SUMMARY AND CONCLUSION

Oral cancer is defined as a malignant neoplasm on the lip or in the mouth and is more common in men than in women. It is a major public health problem in globally with plenty of incidences and severities depending on the region; in South Asian countries, including India, its incidence is particularly high, and is frequently associated with an addiction to chewing paan mixed with tobacco, which contains areca nut-based carcinogens, smoking, excessive alcohol consumption and environmental factors. History of oral cancer is relatively uniform, with squamous cell carcinoma comprising 80-90% of oral cancer is diagnosed in person older than 40 years and more than 50% of all cancers occur in person over the age of 63 years. Prognosis for early cancer is excellent, but advanced cancer has not only high mortality but is also associated with poor quality of life, as extensive facial surgery is usually required with many functional disabilities.

The polycyclic aromatic hydrocarbon of DMBA present in environment as a product of incomplete combustion of complex hydrocarbons. DMBA mediates oral carcinogenesis through chronic inflammation, excessive production of ROS, oxidative DNA damage, impairment of antioxidant defence system and modulating the activities of detoxification cascade and alteration of molecular markers expression that are leads to oral cancer. DMBA is a well known carcinogen and immunosuppressor is commonly used to develop HBP carcinogenesis of golden Syrian hamsters since the precancerous and cancerous lesions as well as biochemical and molecular markers expression have marked similarities with human oral cancer. Many cancer chemotherapeutic agents are nature origin is known to ameliorate health beneficial effect. [6]-shogaol is one of the naturally occurring phytonutrient derived from ginger. Hence, the present study is design to investigate the chemopreventive effect of [6]-shogaol in DMBA induced HBP carcinogenesis.
Present study demonstrates the free radical scavenging potential of [6]-shogaol by assessing different scavenging assays compared with standard ascorbic acid. The results obtained that [6]-shogaol exhibit effective scavenging activity on DPPH, ABTS•⁺, hydroxyl, superoxide anion, hydrogen peroxide, nitric oxide and Fe³⁺ radicals. The findings of this section conclude that above results showed [6]-shogaol has more potent antioxidant and free radical scavenger.

Present study has documented the in vitro cytotoxicity effect of [6]-shogaol was evaluated in Hep-2 cell lines. [6]-shogaol preferentially inhibited the Hep-2 cell proliferation in a concentration dependent manner. Hence, the IC₅₀ value of 20 μM apparent from growth inhibition curves for 24 h. Further, the results also showed that [6]-shogaol inhibits cell proliferation in Hep-2 cells through ROS dependant mitochondrial mediated apoptosis as evidenced by elevation of ROS generation resulting in loss of ΔΨM, oxidative DNA damage, and nuclear fragmentation. Further, the pro oxidant role of [6]-shogaol modulates the apoptotic protein expression such as decreased Bcl-2, increased Bax leads to cytochrome-c release from mitochondria, consequently activation of caspase-9 and -3. These results indicated that [6]-shogaol could be used as a novel therapeutic agent for the medical treatment and/or prevention of laryngeal cancer in the future.

The present study has investigated that dose responsive and chemopreventive efficacy of [6]-shogaol on DMBA induced HBP carcinogenesis. Hamster buccal pouch carcinogenesis induced by topical application of 0.5 % DMBA frees times a weeks for 16 weeks. The analysing body weight, growth rate, lipid peroxidation, antioxidant and phase I and phase II detoxification agents as well as histopathological changes on control and experimental animals. Oral administration of [6]-shogaol (10, 20 and 40 mg/kg b.wt) to DMBA induced hamsters significantly enhance the body weight, inhibits lipid peroxidation and phase I carcinogen metabolic enzymes through antioxidant and phase II detoxification. As well as significantly decreased tumor incidence,
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tumor volume and tumor burden as well as histological features near to normal. However, more sufficient effect was observed at [6]-shogaol 20 mg/kg b.wt compared to other doses.

Furthermore, present study has investigated the protective effect of [6]-shogaol on cell surface glycoconjugates (bound hexose, hexosamine, total sialic acid, lipid-bound sialic acid and fucose) were analysed by using specific colorimetric methods. The levels of glycoconjugates were significantly increased both in plasma and buccal mucosa in tumor bearing hamsters as compared to control hamsters. Oral administration of [6]-shogaol (20 mg/kg b.wt) initiation has significantly restored the status of glycoconjugates in DMBA induced hamsters. Our results suggest that [6]-shogaol protect cell surface glycoconjugates abnormalities during DMBA induced oral carcinogenesis.

Understanding the molecular mechanism and signaling events associated with pathogenesis of oral cancer would help for the early diagnosis and prevention and/or clinical treatment. Abnormal expression of inflammation, cell proliferation angiogenesis, invention and evasion of apoptosis markers are central features of a malignant tumor. In the present study, deregulated expression cytokine and pro-inflammation (IL-1, IL-6, TNF-α, NF-κB, COX-2, iNOS), cell proliferation (Cyclin D1, PCNA, Ki-67), apoptosis (p53, Bax, Bcl-2, caspase-9/-3), angiogenesis (MMP-2, MMP-9, TIMP-2, VEGF) and over expression of transcription factors (NF-κB, AP-1, JAK-1, STAT-3, PI3K and AKT) in DMBA induced hamsters. Oral administration of [6]-shogaol inhibited above noticed molecular markers in hamsters treated with DMBA. Our results thus suggest that [6]-shogaol has anti-inflammatory, anti-cell proliferative, anti-angiogenic and apoptosis inducing potential during DMBA-induced HBP carcinogenesis.
Fig. 10.1. Schematic drawing proposed molecular mechanism and the overall possible signaling pathways for [6]-shogaol in DMBA induce HBP carcinogenesis
CONCLUSION

In the present study, we suggest that [6]-shogaol inhibits cell proliferation and induce apoptosis through modulating biochemical and apoptotic events in Hep-2 cells. Furthermore, present study demonstrated that chemopreventive efficacy of [6]-shogaol in DMBA induced HBP carcinogenesis. Our findings concludes that the chemopreventive potential of [6]-shogaol is probably due to its antioxidant, inhibit abnormality of cell surface glycoconjugates and modulating effect of detoxification cascade as well as due to its anti inflammatory, anti cell proliferative, apoptotic induction, anti-angiogenic and invention potential during DMBA induced HBP carcinogenesis.

Future directions

The present study will be extended to test the chemopreventive effect of [6]-shogaol in other experimental cancer models. The effect of [6]-shogaol will be assessed on other biochemical and molecular pathway that are related to oral carcinogenesis. Also, steps will be taken to improve the efficacy of [6]-shogaol by introducing functional group to [6]-shogaol that fight against carcinogenesis. The study design will be extended to investigate the chemotherapeutic potential of [6]-shogaol in oral carcinogenesis. In addition, studies are required to reveal the metabolism and bioavailability of [6]-shogaol in animal and human systems.