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Salvianolic acid B protects against acetaminophen induced liver injury by inducing Nrf2 and its target gene expression

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Aim: Overdose of Acetaminophen (APAP) can result in severe liver injury. The toxicity develops after the onset of oxidative stress and mitochondrial dysfunction, and preventing these phenomena protects against APAP. Salvianolic acid B (SalB), a major water-soluble compound from *Radix Salvia miltiorrhiza*, has well-known antioxidant and anti-inflammatory activities. Our objectives were to investigate whether Salvianolic acid B (SalB) protects against APAP-induced acute hepatotoxicity and to clarify the molecular mechanisms.

Methods: *In vivo*, mice were randomly exposed to normal control group, SalB group (50 mg/kg SalB once a day for three days), APAP group (300 mg/kg APAP), SalB+APAP group (SalB at 25 and 50 mg/kg once a day for serial three days, APAP was given 2 hours later after the last SalB pretreatment). 24 h after APAP administration, liver pathological alterations, serum aminotransferases and liver GSH levels were measured. The expressions of HO-1, GCLC and Nrf2 in liver were detected. *In vitro*, HepG2 cells were treated for 6 h with different concentrations of SalB, before being exposed to 10 mM APAP. Cell viability, production of intracellular ROS, expressions of Nrf2, HO-1 and GCLC, and phosphorylation of PKC and PI3K were measured.

Results: SalB pretreatment attenuated APAP-induced hepatotoxicity both *in vivo* and *in vitro*. SalB treatment increased the expression of Nrf2, GCLC and HO-1. Though, Buthionine sulfoximine (GCLC inhibitor) and zinc protoporphyrin (HO-1 inhibitor) reversed the protective effect of SalB. Additionally, siRNA-mediated depletion of Nrf2 reduced the induction of GCLC and HO-1 by SalB. Furthermore, SalB treatment activated phosphatidylinositol-3-kinase (PI3K) and protein kinase C (PKC) signaling pathways. Both inhibitors and siRNA (PI3K and PKC/PKC δ) blocked the protective effect of SalB against cell death induced by APAP and also abolished SalB-induced Nrf2 activation and GCLC and HO-1 expression.

Conclusion: The present study indicated that SalB can alleviate APAP-induced hepatic injury through PI3K and PKC δ /Nrf2-mediated up-regulated phase 2 enzyme GCLC and HO-1 expression.

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