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Anti-apoptotic and anti-inflammatory effects of naringin on cisplatin-induced renal injury in the rat

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A B S T R A C T

Nephrotoxicity is a common complication of cisplatin chemotherapy and thus limits the use of cisplatin in clinic. Naringin, a natural flavonoid, plays important roles in inflammation and apoptosis in some inflammatory diseases; however, its roles in cisplatin-induced nephrotoxicity remain unclear. In this study, we first assessed the involvement of ROS overproduction and inflammation in cisplatin-induced nephrotoxicity in aged rats, and then we investigated the changes of renal function, histological injury, inflammatory response, and apoptosis in renal tissues after treatment with naringin (20, 50 or 100 mg/kg body weight). Cisplatin resulted in an increase of renal markers, lipid peroxidation, protein and DNA oxidation, and ROS formation. Renal tumor necrosis factor-α (TNF-α) and nitrite levels were also elevated. Expressions of nuclear factor-kappa B (NF-κB), inductible nitric oxide synthase (iNOS), caspase-3 and p53 were up-regulated in renal tissues of Cis-treated rats compared with the normal control group. Histopathological changes were also observed in cisplatin group. Adminstration of naringin at different doses (25, 50 and 100 mg/kg) was able to protect against the deterioration in kidney function, abrogate the decline in antioxidant enzyme activities and suppressed the increase in TBARS, nitrite and TNF-α concentrations. Moreover, naringin inhibited NF-κB and iNOS pathways, caspase-3 and p53 activation and improved the histological changes induced by cisplatin.

In conclusion, our studies suggest that oxidative stress and inflammation might play important roles in the development of cisplatin-induced nephrotoxicity and naringin might become an effective therapeutic strategy for this disease.

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1. Introduction

Cisplatin emerged as one of the principal chemotherapeutic agents to treat various human malignancies, which exerts its action mainly through formation of DNA adducts, induction of oxidative stress and triggering apoptosis in tumor cells [1,2]. The extensive application of cisplatin in clinical oncology, particularly high dose and repeated cycles of treatment regimen has been limited by its undesirable side effects. Although being very effective in reducing tumor burden, it is extremely toxic and can cause severe tissue damage [2–5]. Nephrotoxicity is one of the most important side-effects of cisplatin therapy, affecting primarily the S3 segment of the proximal tubules [6,7]. The molecular mechanisms underlying cisplatin-induced cell death in renal tubular cells are not fully understood yet but it has been shown that oxidative stress and inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL1β) are involved in the pathogenesis of cisplatin induced nephrotoxicity [7,8]. further, oxidative stress via reactive oxygen species (ROS) has been implicated in renal injury under various pathological conditions [9]. ROS stimulates DNA damage and trigger of p53 activation. Also, ROS can activate an array of signaling pathways including various protein kinases which are involved in p53 phosphorylation and activation [10,11]. These adverse effects from cisplatin exposure have led to the search

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for preventative treatments [12,13]. For these reasons, several strategies are under way to preventor minimize the toxicities and conserve the effectiveness of the platinum chemotherapy drugs.

Nowadays, much of attention has been given to the usage of phytochemicals as a protective strategy against cisplatin toxicity [14]. Flavonoids are natural polyphenolic phytochemicals that are beneficial in preventing and treating many diseases such as cancer, cardiovascular diseases, neurodegenerative diseases as well as diabetes [15]. Naringin (4′,5,7-trihydroxy flavanone 7-rhamnoglucoside), a flavanone glycoside, isolated from the grape and citrus fruit species, contains an array of immense therapeutic potential [16]. Naringin or its metabolite has been reported to possess diverse biological and pharmacological properties including anti-carcinogenic [17,18], lipid-lowering [19], anti-apoptotic [20], anti-atherogenic [21], metal chelating and antioxidant activities [22]. Some growing evidence has indicated that naringin displays anti-inflammatory effects both *in-vitro* and *in-vivo* systems by modulating of the expression of tumor necrosis factor-α (TNF-α) and the transforming growth factor-β (TGF-β) that found to be involved in the pathogenesis of lung injury and pulmonary fibrosis [23]. Although it was observed in our laboratory that naringin and its metabolite prevents cisplatin-induced neurotoxicity [24,25] as far as we know, there are no study showing the effect of naringin against cisplatin-induced nephrotoxicity and the mechanism by which exerts its protective effects. Based on these finding, we hypothesized that combining naringin with cisplatin would be a novel strategy to protect the kidney from cisplatin induced renal side effects. Therefore, the aim of this work was to investigate the potential protective effect of naringin against cisplatin-induced renal damage in aged rats and to elucidate the underlying molecular mechanisms in terms of oxidative stress, inflammatory and apoptotic mediators.

2. Materials and methods

2.1. Chemicals and reagents

Naringin and all other chemicals required for biochemical assays were obtained from Sigma Chemicals Co. (St. Louis, France).

2.2. Animals

middle-aged (18 month-old, 57–61% lifespan) Wistar rats were purchased from the Central Pharmacy (SIPHAT, Tunisia). Animals were kept in an air conditioned room (22 ± 2 °C) with free access to water and commercial diet supplied by the Company of Animal Nutrition, Sfax, Tunisia [26]. All manipulations were carried out between 08:00 a.m. and 04:00 p.m. All animal procedures were conducted in strict conformation with the local Institute Ethical Committee Guidelines for the Care and Use of laboratory animals of our Faculty.

2.3. Cisplatin exposure and treatment with naringin

Experimental procedures were divided in two sets of experiments. In the first set, animals were randomly divided into four groups (10 rats in each group): Control (CT); Naringin (25 mg/kg body weight) (Nar 25); Naringin (50 mg/kg body weight) (Nar 50) or Naringin (100 mg/kg body weight) (Nar 100).

In the second experimental set, animals were divided into 4 groups (10 rats in each group): Cisplatin (Cis) group (5 mg/kg/week for 5 consecutive weeks by intraperitoneal route); Cisplatin with Naringin (25 mg/kg body weight) (Cis + Nar25); Cisplatin with Naringin (50 mg/kg body weight) (Cis + Nar 50); and Cisplatin with Naringin (100 mg/kg body weight) (Cis + Nar 100). Naringin was diluted with buffered saline and propylene glycol 25/75 (v/v), administered by oral gavage, and did not exceed 1.0 ml/kg body weight.

2.4. Biochemical analysis

At the end of the treatment, animals were euthanized by cervical decapitation to avoid stress conditions. Serum was separated by centrifugation at 4000 rpm for 10 min, stored at −80 °C until analyzed and was used for the assessment of renal biomarkers. Kidneys were quickly excised, washed immediately with ice-cold physiological saline, blotted dry, and weighed. Portions were taken for histopathological studies and the remaining parts of kidneys were homogenized in 0.1 M phosphate buffer (pH 7.4) to produce 10%(w/v) homogenates, which were then centrifuged at $12000 \times g$ for 15 min at 4 °C to remove nuclei and debris. The supernatants were separated, aliquoted, and stored at −80 °C until analysis.

2.4.1. Determination of oxidative stress markers

Lipid peroxidation in the kidney tissue was estimated colorimetrically by measuring thiobarbituric acid reactive substances (TBARS) which were expressed in terms of malondialdehyde content according to Draper and Hadley method [27]. Protein carbonyl (PCO) contents were detected by the reaction with 2,4-dinitrophenylhydrazine (DNPH) method as reported by Levine et al. [28]. Hydroperoxide assay (H_2O_2) was determined by the method of Gay et al. [29]. Oxygen reactive species levels in kidney tissue were measured according to Driver et al. method [30]. the fluorescence intensity was measured using a fluorescence plate reader with an excitation wavelength of 485 nm and emission detection at 530 nm. The amount of 8-oxo-dG in kidney was measured using a HPLC system equipped with an electrochemical detector (HP Agilent 1100 module series, E.C.D. HP 1049 A, Agilent Technologies, Waldbronn, Germany), as described previously [31]. The 8-oxo-dG levels were expressed as % vs. control rats.

2.4.2. Estimation of urea, creatinine, uric acid, and creatinine clairance

Urea, uric acid and creatinine levels were estimated spectrophotometrically using commercial reagent kits (refs. 20125, 20143, 20092, 20151 respectively. Biomaghreb Diagnostics, Ariana. Tunisia). Creatinine clearance as an index of glomerular filtration rate was calculated from serum creatinine level According to the 24 h urine volume, urinary creatinine and serum creatinine concentration.

2.4.3. Determination of non-enzymatic antioxidants

Reduced glutathione in hippocampus was determined by the method of Ellman [32] based on the development of a yellow color when 5,5-dithiobis-2-nitrobenzoic acid (DTNB) was added to compounds containing sulfhydryl groups. Acid ascorbic (Vit C) content was determined spectrophotometrically by dinitrophenylhydrazine method described by Jacques-Silva et al. [33].

2.4.4. Determination of enzymatic antioxidant activities

Catalase (CAT) activity was assayed by the decomposition of hydrogen peroxide according to the method of Aebi [34] The enzyme activity was expressed as μmol H_2O_2 consumed/min/mg protein. Total superoxide dismutase activity (SOD) was evaluated by measuring the inhibition of pyrogallol activity as described by Marklund and Marklund [35]. SOD activity was expressed as U/mg protein. Glutathione peroxidase activity (GPx) was measured according to Flohe and Gunzler [36]. The enzyme activity was expressed as nmol of GSH oxidized/min/mg protein. The

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