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A novel chemoprotective effect of tiopronin against diethylnitrosamine-induced hepatocellular carcinoma in rats: Role of ASK1/P38 MAPK-P53 signalling cascade

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Abstract: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Abstract Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death worldwide. Oxidative stress contributes significantly to HCC pathogenesis. In this study, we investigated the possible chemoprotective effect of the thiol group-containing compound, tiopronin, against HCC induced chemically by diethylnitrosamine (DENa) in rats. In addition, we elucidated the possible underlying molecular mechanism. Adult male Wistar rats were divided into: Control group, DENa-treated group and tiopronin + DENa-treated group. Liver function tests (ALT, AST, ALP, albumin, total and direct bilirubin) as well as alpha fetoprotein (AFP) concentration were measured in the sera of samples. Oxidative stress biomarkers such as malondialdehyde, nitric oxide, catalase and glutathione peroxidase were measured in the liver tissue homogenates. Determination of the phosphorylated apoptosis signal-regulating kinase 1 (phospho-ASK1), phospho-P38 and phospho-P53 proteins by western blotting, caspase 3 by immunofluorescence in addition to histopathological examination of the liver tissues were performed. Our results showed that tiopronin prevented the DENa-induced elevation of the liver function enzymes and AFP. It also preserved the activities of antioxidant enzymes as well as providing protection from the appearance of HCC histopathological features. Interestingly, tiopronin significantly decreased the expression level of phospho-ASK1, phospho-P38 and phospho-P53, caspase 3 in the liver tissues. These novel findings suggested that tiopronin is an antioxidant drug with a chemoprotective effect against DENa-induced HCC through maintaining the normal activity of ASK1/ P38 MAPK/ P53 signalling pathway.

KEYWORDS chemoprevention, diethylnitrosamine, hepatocellular carcinoma, oxidative stress, tiopronin