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Targeting Apoptosis by Novel Adamantane Analogs as an Emerging Therapy for the Treatment of Hepatocellular Carcinoma Through EGFR, Bcl-2/BAX Cascade

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Abstract : Cancer is a major public health problem and the second leading cause of death worldwide. In 2020, cancer diagnosis and treatment have been negatively affected by the coronavirus 2019 (COVID-19) pandemic. During the quarantine, because of the limited access to healthcare and avoiding exposure to COVID-19 as a contagious disease; patients of cancer suffered deferments in follow-up and treatment regimens leading to substantial worsening of disease, death, and increased healthcare costs. Thus, this study is designed to investigate the molecular mechanisms by which adamantne derivatives attenuate hepatocllular carcinoma experimentally and theoretically. There is a close association between increased resistance to anticancer drugs and defective apoptosis that considered a causative factor for oncogenesis. Cancer cells use different molecular pathways to inhibit apoptosis, BAX and Bcl-2 proteins have essential roles in the progression or inhibition of intrinsic apoptotic pathways triggered by mitochondrial dysfunction. Therefore, their balance ratio can promote the cellular apoptotic fate. In this study, the in vitro cytotoxic effects of seven synthetic adamantyl isothiorea derivatives were evaluated against five human tumor cell lines by MTT assay. Compounds 5 and 6 showed the best results, mostly against hepatocellular carcinoma (HCC). Hence, in vivo studies were performed in male Sprague-Dawley (SD) rats in which experimental hepatocellular carcinoma was induced with thioacetamide (TAA) (200 mg/kg, i.p., twice weekly) for 16 weeks. The most promising compounds, 5 and 6, were administered to treat liver cancer rats at a dose of 10 mg/kg/day for an additional two weeks, and the effects were compared with doxorubicin (DR), the anticancer drug. Hepatocellular carcinoma was evidenced by a dramatic increase in liver indices, oxidative stress markers, and immunohistochemical studies that were accompanied by a plethora of inflammatory mediators and alterations in the apoptotic cascade. Our results showed that treatment with adamantane derivatives 5 and 6 significantly suppressed fibrosis, inflammation, and other histopathological insults resulting in the diminished formation of hepatocyte tumorigenesis. Moreover, administration of the tested compounds resulted in amelioration of EGFR protein expression, upregulation of BAX, and lessening down of Bcl-2 levels that prove their role as apoptosis inducers. Also, the docking simulations performed for adamantane showed good fit and binding to the EGFR protein through hydrogen bond formation with conservative amino acids, which gives a shred of strong evidence for its hepatoprotective effect. In most analyses, the effects of compound 6 were more comparable to DR than compound 5. Our findings suggest that adamantane derivatives 5 and 6 are shown to have cytotoxic activity against HCC in vitro and in vivo, by more than one mechanism, possibly by inhibiting the TLR4-MyD88-NF-κB pathway and targeting EGFR signaling.

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