were examined, both substances showed similar results. When these results were evaluated as a whole, it was determined that nobiletin had a candidate anti-inflammatory potential for the prevention of inflammation in the stomach and showed a strong gastroprotective effect.

Keywords: Gastric ulcer, Indomethacin, Cytokines, Inflammation pathways, Nobiletin

Indomethacin, is a nonsteroidal anti-inflammatory