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*IN VIVO ASSESSMENT OF SAFRANAL'S NOVEL THERAPEUTIC EFFECTS ON CHEMICALLY
INDUCED HEPATIC NEOPLASIA*

By

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Abstract

Chronic liver insult leads to fibrosis, which often ends up causing cirrhosis and most of the time that progresses into hepatic neoplasms (early Hepatocellular carcinoma; HCC). HCC is the fifth most common cancer, and the third cause of cancer-related deaths. Chemotherapy is the most common treatment of cancer patients. HCC is however, chemo-resistant, and the side-effects of chemotherapy are typically exhausting to the patient. Sorafenib is the only anti-HCC drug approved by the U.S Food and Drug Administration. It is a multikinase inhibitor that blocks tumor cells proliferation and angiogenesis. Although sorafenib is successful treating early and mid HCC lesions, it is not efficient in advanced HCC cases. Safranal, a major biomolecule of saffron "stigmas of the flowers of *Crocus sativus L.*", is known for its anti-oxidant, proapoptotic and anti-inflammatory effects against different cancer types. Compared with monotherapy, combination therapy (safranal + sorafenib) targeting multiple signaling pathways offered a better treatment alternative potentially abolishing resistance, feedback activation, and compensatory activation of survival pathways. This study investigated the therapeutic effect of safranal on DEN-induced HCC, *in vivo*, using male Wistar rats. Safranal was found to be involved in cell cycle arrest particularly at G₂/M phase, and to induce the intrinsic, mitochondrial, apoptotic pathway leading to cell death. This study highlights safranal's therapeutic potential against HCC and introduces it as a novel natural therapeutic and adjuvant agent against HCC.

Keywords: Hepatocellular carcinoma, safranal, sorafenib, apoptosis, cell cycle arrest.