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Investigation of the effects of fucoidan extracted from *Sargassum angustifolium* algae against oxidative stress induced by gentamicin-induced nephrotoxicity in male rats

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In this research was investigated the protective and preventive properties of fucoidan extracted from the *Sargassum angostifolium* algae against oxidative stress on nephrotoxicity induced by gentamicin in male rats. Thirty male Wistar rats were casually divided into 6 equal groups. Positive control, experimental (EXP) 1, 2 and 3 groups received 40 mg/kg B.W of gentamicin for 7 days to induce nephrotoxicity. Then, EXP 1, 2 and 3 groups received fucoidan at doses of 50, 100 and 150 mg/kg B.W, respectively, for 28 days. Animals in EXP4 first received fucoidan at a dose of 150 mg/kg for 28 days and then received gentamicin at a dose of 40 mg/kg for 7 days. Sampling were done on week 14 and 28, and the parameters creatinine (Cr), urea, catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA), total antioxidant capacity (TAC), vitamin C (Vit.C), and glutathione peroxidase (GPX) were measured. Protective and preventive treatment of fucoidan for 28 days improved all measured parameters. The greatest effect was observed at the maximum dose (150 mg/kg B.W). Treatment for 28 days had better results compared to 14 days. Fucoidan has the potential to be used as an antioxidant therapy in gentamicin-induced nephrotoxicity.

Keywords: Antioxidant, Kidney injury, Nephroprotection, Polysaccharide

Introduction

Some of the renal failures are caused due to oxidative stress, for example chronic renal disease, acute kidney injury, and various types of nephropathies. However, current treatments may be associated with increased levels of oxidative stress and thus further impairment[1]. A key component in metabolic disorders, stress, and inflammation is induction of reactive oxygen species (ROS) and reactive nitrogen species (RNS). For this reason, natural antioxidant systems have been developed to neutralize the free radicals in organisms. Disruption of antioxidant defenses leads to oxidative stress, which can cause some problems; kidney disorder is one of them. The cooperation of proinflammatory cytokines, ROS, and apoptotic factors leads to kidney tubular damage[2].

Non-enzymatic antioxidants such as reduced glutathione, peroxiredoxin, vitamin E, VitC, ferritin, transferrin, ceruloplasmin, and albumin, as well as enzymes such as SOD, CAT, thioredoxin reductase, and GPx, are among the natural defense systems against oxidative stress. These antioxidant parameters are strongly correlated to different stages of chronic kidney disease[3]. Currently, study concentrates on increasing the body's antioxidant level via the addition of food additives has attracted a lot of consideration. Prior researches have shown that functional food additives can strengthen the body's antioxidant immune system[4,5] and improve mitochondrial function[6]. Therefore, the use of compounds with oxidative stress reducing properties and antioxidant effects could be suitable for prevent and/or treat oxidative stress-induced damage[7]. An important marine biological resource that can contribute to the transformation of the global food system as one of the 50 food sources is seaweed[8]. Nutritional and medicinal properties of specifications brown algae are due to the presence some numerous bioactive compounds such as proteins, polyphenols, sulfated polysaccharides, vitamins, dietary fibers, and fatty acids[9]. Many researchers have confirmed that brown algae or their extracts are useful for the production of

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highly nutritious food products[10,11]. The most popular natural compounds found in brown algae are fucoidans. These compounds have diverse medicinal properties and a few side effects[12].

Fucoidans, due to their physicochemical properties, have diverse biological activities, including ROS scavenging, antifungal[13], antiviral[14], antidiabetic[15], anti-inflammatory[16], and antioxidant[17] effects. The molecular weight and grade of sulfation of fucoidan determine its antioxidant capacity[18]. Various researches have evaluated the protective effects of fucoidan against oxidative damage in various biological models. For example, the protective effects of fucoidan isolated from *Sargassum fusiforme* against ethanol-induced oxidative damage in hepatocytes are remarkable[19]. Thukorala *et al*. first demonstrated the antioxidant activity of fucoidans[20]. Since then, various studies have investigated the antioxidant properties of fucoidans, including: Kalita *et al.* [21], Wang *et al.*[22], Yang and Lim[23], and Pradhan *et al.*[24] It has been proven that fucoidan has many biological effects on liver and kidney[25,26]. Fucoidan improves renal dysfunction through the regulation of signaling pathways[27]. In addition, low molecular weight fucoidan protects the kidneys from diabetic nephropathy[28]. More than 250 species of different algae have been identified on the coasts of the Persian Gulf and the Sea of Oman, but the biological properties of most of them have not yet been discovered. In the coastal waters of the Persian Gulf, the seaweed Sargassum angustifolium is the dominant species, which contains large amounts of fucoidan[7]. Therefore, in this study was investigated the protective and preventive properties of fucoidan extracted from the *Sargassum angostifolium* algae against oxidative stress on nephrotoxicity induced by gentamicin in rats.

Materials and Methods

Animals

In this experimental study the animals were 30 adult male Wistar rats with weigh approximately 230 ± 20 g and approximately 80-90 days old, which were purchased from the Comparative Medicine Animal Breeding House of Shiraz University of Medical Sciences and kept in Islamic Azad University of Kazerun animal house. This study procedure was accepted by the Ethics Committee of Islamic Azad University of Kazerun Branch (IR.IAU.KAU.REC.1404.005) based on the rules and regulations for working with laboratory animals. Prior to the experiment, the animals were acclimated for one week to the laboratory conditions to reduce stress. The rats were kept at a temperature of 22 to 24 °C, 12 hours of light and 12 hours of darkness, and 60% humidity throughout the study period. The animals were kept in polycarbonate cages with dimensions of 14 × 21 × 27 cm with a steel mesh roof. Five adult male rats were housed in each cage. The animals were fed a concentrated diet for rats, which was purchased from the Estakhr Livestock and Poultry Company, Marvdasht, Iran and they received equal access to food and water.

Study protocol and treatments

Animals were casually divided into 6 equivalent groups (n=5). Animals in the healthy control group received just regular food. Animals in the positive control group received 40 mg/kg/day of gentamicin by IP injection for a week to induce nephrotoxicity and then received 1 ml of distilled water daily for 28 days[29,7]. Animals in EXP 1, 2 and 3 groups at the begining received 40 mg/kg/day gentamicin intraperitoneally for a week and then received 50, 100 and 150 mg/kg/day fucoidan extract by gavage for 28 days, respectively. Animals in EXP4 group initially received 50, 100 and 150 mg/kg/day fucoidan extract by gavage daily for 28 days and then received 40 mg/kg/day gentamicin intraperitoneally for 7 days. Blood collection was performed in two stages on days 14 and 28 of fucoidan extract administration. 14 days later, all animals were lightly anesthetized with ether (Merck, Germany) and sampling was done from the tail vein. On day 28 of the study, blood was collected directly from the left ventricle of the heart by opening the chest and using a 5 cc syringe. The bloods were kept in an incubator at 37°C for 30 minutes to complete the agglutination process. Then, they were centrifuged at 3000 rpm for 5 minutes to separate the serum. The serum was collected into labeled microtubes and saved at -20°C until the serum levels of Cr, Urea, TAC, Vit.C, CAT, GPX, MDA, and SOD were measured.

Gentamicin

Gentamicin was purchased from Exir Pharmaceutical Company, Borujerd, Iran. The drug dose was selected based on previous studies (as pharmaceutical ampules 40 mg/1 ml)[29].

Fucoidan

Fucoidan was obtained as powder from Persian Gulf Algae Development Technology Company,

Bushehr, Iran (Patent No.: 101428; International Classification: A61K36/03). Fucoidan was administered as 50, 100, and 150 mg/kg/day body weight by gavage based on previous studies[7]. Distilled water was used as a solvent and to dilute fucoidan.

Biochemical parameters and oxidative stress profile analysis

The Cr serum level (Biorexfars Kit, Iran) was measured by Jaffe method[30] and Urea level was measured by Urease method (Darman Faraz Kave Kit, Iran)[31]. MDA and TAC were measured by ELISA method (Teb Pazhouhan Razi Kit, Iran)[32]. GPX, SOD and CAT activity were measured by spectrophotometry (Kiazist Kit, Iran)[33]. Vit.C level (Kiazist Kit, Iran) was also measured by HPLC (high-performance liquid chromatography) method[34].

Statistical analysis

Data from blood parameters were analyzed using SPSS version 20 statistical software (SPSS Inc, Chicago, IL, USA). One-way analysis of variance (ANOVA) and LSD post hoc test were used to compare the mean data, and the resulting values were expressed as Mean±SEM in the graphs, and the significance level was considered to be $P<0.05$. Excel version 2019 software was used to draw the graphs.

Results

Biochemical parameters findings

On days 14 and 28 of treatment, the positive control group had a significant increase in Cr (Fig. 1a) and urea (Fig. 1b) compared to the healthy control, indicating impaired renal function. Treatment with fucoidan caused a decrease in the Cr level, such that EXP3 showed a significant improvement. EXP4 also had similar values to the healthy control. On day 28 of treatment, the improvement in renal function in the EXP groups was more evident than on day 14. The EXP 3 and 4 almost reached the healthy control level. These results emphasize that fucoidan not only prevents the deterioration of renal function but can restore it to a large extent.

Oxidative stress profile findings

On days 14 and 28 of the study, serum TAC in the healthy control group indicated a favorable state of the antioxidant system under normal conditions. In contrast, the patient rats, which had suffered from gentamicin-induced renal injury, showed a significant decrease, indicating a weakening of antioxidant defense and increased oxidative stress. Fucoidan consumption in EXP 1, 2, and 3 groups caused a

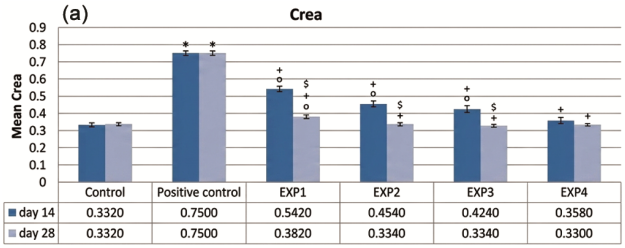

Fig. 1 — Comparison of Mean±SEM of the Cr and Urea levels. *: $P<0.05$ in comparison with healthy control group. +: $P<0.05$ in comparison with positive control group. $: $P<0.05$ in comparison with 14-day group. EXP: Experimental.

gradual improvement in TAC, and this effect was observed in a dose-dependent manner, such that in EXP3 with the maximum dose on day 28 of treatment, there was a significant increase in comparison with the positive control group and also on day 14 of treatment. EXP4 also had a significant increase compared to the positive control group, indicating a protective effect of fucoidan before the onset of injury (Fig. 2a).

SOD activity on days 14 and 28 of treatment showed a significant reduction in SOD level in the positive control group in comparison with healthy control group, indicating impaired inhibition of superoxide ions. Treatment with fucoidan increased SOD activity, with EXP3 showing the greatest effect. These data indicated the effect of the maximum dose of fucoidan on restoring superoxide removal capacity. On day 28 of treatment, compared to day 14, SOD levels improved in all EXP groups. EXP3 almost reached the control level, and EXP2 also indicated a significant improvement. Prevention with fucoidan in EXP4 also indicated a significant effect. The significant increase in SOD amount in the EXP groups indicated a gradual return of enzymatic defense against oxidative stress under the influence of treatment (Fig. 2b).

On days 14 and 28 of treatment, the level of Vit.C in the positive control group was significantly decreased in comparison with healthy control group, indicating a decrease in non-enzymatic antioxidant capacity due to renal damage. Treatment with fucoidan caused a gradual increase in Vit.C levels,

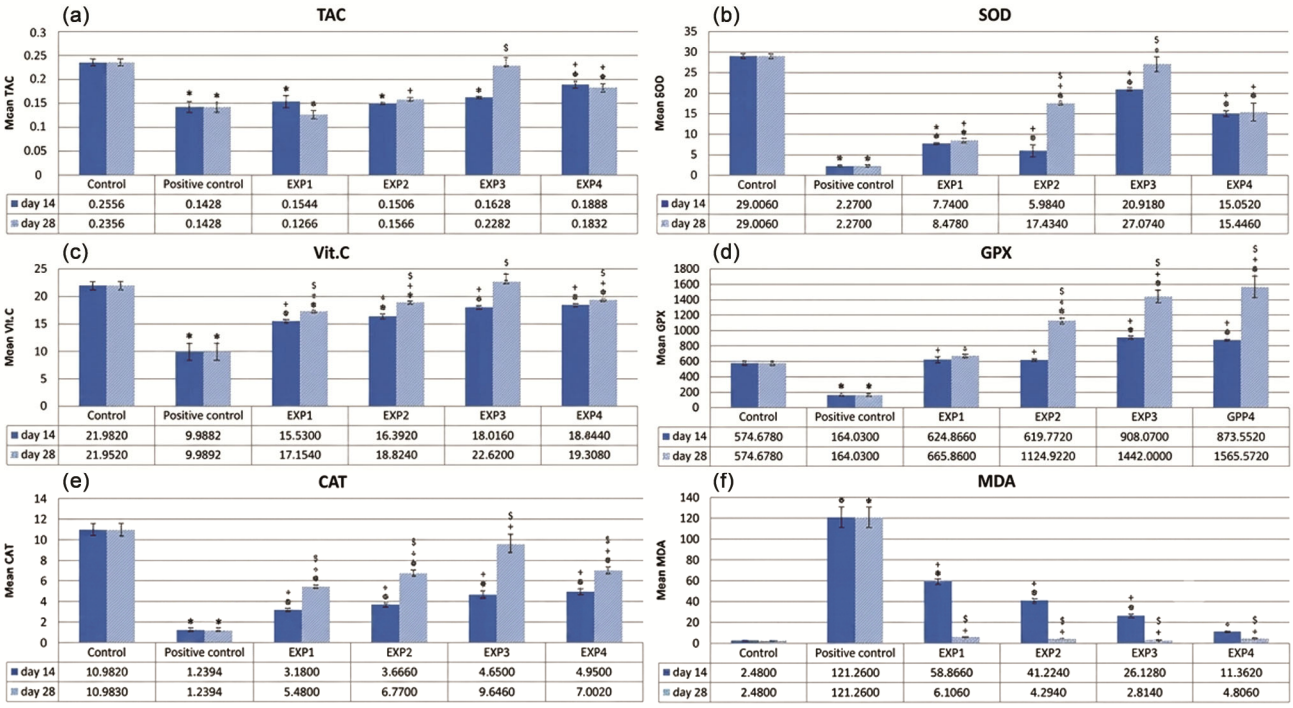

Fig. 2 — Comparison of Mean±SEM of the levels of A) TAC, B) SOD, C) Vit.C, D) GPX, E) CAT and F) MDA . *: P<0.05 in comparison with healthy control group. +: P<0.05 in comparison with positive control group. $: P<0.05 in comparison with 14-day group. EXP: Experimental.

especially in EXP3. Vit.C levels on day 28 of treatment were not significantly different from the healthy control group. On day 28 of treatment, Vit.C levels in EXP4 were significantly higher in comparison with patient rats and day 14 of treatment, and this increase was also observed in EXP 1 and 2 groups. These data indicate that fucoidan, in addition to enhancing enzymatic defense, also restores the reserves of water-soluble antioxidants such as Vit.C (Fig. 2c).

On days 14 and 28 of treatment, GPx activity in the positive control group was significantly reduced in comparison with healthy control group. Administration of fucoidan in all EXP groups significantly increased GPx activity. The highest increase was observed in EXP 2, 3, and 4 groups on day 28 of treatment (Fig. 2d). These results indicate that fucoidan effectively activates the enzymatic pathways of peroxide removal and has a strengthening and sustainable role in antioxidant enzymatic function.

CAT activity on days 14 and 28 of treatment in the control group indicated a significant decrease in renal injury conditions in comparison with positive control group. Fucoidan consumption at the maximum dose improved enzyme activity on day 14 of treatment, especially in EXP 3 and 4 groups. This increase indicates a dose-dependent role of fucoidan in inhibiting H_2O_2 accumulation and improving enzymatic defense against ROS. On day 28, CAT level in all EXP groups significantly increased in comparison with day 14 of treatment (Fig. 2e). These results indicate that long-term consumption of fucoidan can restore catalase activity and help effectively eliminate hydrogen peroxide, which leads to reduced oxidative stress and tissue protection.

On days 14 and 28 of treatment, the MDA amount the positive control group was significantly increased in comparison with healthy control group, indicating a severe increase in lipid peroxidation due to renal injury. Fucoidan administration caused a dose-dependent decrease in MDA levels. This decrease indicates that fucoidan inhibits the process of cell membrane destruction by neutralizing free radicals and strengthening the antioxidant system. On day 28 of treatment, a significant decrease in MDA levels was observed in the EXP groups compared to day 14 of treatment. The greatest decrease was observed in EXP 3 and 4 groups (Fig. 2f). These results indicate that fucoidan consumption not only inhibits lipid peroxidation but also returns oxidative conditions to physiological states over time.

Discussion

Fucoidan is a sulfated polysaccharide extracted from brown algae that has significant biological properties due to its complex structure and rich in sulfate groups. Several studies have shown that fucoidan, in addition to its anticancer and anti-inflammatory effects, has significant impacts in decreasing oxidative stress and protecting various body tissues, especially the kidney, in conditions of acute or chronic injury. This compound exerts its protective effects through various mechanisms such as direct removal of free radicals, strengthening the antioxidant system, preventing inflammatory pathways, and inhibiting cell apoptosis[35]. One of the main mechanisms of fucoidan is direct antioxidant activity. The sulfate groups in its structure are able to absorb and neutralize ROS and RNS. This ability reduces oxidative damage to lipids, proteins, and DNA and prevents structural destruction of the cell. This feature is especially important in kidney tissue, which is highly sensitive to oxidative damage[7].

The findings of this study showed that gentamicin-induced renal injury significantly decreased TAC levels, which is associated with increased oxidative stress and reduced free radical scavenging capacity. Administration of fucoidan dose-dependently improved TAC levels on days 14 and 28, with the greatest effect observed at the maximum dose. These effects are compatible with prior researches that express that marine sulfated polysaccharides such as fucoidan, with strong antioxidant properties, can increase the body's defense capacity against reactive oxygen species[36].

The levels of key antioxidant defense enzymes such as catalase, superoxide dismutase, and glutathione peroxidase were severely reduced in the positive control group, which is associated with impaired renal enzymatic defense system. Treatment with fucoidan significantly increased the activities of these enzymes, such that on day 28, some treatment groups even reached levels higher than the control group. These results are consistent with similar researches that have showed the rise effect of fucoidan on antioxidant defense system[37,38].

MDA, as an indicator of lipid peroxidation, was remarkably higher in the patient rats in this study, indicating cell membrane damage caused by free radicals. Administration of fucoidan at different doses significantly reduced MDA, especially on day 28 of treatment, when the experimental groups reached values close to or similar to the healthy rats. These findings are constant with existing evidence that fucoidan can prevent tissue damage by inhibiting lipid peroxidation[38,39].

The level of Vit.C, as a water-soluble antioxidant, was significantly reduced in the positive control group, but administration of fucoidan caused it to return and even increase significantly in comparison with healthy rats. This effect can be because of the reduction in Vit.C consumption in the free radical neutralization process and also the increase in its regeneration under the influence of fucoidan. Previous studies have also shown that marine polysaccharide compounds are able to improve the levels of Vit.C and other non-enzymatic antioxidants[40].

Serum Urea and Cr measurements showed that gentamicin-induced renal injury significantly increased these indices, indicating a decrease in glomerular filtration rate and impaired renal function7. Treatment with fucoidan at the maximum dose as well as prophylactic administration was able to restore these indices to normal ranges. These results are coordinated with prior reports that have confirmed the protective effect of fucoidan on renal function in nephrotoxicity models[35].

Based on the available evidence, the mechanism of action of fucoidan in improving antioxidant status and renal function includes direct neutralization of reactive oxygen species, increased expression of genes encoding antioxidant enzymes, inhibition of NF-κB-dependent inflammatory pathways, and protection of cell membranes against peroxidation. Some studies have also reported anti-inflammatory, anti-apoptotic, and immune response-modulating effects of fucoidan[41].

In addition to its direct effect, fucoidan can increase the level of endogenous antioxidant enzymes. Increased expression of these enzymes reduces the concentration of superoxide, hydrogen peroxide, and organic peroxides and enhances cellular defense against oxidative damage. This mechanism, along with the reduction of lipid peroxidation, is effective in improving kidney and other organ function[42]. The anti-inflammatory properties of fucoidan also form an important part of its protective mechanisms. This compound reduces the severity of inflammation in the tissue by reducing the induction and secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as restraint the activity of inflammatory enzymes such as COX-2 and iNOS[43,44].

The activation of the Nrf2/ARE pathway by fucoidan is one of key mechanisms of signaling pathways. Nrf2 is a transcription factor that, after activation, translocates to the cell nucleus and increases the induction of genes encoding antioxidant enzymes such as HO-1, NQO1, and GST. This pathway not only increases cell resistance to oxidative stress, but also improves the cellular detoxification process[41]. Fucoidan inhibits the expression of inflammatory genes by inhibiting the phosphorylation of IκBα and preventing the translocation of NF-κB to the nucleus. It also affects the pathways regulating inflammation, proliferation, and apoptosis by modulating the phosphorylation of MAPK proteins such as ERK, JNK, and p38. These mechanisms play an importance role in reducing the hyperactive inflammatory response and preventing cell death in kidney tissue[45].

Inhibition of the TLR4/MyD88/NF-κB pathway is another proposed mechanism of fucoidan. This pathway is involved in the activation of innate inflammation, and its inhibition can lead to a reduction in inflammation and renal fibrosis. Fucoidan also increases cell survival and resistance to oxidative stress and inhibits apoptosis via acting of the PI3K/Akt pathway[46]. The combination of these mechanisms suggests that fucoidan is a multifaceted agent with synergistic antioxidant, anti-inflammatory, and anti-apoptotic impacts that prevent tissue injury and renal dysfunction through diverse signaling pathways and regulation of gene expression. These properties, together with its relative safety and high biocompatibility, make fucoidan a suitable candidate for the development of nephroprotective drugs and the reduction of complications caused by oxidative stress and inflammation.

Studies show that fucoidan can reduce inflammation induced by bacterial lipopolysaccharide. Among the anti-inflammatory activities of fucoidan is the inhibition of leukocyte migration into inflamed tissues[47]. It is noteworthy that fucoidan can affect the inflammatory response in patients with advanced cancer[48]. In addition, fucoidan can synergistically enhance the efficacy of anti-inflammatory drugs. Compared with other small molecule anti-inflammatory drugs, fucoidan as a macromolecule has broad prospects as a direct drug or nutritional adjuvant[49].

In vitro studies show that fucoidan can inhibit proliferation and induce apoptosis in human lymphoma cell lines HS-Sultan. Fucoidan-induced apoptosis appears to be associated with the activation of caspase-3. Aisa *et al.* showed that mitochondrial potential in HS-Sultan cells decreased 24 h after fucoidan treatment, indicating that fucoidan induced apoptosis through a mitochondrial pathway. When HS-Sultan was treated with 100 μg/ml fucoidan for 24 h, the phosphorylation of ERK and GSK was significantly reduced. In contrast, the phosphorylation of p38 and Akt was not changed by fucoidan treatment. Therefore, fucoidan may induce apoptosis through different receptors. These results indicate that fucoidan has direct anticancer effects on human HS-Sultan cells through the caspase and ERK pathways[50].

Antioxidants can exhibit different functional effects to induce and suppress oxidative stress at high and physiological concentrations, respectively. Similarly, fucoidan is a potential radical scavenger and protects against peroxide-induced cellular damage. On the other hand, fucoidan induces oxidative stress in breast, bladder, acute myeloid leukemia, colon, liver, and tongue cancer cells. This is a slight contradiction because some studies have pointed out the strong antioxidant properties of fucoidan. Perhaps the antioxidant properties only apply to healthy cells. Accordingly, fucoidan may exhibit different functional effects, suppressing or inducing oxidative stress in different cellular tissues to protect normal cells but damaging cancer cells. Based on the results of our study, further studies on the biological and antioxidant properties of fucoidan are needed to elucidate its molecular pathways and mechanisms[51].

Conclusions

The findings of this study showed that fucoidan as an antioxidant agent can improve antioxidant indices and inhibit oxidant indices in gentamicin-treated rats, thereby improving renal function. Overall, the findings of this study suggest that fucoidan could be effective not only as a protective agent after the onset of renal injury, but also as a preventive agent in improving renal injury in rats. These effects were particularly prominent at the maximum dose in this study, and if confirmed in human studies, it can be used as a supplement to reduce the side effects of nephrotoxic drugs such as gentamicin.

Conflicts of interest

There are no conflicts of interest.

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