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Phloretin and phloridzin guard against cisplatin-induced nephrotoxicity in mice through inhibiting oxidative stress and inflammation

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ABSTRACT

Aim: Cisplatin (Cis) is widely used chemotherapeutic and has some serious side effects as nephrotoxicity. Phloretin (PH) and Phloridzin (PZ) are known their anti-oxidant anti-inflammatory effects. We aimed to examine the protective effects of PH and PZ on cisplatin-induced nephrotoxicity.

Main methods: Totally, 48 Balb/C female mice were separated into eight groups ($n = 6$). First day, single dose of cisplatin (20 mg/kg intraperitoneal) was administered to induce toxicity. PH and PZ were given (50 and 100 mg/kg orally) to treatment groups during 3 days. After the experimental procedures serum renal function enzymes (BUN and Creatinine), oxidative parameters (SOD, GSH and MDA), nuclear agent NFKβ, inflammatory cytokines (Tnf-α and IL1β) and HSP70 expressions and histopathological assessments were analyzed.

Key findings: Serum enzymes, tissue cytokines and oxidative stress were increased after the Cis treatment. PH and PZ treatments normalized all parameters compared to Cis administrated group. After the treatments, SOD activities and GSH levels were increased while MDA levels were decreased. PH and PZ treatments decreased Tnf-α, IL1β and NFKβ mRNA expressions. Cis significantly increased the HSP70 expression while PH and PZ administrations significantly decreased. Similar the biochemical and molecular results, PH and PZ showed positive effects on tissue pathological parameters. Cisplatin cause a lot of abnormal structures as tubular and glomeruli damages on the kidney.

Significance: PH and PZ play important physiological roles in the prevention of nephrotoxicity. Antioxidant and anti-inflammatory effects of PH and PZ demonstrated visible protective effects in the cisplatin-induced nephrotoxicity model.

1. Introduction

Cisplatin (Cis) is an organic platinum derivative and one of the well-known chemotherapeutic agents used in cancer treatment [1]. Chemotherapeutic drugs destroy rapidly growing cancer cells as well as destroy healthy cells. For this reason, most cancer drugs have some side effects on healthy cells and tissues [2]. Nephrotoxicity is one of the most common side effects of Cis treatment [3].

Cis affects the proximal and distal tubules and destroys cell membrane and increases reactive oxygen species (ROS) and as a result of this Cis treatment induces lipid peroxidation, inflammation and hypoxia [3,4]. Cis also causes ROS dependent tubular damage and renal apoptosis [5]. Renal tubular damage may lead a rise in blood urea nitrogen (BUN) level, high serum creatinine levels [3]. On the other hand some inflammatory cytokines and agents were activated by regulatory cells during nephrotoxicity [6,7]. Tumor necrosis factor alpha (Tnf-α), interleukin 1 beta (IL1β) and nuclear factor kappa beta (NFKβ) play central role in the inflammatory response triggered by Cis [6]. Heat shock protein 70 (HSP70) is released from cisplatin-injured proximal tubular cells and initiate immune response in Tnf-α dependent manner [8]. For this reason inflammatory cytokines and their second messengers are important targets for the nephrotoxicity treatments.

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