We investigated the effect of natural sweetener Stevia rebaudiana and its constituent stevioside in cisplatin (CP)-induced kidney injury. Male BALB/cN mice were orally administered 10, 20, and 50 mg/kg body weight of Stevia rebaudiana ethanol extract (SE) or stevioside 50 mg/kg, 48 h after intraperitoneal administration of CP (13 mg/kg). Two days later, CP treatment resulted in histopathological changes showing kidney injury. Increased expression of 4-hydroxynonenal (4-HNE), 3-nitrotyrosine (3-NT), and heme oxygenase-1 (HO-1) in mice kidneys suggested oxidative stress. CP treatment also increased renal expression of nuclear factor-kappaB (NF-κB) p65 subunit and phosphorylated inhibitor of NF-κB (IκBα), as well as expression of pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α). Induction of apoptosis and inhibition of the cell cycle in kidneys was evidenced by increased expression of p53, Bax, caspase-9, and p21, proteolytic cleavage of poly (ADP-ribose) polymerase (PARP), with concomitant suppression of Bcl-2 and cyclin D1 expression. The number of apoptotic cells in kidneys was also assessed. CP administration resulted in activation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) and signal transducer and activator of transcription 3 (STAT3). Both SE and stevioside attenuated CP nephrotoxicity by suppressing oxidative stress, inflammation, and apoptosis through mechanism involving ERK1/2, STAT3, and NF-κB suppression.

Authors: Potočnjak I, Broznić D, Kindl M, Kropek M, Vladimir-Knežević S, Domitrović R.
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