Protective effect of [6]-shogaol on 7,12-dimethylbenz(a)anthracene (DMBA) induced oral carcinogenesis in male golden Syrian hamsters

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Executive Summary

Oral cancer is a major cause of morbidity and mortality in developing countries. Despite advances in chemotherapy for the cancer management, the survival rate has not yet been improved. Dietary nutrient has been receiving a lot of attention and interest in the chemotherapeutic development. [6]-Shogaol is a major bioactive compound identified in ginger that possesses many pharmacological properties. The aim of the present study is to investigate the effect of [6]-shogaol on 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch (HBP) carcinogenesis. Oral squamous cell carcinoma induced in HBP by painting with 0.5% 7,12-dimethylbenz(a)anthracene (DMBA), thrice in a week for 16weeks. We observed 100% tumour incidence, decreased levels of lipid peroxidation, antioxidant, and phase II detoxification enzymes (GST, GR and GSH) in DMBA-induced hamsters. Further, enhanced activity of phase I enzymes (cytochrome p450 and b5) and over-expression of mutant p53, Bcl-2 and decreased expression of wild type p53 and Bax were noticed in DMBA-induced hamsters. Our results indicated that [6]-shogaol (10, 20 and 40mg/kg body weight) treated with DMBA-painted hamsters, considerably reversed tumour incidence, improved antioxidant status, phase II detoxification enzymes, and also inhibit lipid peroxidation and phase I enzymes. Moreover, [6]-shogaol inhibits mutant p53 and Bcl-2 expression and significantly restored normal p53, Bax levels. Thus, we concluded that [6]-shogaol prevents DMBA-induced HBP carcinogenesisthroughits antioxidantaswellasmodulatingapoptoticsignals.

Ginger (Zingiber officinale) is a well-known herb used in ethnomedicine. [6]-shogaol, a phenolic nature is a major constituent of ginger. In this study, we investigated the anticancer activity of [6]-shogaol in Laryngeal cancer (Hep-2) cells. We demonstrated the effects of [6]-shogaol on the cell growth and apoptosis in Hep-2 cells were analyzed by the generation of reactive oxygen species (ROS), the level of mitochondrial membrane potential (DYm), DNA damage and apoptotic morphological changes were analyzed by AO/EtBr, AO and Hoechst staining. Further, apoptotic protein expressions were analyzed by western blot analysis. Our results indicated that [6]-shogaol induces apoptosis as evidenced byloss of cell viability, enhanced ROS, lipid peroxidation results in altered mitochondrial membrane potential, increased DNA damage in Hep-2 cells. Further, the prooxidant role of [6]-shogaol inhibit Bcl-2 expression with the simultaneous up regulation of Bax, Cytochrome c, Caspase-9 and -3 protein expressions were observed in Hep-2 cells. Thus, [6]-shogaol induces apoptosis in Hep-2 cells through inducing oxidative damage and modulate apoptotic marker expressions. Therefore, [6]-shogaol might be used as a therapeutic agent for the treatment of laryngeal cancer.

Nuclear factor-kappaB (NF-κB) and activator protein 1 (AP-1) is a major transcription factor which regulates many biological and pathological processes such as inflammation and cell proliferation, which are major implicates in cancer progression. [6]-shogaol ([6]-SHO) is a major constituent of ginger, exhibits various biological properties such as antioxidants, anti-inflammation and anti-tumor. Recently, we proven that [6]-SHO prevents oral squamous cell carcinoma by activating proapoptotic factors in in vitro and in vivo experimental model. However, the preventive efficacy of [6]- SHO in 7,12-dimethylbenz[a]anthracene (DMBA) induced hamster buccal pouch carcinogenesis (HBP) has not been fully elucidated, so far. Hence, we aimed to investigate the effect of [6]-SHO on inflammation and cell proliferation by inhibiting the translocation of NF-κB and AP-1 in DMBA induced HBP carcinogenesis. In this study, we observed upregulation of inflammatory markers (COX-2, iNOS, TNF-α, interleukin-1 and -6), cell proliferative markers (Cyclin D1, PCNA and Ki-67) and aberrant activation of NF-κB, AP-1, IKKβ, c-jun, c-fos and decreased IκB-α in DMBA induced hamsters. Conversely, oral administration of [6]-SHO strongly inhibited constitutive phosphorylation and degradation of IκB and inhibit phosphorylation of c-jun, c-fos, resulting in inhibition of nuclear translocation of NF- κBp65 and AP-1. Thus, inhibition of NF-κB and AP-1 activation by [6]-SHO attenuates inflammation and cell proliferative response in DMBA induced hamsters. Our finding suggested that [6]-SHO is a novel functional agent capable of preventing DMBA induced inflammation and cell proliferation associated tumorigenesis by modulating multiple signalling molecules.