

Abstract

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death worldwide. Diethylnitrosamine (DENa) is one of the existing nitrosamines that induces oxidative stress and contributes significantly to HCC pathogenesis. Interestingly, tiopronin is a thiol group-containing compound that is used to control cysteine nephrolithiasis while hesperidin is a flavanone glycoside that is found in the *Citrus* species. Both tiopronin and hesperidin showed antioxidant activities that protect against several liver diseases.

Forty adult male Wistar rats were divided into: Control group (rats were injected with saline), DENa treated group (rats were provided with 100 mg/l of DENa solution in the drinking water for 8 weeks and then DENa-free water from week 9 to week 16), Tiopronin + DENa treated group (rats were injected intraperitoneally with 60 mg/Kg b.wt of tiopronin daily for 16 weeks in addition to DENa as the DENa treated group), Hesperidin+ DENa treated group (rats were given 200 mg/Kg b.wt of hesperidin by oral gavage for 16 weeks and DENa as the DENa treated group). At the end of the experimental period (at week 16), the liver function tests and the oxidative stress markers were assessed. The protein levels of phospho-ASK1, phospho- P38, phospho- P53, PI3K, phospho-Akt and CDK2 were measured in the liver tissues by western blotting analysis.

The results showed that tiopronin and hesperidin prevented the elevation of liver function enzymes, serum alpha fetoprotein level and oxidative stress markers such as malondialdehyde, nitric oxide, catalase and glutathione peroxidase. Furthermore, both tiopronin and hesperidin prevented the pathological alterations induced by DENa on the liver tissues macroscopically and microscopically. Remarkably, both tiopronin and hesperidin effectively protected against DENa-induced HCC by different molecular mechanisms. Tiopronin preserved the activity of ASK1/ P38 MAPK/ P53 signaling cascade while hesperidin suppressed DENa-induced up- regulation of PI3K/Akt signaling pathway. Therefore, the use of tiopronin and hesperidin showed a chemoprotective role against the induced hepatocellular carcinoma in rats.