Original Article

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KIDNEY RESEARCH AND CLINICAL PRACTICE

Protective effects of D-005, a lipid extract from *Acrocomia crispa* fruits, against ischemia/reperfusion-induced acute kidney injury in rats

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Background: Acute kidney injury (AKI) induced by renal ischemia/reperfusion (IR) is associated with enhanced production of reactive oxygen species in renal tissues. D-005, a lipid extract obtained from *Acrocomia crispa* fruit, has previously shown antioxidant effects. The aim of this work was to evaluate the effects of D-005 on renal IR-induced AKI in rats.

Methods: Rats were randomized into seven groups including a negative control group (vehicle) without AKI and six groups with renal IR-induced AKI as follows: a positive control (vehicle); D-005 treatment at 25, 100, 200, or 400 mg/kg; and dexamethasone at 3 mg/kg. All treatments were orally administered as single doses 1 hour before AKI induction. Biomarkers (serum creatinine, urea, and uric acid concentrations), oxidative variables, and histopathological AKI changes were evaluated in blood and kidney tissues.

Results: All D-005 doses protected against IR-induced AKI in rats by significantly decreasing biomarkers and histopathological AKI changes as assessed by reduced serum concentrations of creatinine, urea, and uric acid. In addition, all D-005 doses decreased tubular damage, as shown by fewer detached cells and casts in the tubular lumen. D-005 reversed oxidation disturbance markers by decreasing malondialdehyde and sulfhydryl group concentrations in plasma and in kidney homogenates and by increasing kidney catalase activity. Dexamethasone, the reference substance, protected against IR-induced AKI in rats by reducing biochemical and histological variables of renal damage in a similar manner.

Conclusion: Administration of single oral doses of D-005 markedly and significantly protected against renal IR-induced AKI, possibly due to its known antioxidant effects.

Keywords: *Acrocomia crispa*, Acute kidney injury, D-005, Rats, Renal ischemia/reperfusion

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Introduction

Renal ischemia/reperfusion (IR) occurs under different clinical conditions, including kidney transplantation, cardiopulmonary and aortic aneurysm surgeries, severe hemorrhagic shock, and endotoxin sepsis. IR can lead to acute kidney injury (AKI) depending on the extent of blood flow reduction and the length of the ischemic period. AKI is associated with high mortality and morbidity worldwide [1–3].

During IR-induced AKI, renal cells undergo necrosis and apoptosis as a result of anoxia and generation of reactive oxygen species (ROS), as well as accumulation of neutrophils, which triggers the inflammatory process [4–6]. On the other hand, ROS enhancement and the resulting inflammation decrease glomerular filtration, impairing normal renal function. The decrease in glomerular filtration rate during AKI results in nitrogenous waste retention, of mainly creatinine and blood urea nitrogen [7].

Current clinical therapies to prevent or treat IR-induced AKI have a limited scope in kidney recovery [8]. Additionally, they are not effective to avoid progression of AKI to chronic kidney disease [9]. In this context, new drugs have been evaluated to prevent or treat AKI, but new treatments that can be translated to clinical practice have not yet been established [10]. Therefore, it is necessary to search for new therapeutic strategies to prevent and/or treat AKI.

Considering the role of ROS in AKI development and progression, several antioxidant agents are promising therapeutic alternatives for treatment and prevention of this pathology [11]. These results are supported based on the well-established use of antioxidant substances to prevent oxidative stress and concomitant inflammation [12]. Natural products and phytochemical compounds with inhibitory effects on antioxidant mechanisms have shown beneficial influence in models of IR-induced AKI [13–15].

D-005, a lipid extract obtained from the fruit of the Cuban endemic palm *Acrocomia crispa*, belonging to the *Arecaceae* family, contains a reproducible fatty acid mixture consisting of mainly oleic, palmitic, lauric, and myristic fatty acids, with palmitoleic, caprylic, capric, and stearic fatty acids as minor components [16]. Previous *in vitro* and *in vivo* studies have demonstrated anti-inflammatory and antioxidant effects of D-005. *In vitro*, D-005 inhibited cyclooxygenase type 2 (COX-2) activity in the microsomal fraction of rat seminal vesicles and 5-lipoxygenase (5-LOX) activity in the cytosolic fraction of rat polymorphonuclear leukocytes [17]. *In vivo*, D-005 significantly attenuated neutrophil infiltration in lipopolysaccharide-induced acute lung injury in mice [18]. In addition, D-005 decreased prostate malondialdehyde (MDA) and sulfhydryl (SH) group levels in rats with testosterone-induced prostatic hyperplasia [19]. Also, a recent study in rats that evaluated the effects of D-005 on kidney histological changes with IR-induced AKI showed a nephro-protective effect, although this result needs to be corroborated and the study expanded with different efficacy variables [20].

Considering the pivotal role of oxidative stress and inflammation in AKI etiology, the demonstrated anti-inflammatory and antioxidant properties of D-005, and its preliminary nephro-protective effects [20], we aimed to evaluate the effects of D-005 on histological biomarkers and oxidative variable changes in renal IR-induced AKI in rats.

Methods

Extracts and drugs

D-005 (batch 5080316) was obtained from the Natural Products Center of the National Center for Scientific Research, Havana, Cuba, and its quality was verified by a gas chromatography-validated method [16]. D-005 was suspended in Tween 65/H_2O (2%) prior to use. Dexamethasone (DEX, batch: B0112/015040, Pharmaceutical Industry, Havana, Cuba) was dissolved in citrate buffer (0.1 mol/L; pH 4.2).

Animals and treatments

Adult male Sprague-Dawley rats (300–350 g), supplied from the National Center for the Production of Laboratory Animals (CENPALAB, Havana, Cuba), were adapted to laboratory conditions (22°C±2°C temperature, 60±5% relative humidity, 12:12 hours light/dark cycles) for 7 days. They were fed daily with standard rodent pellets (CENPALAB) and water *ad libitum*. Experiments were conducted in accordance with the Cuban Guidelines for Animal Handling and the Cuban Code of Good Labora-

tory Practices. The independent ethical board of Natural Products Center approved the animal use and study protocols.

The animals were randomized into seven groups (n = 8, each group) including a negative control without AKI and six groups with renal IR-induced AKI including a positive control group orally treated with vehicle (Tween 65/H_2O); four groups orally treated with D-005 at 25, 100, 200, or 400 mg/kg; and one group intraperitoneally (i.p.) administered DEX (3 mg/kg). The treatments were provided 1 hour before inducing renal IR. In this work, DEX was used as a reference substance, taking into account the beneficial effects shown in preclinical studies based on AKI models [21,22], as well as its well-known clinical usefulness in prevention of AKI [23,24].

AKI induction by renal IR

This study used the same conventional reproducible AKI model as used previously in preclinical studies of other natural products [25,26] and that is known to induce pathological changes similar to the human disease [27]. Rats were anesthetized with sodium thiopental (30 mg/kg; i.p.), and laparotomy was performed by longitudinal incision in the ventral midline. Both renal pedicles were exposed, and occlusion clamps were placed on both renal veins and arteries. Thirty minutes later, the clamps were removed, allowing reperfusion of the kidneys. During the surgical procedure to induce renal ischemia, rat body temperature was kept at 35ºC to 37ºC. At the end of the reperfusion period (24 hours), animals were anesthetized in a halothane atmosphere, and blood samples (with and without anticoagulant) were collected from the abdominal aorta for biochemical assays. Immediately, both kidneys were removed: the left one was used for histopathological evaluation and the right one for biochemical analyses of oxidative stress markers.

Biochemical assays

Biochemical assays allowed determination of AKI biomarkers in blood and oxidative variables in blood and renal tissues. Serum was obtained from blood samples without anticoagulant, and creatinine, uric acid, and urea concentrations were assessed. Likewise, plasma obtained from blood samples with anticoagulant was used for MDA and SH group determinations. The right kidneys were homogenized using an Ultra-Turrax homogenizer in an ice bath and a suitable buffer solution according to the technique to be performed. Homogenized samples were stored at −20°C until use for MDA and SH group concentration determination and catalase (CAT) enzyme activity.

AKI biomarker determination

Serum creatinine, uric acid, and urea were measured using a corresponding reactive kit (Spinreact, Barcelona, España), and absorbance values were assessed at 492, 520 and 340 nm, respectively, in a spectrophotometer. The values are reported as mg/dL.

Oxidative variable determination

Thiobarbituric acid reactive substance determination

Determination of thiobarbituric acid reactive substance (TBARS) was carried out according to the Ohkawa technique [28]. Briefly, the reaction mixture (plasma or kidney homogenate) was treated with 0.2 mL sodium dodecyl sulfate (8.1%), 1.5 mL acetic acid (20%, pH 3.5), and 1.5 mL of aqueous thiobarbituric acid (0.8%) and heated to 95°C for 1 hour. To avoid production of additional peroxidates that can lead to errors in measurement, butylated hydroxytoluene (1 mmol/L) was added to the medium during heating. Then, the samples were cooled, and 5 mL of n-butanol:pyridine mixture (15:1 v/v) was added. The samples were shaken vigorously with the aid of a vortex and centrifuged at 4,000 rpm for 20 minutes. The resulting organic layer was removed, and its absorbance was measured at 534 nm in a spectrophotometer. An MDA bis(dimethyl acetal) standard curve was used to calculate TBARS level. MDA values are reported as nmol of MDA/mg protein. Protein concentrations were determined by the modified Lowry method [29].

Determination of sulfhydryl groups associated with proteins

For SH group determination [30], a 200 μL aliquot of each sample (plasma or kidney homogenate) was collected; and 600 μL tris-ethylenediamine tetraacetic acid buffer, pH 8.2 (20 mmol/L), 40 μL 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) (10 mmol/L), and 3.16 mL ethanol

(100%) were added. Treated samples were incubated for 15 to 20 minutes at room temperature and subsequently centrifuged at 3,000 rpm for 10 minutes. The supernatant absorbance was measured at 412 nm. A blank was prepared with DTNB, and total amount of SH was calculated using an 13,600 $cm^{-1}M^{-1}$ absorptivity and expressed in mmol/L.

Determination of catalase activity

For CAT activity assays, removal of H_2O_2 was monitored for 5 minutes in a spectrophotometer at 240 nm [31]. Then, 2.89 mL potassium phosphate buffer, pH 7.4 (50 mmol/L) was added to 10 μL of sample. The reaction was initiated with addition 0.1 mL of H_2O_2, reaching a final volume of 3.00 mL at 25°C. CAT activity was calculated using the molar extinction coefficient (43.6×10^{-3}) and expressed in IU/min/mg protein $\times 10^{-1}$.

Histological analysis

Left kidneys were sagittally sectioned through the hilum and fixed by immersion in 4% neutral buffered formalin. Subsequently, kidneys were prepared for paraffin embedding, and hematoxylin-eosin- and periodic acid-schiff-stained sections (3–5 μm thick) were obtained. Histological analysis was performed using a Zeiss Primo Star light microscope (Carl Zeiss, Oberkochen, Germany). Tubular damage was assessed in images (micrographs) from 10 renal cortex histological fields, captured at regular distances from the upper to the lower pole of each kidney. A Canon EOS 1000 D # 2 digital camera (Tokyo, Japan) was used at a magnification of 64×.

The condition of each tubule was evaluated and classified as 0 (without damage) or 1 (with irreversible damage) in each image. Detached necrotic cells and hyaline casts in tubular lumens were considered irreversible changes. The average value of tubular damage was calculated for each image, and the results are expressed as percentage of damaged histological fields per animal.

Statistical analyses

Data are expressed as mean ± standard error. Mann–Whitney *U* tests were used to compare biochemical variables among the groups, and Student's *t* tests were used to compare histological analysis of tubular damage. Differences were considered statistically significant at a P value < 0.05. All analyses were performed using STATISTICA software for Windows (Release 4.2; StatSoft, Inc., Tulsa, OK, USA). The dose/effect relationship analysis was carried out with the linear regression and correlation method using the Origin 8.0 program.

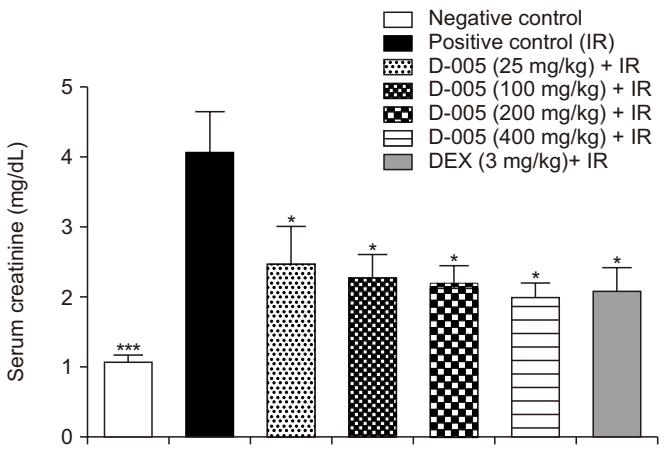

Figure 1. Effects of D-005 on serum creatinine concentrations in rats with IR-induced acute kidney injury. Data are presented as mean ± standard error. *P < 0.05, ***P < 0.001, compared to the positive control group (Mann–Whitney *U* test).
DEX, dexamethasone; IR, renal ischemia/reperfusion.

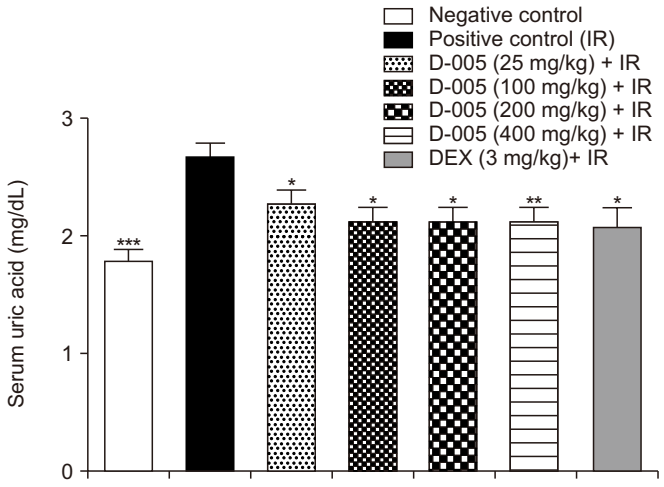

Figure 2. Effects of D-005 on serum uric acid concentration in rats with IR-induced acute kidney injury. Data are presented as mean ± standard error. *P < 0.05, **P < 0.01, ***P < 0.001, compared to the positive control group (Mann–Whitney *U* test).
DEX, dexamethasone; IR, renal ischemia/reperfusion.

Results

Effects of D-005 on AKI biomarkers

Fig. 1, 2, and 3 show the effects of single oral doses of D-005 on blood creatinine, uric acid, and urea concentrations, respectively. Induction of AKI by renal IR produced a significant increase of these markers in the positive control rats compared to the negative control rats. However, D-005 treatment at 25, 100, 200, or 400 mg/kg significantly decreased serum creatinine, uric acid, and urea concentrations compared to the positive control group. The dose/effect relationship study revealed a dose-dependent effect of D-005 on serum creatinine concentration (r = 0.998; P = 0.001); however, the other biomarkers were not significantly different among the groups. DEX, the reference substance, significantly prevented nitrogenous compound increase.

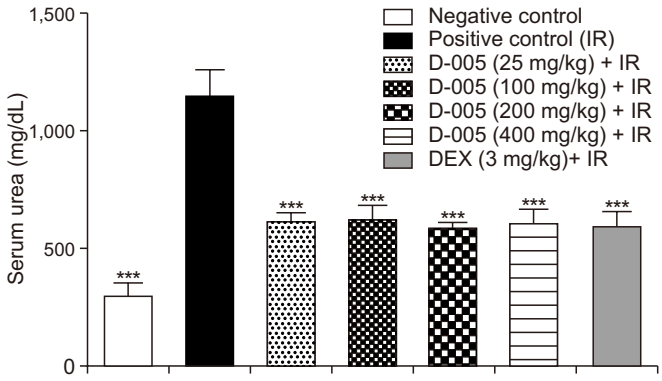

Figure 3. Effects of D-005 on serum urea concentration in rats with IR-induced acute kidney injury. Data are presented as mean ± standard error. ***P < 0.001, compared to the positive control group (Mann–Whitney U test).
DEX, dexamethasone; IR, renal ischemia/reperfusion.

Histological analysis

The normal structure of the renal parenchyma, including the renal cortex, was observed in negative control rats (Fig. 4A, B). The positive control group exhibited extensive areas of necrosis extending across the deepest cortex, showing occluded tubular lumens with detached necrotic cells and hyaline casts (Fig. 4C, D). Treatment with D-005 (25, 100, 200, or 400 mg/kg) and DEX prevented the characteristic morphological changes of tubular damage, mainly by decreasing accumulation of detached cells and casts in tubular lumens (Fig. 4E–J). Quantitative analysis showed the highest levels of tubular damage in the positive control group, while D-005 at all doses studied significantly decreased tubular damage. The highest inhibition percentage was achieved at 100 mg/kg D-005 (71.1%). The reference substance (DEX) also significantly decreased tubular damage in the renal cortex (Fig. 5).

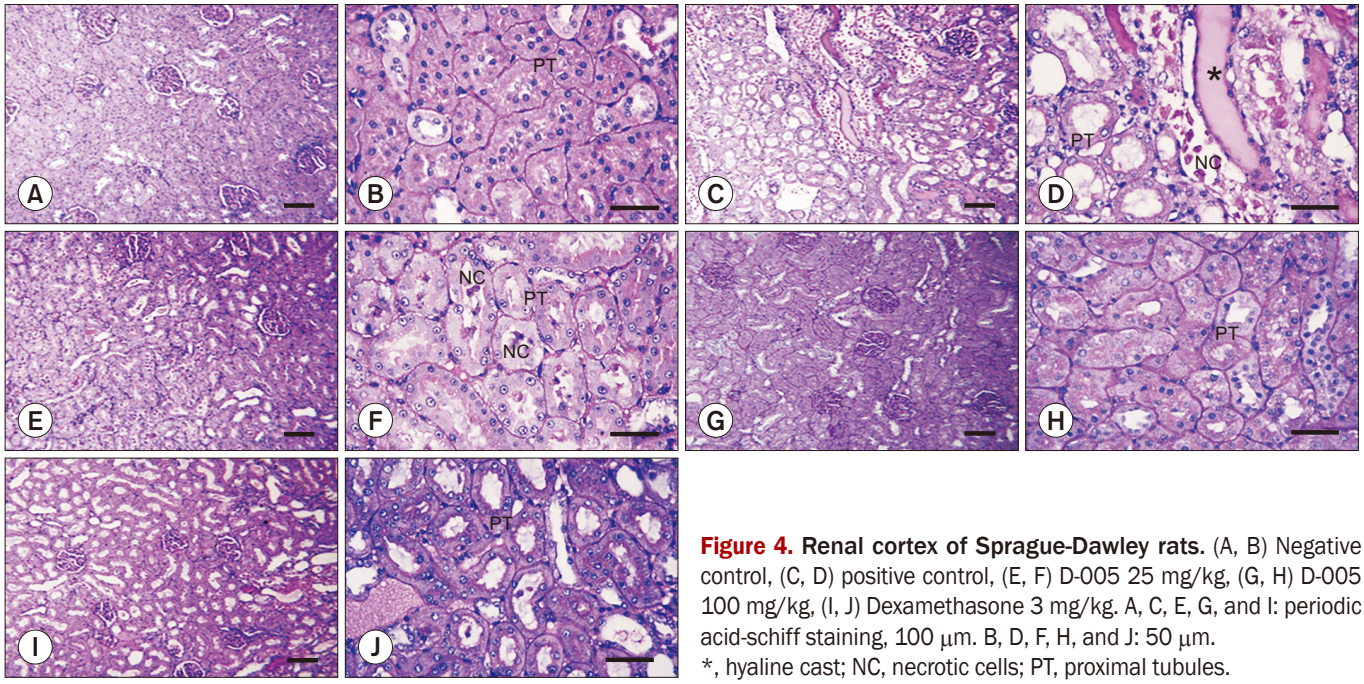

Figure 4. Renal cortex of Sprague-Dawley rats. (A, B) Negative control, (C, D) positive control, (E, F) D-005 25 mg/kg, (G, H) D-005 100 mg/kg, (I, J) Dexamethasone 3 mg/kg. A, C, E, G, and I: periodic acid-schiff staining, 100 μm. B, D, F, H, and J: 50 μm.
*, hyaline cast; NC, necrotic cells; PT, proximal tubules.

Effects of D-005 on oxidative stress variables

Positive control animals with renal IR damage demonstrated high levels of MDA and SH in plasma and kidney homogenates, as well as a decrease in CAT activity in kidney homogenates compared with the positive control group (Fig. 6–10). D-005 (25, 100, 200, or 400 mg/kg) significantly decreased the MDA and SH plasma values, showing the highest inhibition percentage in MDA (77.6%) at 400 mg/kg D-005 and total inhibition (100%) in SH at 200 mg/kg D-005. Meanwhile, DEX slightly decreased MDA plasma concentration and completely inhibited the increase of SH groups (Fig. 6, 7).

The results obtained in kidney homogenates were similar to those obtained in plasma since D-005 significantly decreased MDA and SH levels. The effect of D-005 on MDA plasma concentration was dose-dependent (r = 0.993; P = 0.006), demonstrating the highest inhibition (63.3%) at 400 mg/kg D-005, while 100% inhibition in SH groups was noted at the lowest dose tested (25 mg/kg D-005). DEX slightly decreased MDA level, although the

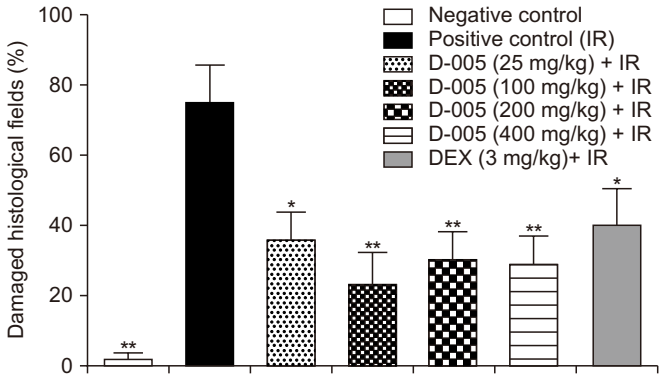

Figure 5. Effects of D-005 on tubular damage in rats with IR-induced acute kidney injury. Data are presented as mean ± standard error. *P < 0.05, **P < 0.01, compared to the positive control group (Student's t test).
DEX, dexamethasone; IR, renal ischemia/reperfusion.

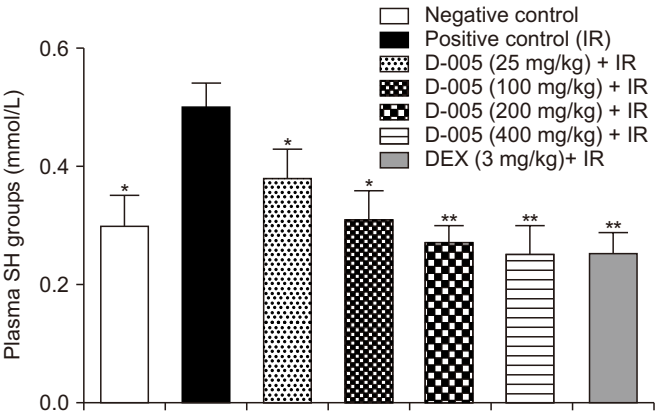

Figure 7. Effects of D-005 on plasma concentration of sulfhydryl (SH) groups. Data are presented as mean ± standard error. *P < 0.05, **P < 0.01, compared to the positive control group (Mann–Whitney U test).
DEX, dexamethasone; IR, renal ischemia/reperfusion.

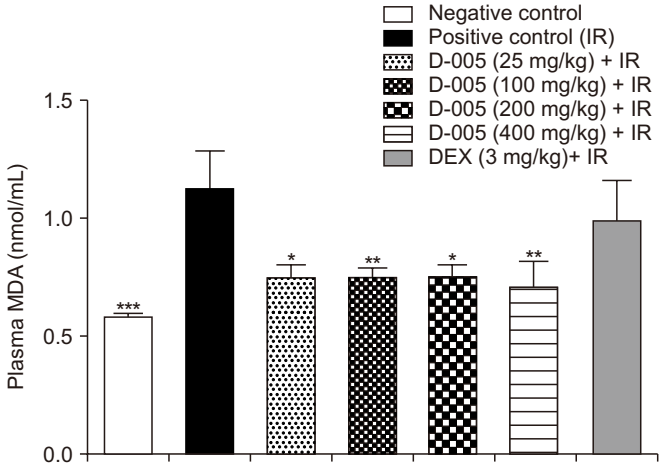

Figure 6. Effects of D-005 on plasma concentration of malondialdehyde (MDA) in rats with IR-induced acute kidney injury. Data are presented as mean ± standard error. *P <0.05, **P < 0.01, ***P < 0.001, compared to the positive control group (Mann–Whitney U test).
DEX, dexamethasone; IR, renal ischemia/reperfusion.

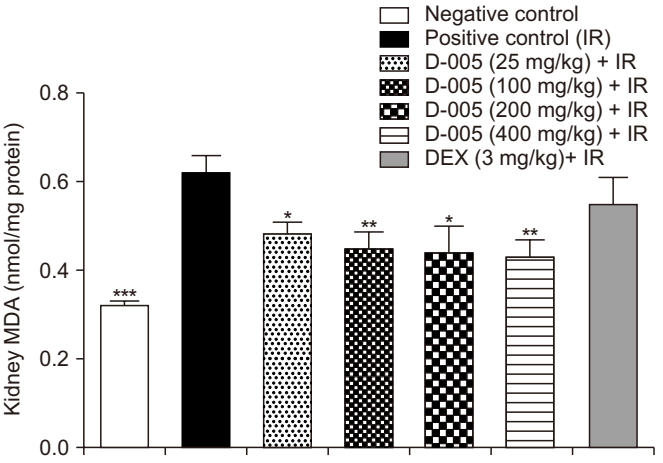

Figure 8. Effects of D-005 on malondialdehyde (MDA) concentration in rats with IR-induced acute kidney injury. Data are presented as mean ± standard error. *P < 0.05, **P < 0.01, ***P < 0.001, compared to the positive control group (Mann–Whitney U test).
DEX, dexamethasone; IR, renal ischemia/reperfusion.

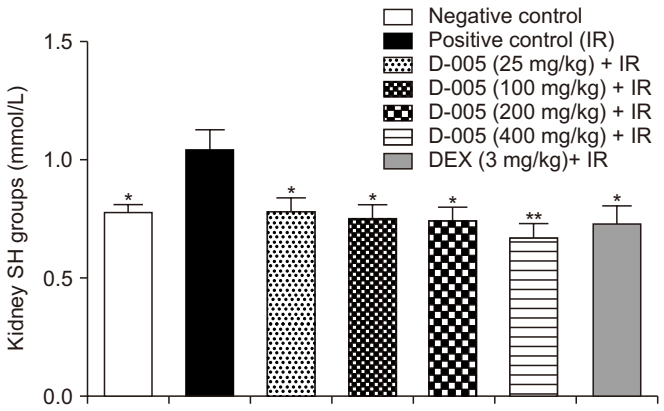

Figure 9. Effects of D-005 on sulfhydryl (SH) group concentration in rats with IR-induced acute kidney injury. Data are presented as mean ± standard error. *P < 0.05, **P < 0.01, compared to the positive control group (Mann–Whitney U test).
DEX, dexamethasone; IR, ischemia/reperfusion.

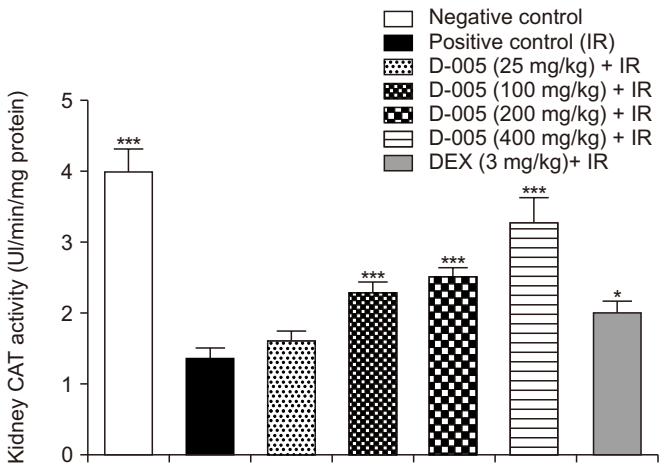

Figure 10. Effects of D-005 on catalase (CAT) activity in rats with IR-induced acute kidney injury. Data are presented as mean ± standard error. *P < 0.05, ***P < 0.001, compared to the positive control group (Mann–Whitney U test).
IR, ischemia/reperfusion.

change was not significant, while it produced 100% inhibition of the SH groups in plasma (Fig. 8, 9).

IR-induced AKI reduced renal CAT activity in the positive control group compared to the negative control group. D-005 significantly and dose-dependently restored CAT activity at 100 mg/kg D-005 (r = 0.975; P = 0.02), achieving the highest percentage (72.6%) at 400 mg/kg D-005. DEX also slightly restored CAT activity by 23.9% (Fig. 10).

Discussion

The results of this study demonstrated the protective effects of D-005 on IR-induced AKI in rats. The positive control group (with renal IR) presented biochemical and morphological changes in correspondence with that described previously in similar conditions [25,26]. Thus, high concentrations of creatinine, urea, and uric acid were demonstrated in these animals as a consequence of decrease in glomerular filtration rate during AKI, which leads to accumulation of nitrogenous waste in the blood [32]. The deep renal cortex is considered the most affected area of the kidney by renal IR, as was observed in the positive control group of this study. This has been attributed to the high susceptibility of the renal cortex to hypoxia, since it requires ample oxygen under physiological conditions [33].

The results of increased tubular damage in the positive control group agree with previous findings recognizing cast formation with resulting tubular occlusion due to proximal tubule injury [20]. Tubular epithelial cell death, both by necrosis and apoptosis, represents the main histopathological feature in renal IR. Consequently, loss of viability of these cells is considered the main cause of development and progression of AKI as a result of renal IR [34]. D-005 prevented glomerular filtration rate reduction as evidenced by the decrease in serum creatinine, uric acid, and urea concentrations. This renal parenchyma protection activity, especially on renal cortex proximal tubules, is consistent with previous findings [20]. However, a limitation of this study was that we did not characterize the minimum effective dose of D-005 on the tested clinical biochemistry variables.

The protection of tubular epithelial cells by D-005 has been identified as an important strategy to attenuate renal IR [35]. DEX, the reference substance, also restored the clinical biochemistry variables and protected renal tubules damaged by renal IR, consistent with previous reports [21,22]. The positive control group showed an increase in serum creatinine, which is considered the gold standard biomarker for AKI diagnosis and is associated with acute tubular necrosis. Since both DEX and D-005 prevented IR-induced AKI, the validity of this model and of the results obtained in our experimental conditions are demonstrated. During renal IR, reduced blood flow and glomerular filtration rate contribute to tubular damage, most likely by limiting the availability of oxygen and nu-

trients and facilitating oxidative stress [34]. This explains the increase of MDA and SH group concentrations in plasma and kidney homogenates, as well as the decline of renal CAT activity in the positive control group in this study.

The ROS increase in renal tissues during ischemia is due to the hypoxia state, which affects microcirculation, cellular enzymes, and mitochondrial function to trigger cell death pathways. In addition, ischemic injury activates production of pro-inflammatory cytokines, which also contribute to ROS formation by nicotinamide adenine dinucleotide phosphate oxidase and myeloperoxidase (MPO). Another possibility for ROS generation in this model is modification of nitric oxide synthase activity due to vascular dysfunction promoted by ischemia [12]. However, the source of ROS is found not only in the ischemic state, but also in the reperfusion period, since blood flow restoration and subsequent molecular oxygen reintroduction during this step exacerbate ROS formation and previous ischemic injury [36].

Due to the role of oxidative stress in IR-induced AKI, natural substances with antioxidant properties have shown protective results in animal models of renal IR [25,26]. Therefore, the beneficial effects of D-005 in this model could be linked, at least partially, to its antioxidant capacity by decreasing plasma and kidney MDA and SH groups and stimulating kidney CAT activity. Treatment with DEX protected against renal IR-induced oxidative damage by decreasing SH group concentrations and increasing CAT activity. However, DEX did not show any effects on lipid peroxidation increase (MDA) in blood or in kidney. In this sense, more complete antioxidant protection with D-005 is shown by acting on different targets relative to that obtained with DEX.

Oxidative stress and inflammation are closely interconnected in the pathophysiology of renal IR. The ischemic process activates LOX and COX pathways, resulting in endothelial leukocyte adhesion and activation and in vasoconstrictor prostaglandin production, respectively [37]. In light of these findings, other researchers have evaluated the effects of anti-inflammatory drugs in murine models of renal IR-induced AKI. Indomethacin improved renal function and reduced histological renal damage in mice by modulating the inflammatory response via COX inhibition [38]. Also, paricalcitol protected against ischemic damage by regulating COX-2 and prostaglandin E2 [39]. Therefore, the protective effect of D-005 on renal IR-induced AKI in the rat model could also be associated with dual inhibition of LOX and COX-2 enzymes [17]. Similarly, an extract obtained from the palm *Euterpe oleracea*, also belonging to the *Arecaceae* family, attenuated IR-induced AKI in rats due to its antioxidant and anti-inflammatory effects, since it was shown to decrease renal levels of MDA and MPO, which are markers of lipid peroxidation and inflammation, respectively [40].

The results described here demonstrate the protective effects of D-005 in AKI as measured by clinical biomarkers, histological changes in renal tissue, and oxidative variables. Overall, these results show that 100 mg/kg is the best dose for preventing renal injury under these experimental conditions. However, future studies must elucidate the mechanism by which D-005 exerts its nephron-protective effects in AKI induced by renal IR.

In conclusion, administration of single oral doses of D-005 markedly and significantly protected renal IR-induced AKI, which is most likely due to the antioxidant effects of D-005 extract.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

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Authors' contributions

Ambar Oyarzábal-Yera participated in protocol preparation, collection and analysis of data, manuscript preparation, and critical revision of the manuscript. Sandra Rodríguez-Salgueiro performed collection and analysis of data and preparation of draft manuscript. Nelson Merino-García participated in the analysis of data and accomplished a critical revision of the manuscript. Leyanis Ocaña-Nápoles participated in collection, analysis, and interpretation of data. Lucía González-Núñez carried out the interpretation of data, preparation and critical revision of the manuscript. Licet Mena-Valdés and Zullyt Zamora-Rodríguez participated in experimental

procedures and collection of data. Jose A. Medina-Pírez participated in experimental procedures and made the processing of histological samples. Sonia Jiménez-Despaigne participated in experimental procedures, made the processing of biochemical samples, and collection of data. Vivian Molina Cuevas has critically revised and approved the manuscript for submission.

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