

## **Effect of protocatechuic acid-layered double hydroxide nanoparticles on diethylnitrosamine/phenobarbital-induced hepatocellular carcinoma in mice**

### **ABSTRACT**

Researchers investigating cancer chemotherapy and management continue to search for agents that selectively kill malignant cells and leave healthy neighboring cells intact. Natural products provide relevant resources for anti-cancer drug discovery. However, the physicochemical properties of these compounds limit their efficient uptake and bioavailability. We introduced a nanocarrier system, namely, zinc-aluminum-layered double hydroxide (ZnAl-LDH) intercalated with protocatechuic acid. In this study, the efficacy and toxicity of protocatechuic acid intercalated in zinc aluminum-layered double hydroxide nanoparticles (PCA-ZnAl) against diethylnitrosamine/phenobarbital (DEN/PB)-induced hepatocellular carcinoma (HCC) in BALB/c mice was evaluated. HCC in male mice was induced by a single-dose intraperitoneal administration of DEN and was promoted by the introduction of PB via drinking water for 12 weeks. HCC induction was confirmed after the DEN/PB introduction period by measurement of the elevated level of serum  $\alpha$ -feto protein (AFP). The results showed that the level of  $\alpha$ -fetoprotein was significantly reduced in PCA-ZnAl ( $350 \pm 43.90$  ng/mL), doxorubicin (DOX) ( $290 \pm 20.52$  ng/mL) and ZnAl-LDH ( $390 \pm 19.65$  ng/mL) treated animals compared to HCC mice treated with normal saline ( $580.4 \pm 52.04$  ng/mL). Superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) levels were significantly increased, whereas the level of lipid peroxidation was significantly decreased in HCC mice treated with DOX, PCA-ZnAl and ZnAl-LDH compared with those in HCC mice treated with saline. Restoration of hepatocyte morphology was observed following treatment that was comparable to that in the normal control group. Deterioration of hepatic cells and a significant increase of aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) were observed in the cancer-induced untreated group compared with that in the groups treated with nanoparticles. The histopathological features of the liver obtained from PCA-ZnAl-treated mice showed a uniform size with a similar distribution of the nuclear-cytoplasmic ratio and nucleus centrally located in the cytoplasm, similar to the normal liver cells. The results underscored the potential of PCA-ZnAl for the treatment of hepatocellular carcinoma.