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IH-901, AN INTESTINAL BACTERIAL METABOLITE DERIVED FROM THE PROTOPANAXADIOL GINSENOSIDE, HAS ANTI-TUMOR PROMOTING EFFECTS IN MOUSE SKIN.

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Ginseng saponins (ginsenosides) have been regarded as principal components responsible for the majority of pharmacological activities exerted by ginseng. IH-901, an intestinal bacterial metabolite derived from the protopanaxadiol saponin of *Panax ginseng* C.A. Meyer, has been reported to have anti-tumor effects including inhibition of angiogenesis, invasion and metastasis, as well as induction of tumor cell apoptosis. In the present work, we have evaluated the anti-tumor promoting effects of IH-901 using a two-stage mouse skin carcinogenesis model. Topical application of 0.5 or 2.5 ¥mole of IH-901 onto dorsal skins of 7,12-dimethylbenz[a]anthracene (DMBA)-treated female ICR mice 30 minutes before each topical dose of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) suppressed the incidence (by 13 and 27%, respectively) and multiplicity (by 47 and 63%, respectively) of papillomas at 19 weeks. In addition, ear edema and expression of epidermal ornithine decarboxylase induced by TPA in mice were inhibited by IH-901 pretreatment. Recent studies have demonstrated that the eukaryotic transcription factor NF-κB is involved in intracellular signaling pathways associated with inflammation and carcinogenesis. In an attempt to elucidate the molecular mechanisms underlying anti-tumor promoting activities of IH-901, we have determined its effect on activation of NF-κB in mouse skin using the electrophoretic mobility shift assay (EMSA). Pretreatment of dorsal skins of mice with IH-901 inhibited TPA-induced epidermal NF-κB DNA binding in a dose-dependent manner. The compound also attenuated TPA-induced degradation of IκB-α and subsequent translocation of p65 subunit to nucleus. IH-901 pretreatment led to inhibition of TPA-induced expression of cyclooxygenase-2 and prostaglandin E_2 production in mouse skin, which appeared to be mediated

through NF-κB inactivation. TPA-induced activation of extracellular-regulated protein kinase (ERK), one of the mitogen-activated protein kinases, was inhibited by IH-901 pretreatment in mouse skin. In addition, the compound inhibited activation of Akt, an upstream signaling enzyme that is known to phosphorylate IκB kinase (IKK) and to activate NF-κB.