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DUNNIONE AMELIORATES CISPLATIN-INDUCED SMALL INTESTINAL DAMAGE BY MODULATING NAD+ METABOLISM

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Although cisplatin is a widely used anticancer drug for the treatment of a variety of tumors, its use is critically limited because of adverse effects such as ototoxicity, nephrotoxicity, neuropathy, and gastro-intestinal damage. Cisplatin treatment increases oxidative stress biomarkers in the small intestine, which may induce apoptosis of epithelial cells and thereby elicit damage to the small intestine. Nicotinamide adenine dinucleotide (NAD+) is a cofactor for various enzymes associated with cellular homeostasis. In the present study, we demonstrated that the hyper-activation of poly(ADP-ribose) polymerase-1 (PARP-1) is closely associated with the depletion of NAD+ in the small intestine after cisplatin treatment, which results in down regulation of sirtuin1 (SIRT1) activity. Furthermore, a decrease in SIRT1 activity was found to play an important role in cisplatin-mediated small intestinal damage through nuclear factor (NF)-κBp65 activation, facilitated by its acetylation increase. However, use of dunnione as a strong substrate for the NADH:quinone oxidoreductase 1 (NQO1) enzyme led to an increase in intracellular NAD+ levels and prevented the cisplatin-induced small intestinal damage correlating with the modulation of PARP-1, SIRT1, and NF-κB. These results suggest that direct modulation of cellular NAD+ levels by pharmacological NQO1 substrates could be a promising therapeutic approach for protecting against cisplatin-induced small intestinal damage.

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