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The Hidden Mechanism beyond Ginger (Zingiber officinale Rosc.) Potent in vivo and in vitro Anti-Inflammatory Activity

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Abstract : Background: In order to decrease the burden of the high cost of synthetic drugs, it is important to focus on phytopharmaceuticals. The aim of our study was to search for the mechanism of ginger (Zingiber officinale Roscoe) anti-inflammatory potential and to correlate it to its biophytochemicals. Methods: Various extracts viz. water, 50%, 70%, 80%, and 90% ethanol were prepared from ginger rhizomes. Fractionation of the aqueous extract (AE) was accomplished using Diaion HP-20. In vitro anti-inflammatory activity of the different extracts and isolated compounds was evaluated by protein denaturation inhibition, membrane stabilization, protease inhibition, and anti-lipoxygenase assays. In vivo anti-inflammatory activity of AE was estimated by assessment of rat paw oedema after carrageenan injection. Prostaglandin E2 (PGE2), certain inflammation markers (TNF-α, IL-6, IL-1α, IL-1β, INFr, MCP-1MIP, RANTES, and Nox) levels and MPO activity in the paw edema exudates were measured. Total antioxidant capacity (TAC) was also determined. Histopathological alterations of paw tissues were scored. Results: All the tested extracts showed significant ($p < 0.1$) anti-inflammatory activities. The highest percentage of heat induced albumin denaturation (66%) was exhibited by the 50% ethanol (250 µg/ml). The 70 and 90% ethanol extracts (500 µg/ml) were more potent as membrane stabilizers (34.5 and 37%, respectively) than diclofenac (33%). The 80 and 90% ethanol extracts (500 µg/ml) showed maximum protease inhibition (56%). The strongest anti-lipoxygenase activity was observed for the AE. It showed more significant lipoxygenase inhibition activity than that of diclofenac (58% and 52%, respectively) at the same concentration (125 µg/ml). Fractionation of AE yielded four main fractions (Fr I-IV) which showed significant in vitro anti-inflammatory. Purification of Fr-III and IV led to the isolation of 6-poradol (G1), 6-shogaol (G2); methyl 6- gingerol (G3), 5-gingerol (G4), 6-gingerol (G5), 8-gingerol (G6), 10-gingerol (G7), and 1-dehydro-6-gingerol (G8). G2 (62.5 ug/ml), G1 (250 ug/ml), and G8 (250 ug/ml) exhibited potent anti-inflammatory activity in all studied assays, while G4 and G5 exhibited moderate activity. In vivo administration of AE ameliorated rat paw oedema in a dose-dependent manner. AE (at 200 mg/kg) showed significant reduction (60%) of PGE2 production. The AE at different doses (at 25-200 mg/kg) showed significant reduction in inflammatory markers except for IL-1α. AE (at 25 mg/kg) is superior to indomethacin in reduction of IL-1β. Treatment of animals with the AE (100, 200 mg/kg) or indomethacin (10 mg/kg) showed significant reduction in TNF-α, IL-6, MCP-1, and RANTES levels, and MPO activity by about (31, 57 and 32%) (65, 60 and 57%) (27, 41 and 28%) (23, 32 and 23%) (66, 67 and 67%) respectively. AE at 100 and 200 mg/kg was equipotent to indomethacin in reduction of NO_x level and in increasing the TAC. Histopathological examination revealed very few inflammatory cells infiltration and oedema after administration of AE (200 mg/kg) prior to carrageenan. Conclusion: Ginger anti-inflammatory activity is mediated by inhibiting macrophage and neutrophils activation as well as negatively affecting monocyte and leukocyte migration. Moreover, it produced dose-dependent decrease in pro-inflammatory cytokines and chemokines and replenished the total antioxidant capacity. We strongly recommend future investigations of ginger in the potential signal transduction pathways.

Keywords : anti-lipoxygenase activity, inflammatory markers, 1-dehydro-6-gingerol, 6-shogaol
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