CHEMOTHERAPEUTIC PHOTOCHEMICALS AS SPEED BREAKERS IN INFLAMMATORY AND STRESS SIGNALLING INVOLVED IN THE JOURNEY TO CANCER: A CASE FOR PROTOCATECHUIC ACID AND 6-GINGEROL

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Abstract: Preclinical and clinical investigations have identified unresolved inflammation and oxidative/nitrosative stress as two co-conspirators, which play multifaceted role and serve as driving force in the journey to cancer development. Overexpression, of pro-inflammatory mediators, a distinct network of intracellular signaling molecules including upstream kinases and transcription factors facilitate tumor promotion and progression. Several investigations indicate that plant-based diet rich in a wide variety of fruits and vegetables are effective in preventing or reversing premalignant lesions. Thus the search for novel chemo preventive agents of physiological relevance acting on specific and/or multiple molecular and cellular targets holds promise as a rational strategy to the control of health threatening diseases such as cancer. Our study demonstrates that 6-gingerol from Ginger (Zingiber officinale) protects against Dextran Sulfate Sodium (DSS) induced ulcerative colitis in BalBc mice. 6-gingerol attenuated DSS mediated increase in immune expression of Nuclear Factor Kappa B (NF-κB (p65), tumor necrosis factor alpha (TNF-α), interleukin -1β (IL-1 β), cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), mitogen activated kinase (P 38), RANTES, Bcl2, Monocyte Chemo attractant Protein (MCP-1) and β-catenin expression. Similarly, 6-gingerol modulated DSS decrease in adenomatous polyposis coli (APC), DESMIN, Interleukin 10 and levels of antioxidant enzymes. In the two-stage (DMBA initiation and TPA promotion) mouse skin carcinogenesis model, 6-gingerol downregulated the expression of COX-2 and NF-κB. Protocatechuic acid (PCA), a simple hydrophilic phenolic compound commonly found in many edible vegetables elicited striking antioxidant and anti-inflammatory effects in DSS-induced ulcerative colitis and associated hepatotoxicity rat model. Specifically, PCA prevented increase in the plasma levels of pro-inflammatory cytokines, markers of liver toxicity and markedly suppressed DSS mediated elevation in colonic nitric oxide concentration and myeloperoxidase activity in the treated rats. Immunohisto chemical analysis showed that PCA significantly inhibited COX-2 and iNOS protein expression in the colon of DSS-treated rats. These anti-inflammatory compounds exert chemo preventive effects by modulating intracellular signaling cascades and pro-inflammatory mediators and therefore qualify as therapeutic signatures for chemoprevention of inflammation-associated carcinogenesis.