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Effect of curcumin on acute chronic kidney disease due to ischemia-reperfusion syndrome*

Efeito da curcumina na doença renal crônica agudizada pela síndrome isquemia-reperfusão

Efecto de la curcumina en la enfermedad renal crónica agravada por el síndrome de isquemia-reperfusión

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ABSTRACT

Objective: To evaluate the effect of curcumin on renal function, hemodynamics, and renal oxidative profile of rats with chronic kidney disease (CKD) subjected to renal ischemia-reperfusion injury (IRI). **Methods:** Wistar rats, 250–300 g, distributed in four groups: Sham (n = 5), CKD simulation; CKD (n = 5), 5/6 renal ablation for CKD induction; CKD + IRI (n = 5), CKD and renal pedicle clamping for 30 minutes; and CKD + IRI+curcumin (n = 5), CKD + IRI, curcumin administration 30 mg/kg/day, orally, for 10 days. Renal function (inulin clearance, urine flow, plasma creatinine), hemodynamics (blood pressure), and oxidative profile (peroxides, TBARS, and urine nitrate, non-protein soluble thiols in renal tissue) were evaluated. **Results:** The CKD + IRI + curcumin group showed increased inulin clearance and reduced plasma creatinine, decreased RVR and increased RBF, decreased oxidative metabolites in urine and increased thiols in renal tissue when compared with the CKD + IRI group. **Conclusion:** The treatment with curcumin preserved renal function and hemodynamics of animals with acute CKD, improving oxidative profile, with reduction of oxidants and preservation of antioxidant reserve.

DESCRIPTORS

Renal Insufficiency, Chronic; Ischemia; Reperfusion; Curcumin.

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INTRODUCTION

Chronic kidney disease (CKD) consists of gradual, progressive, and irreversible loss of renal function at glomerular, tubular, and endocrine level[1]. Estimates suggest that 13.4% of the world population is affected by CKD and that approximately from 4.902 to 7.083 million people require renal replacement therapy[2]. The main causes of CKD are systemic arterial hypertension and diabetes mellitus. The diagnosis of the disease has severe implications in an individual's life, since it changes physical, psychological, and social spheres resulting from the syndrome itself and its treatment[3]. The CKD progression to stages dependent on renal replacement therapy is related to episodes of acute insults, such as reperfusion-ischemia injury (IRI) derived events, among others, from situations of hemodynamic instability and infections[3].

Clinically, CKD is found when, regardless of the cause, the glomerular filtration rate (GFR) is below 60 mL/min/1.73m^2, or when GFR is above 60 mL/min/1.73m^2 associated with albuminuria and glomerular hematuria sustained for three months[4] and normal GRF is greater than 90 mL/min/1.73m^2[1].

CKD is described as a risk factor for acute kidney injury (AKI), whereas AKI is considered a factor promoting the progression of CKD[5]. Ischemia and reperfusion injury (IRI) is one of the main causes of AKI[5]. IRI shows pathophysiological mechanisms, such as hemodynamic alteration, tubular dysfunction, inflammation, generation of reactive oxygen species, and lesion in epithelial cells and endothelium, which may evolve to renal injury and cell death, contributing to unfavorable chronicity evolution[5].

Despite the severity, AKI by IRI is considered reversible and can be prevented. Conventional treatment comprises measures to restore hemodynamic conditions, drug therapy to treat the primary cause of hypoperfusion or, in cases of local mechanical obstruction, interventional therapy by renal revascularization[6].

Drug therapy aims to reduce the inflammatory and oxidative process resulting from the IRI pathogenesis to restore hemodynamics and renal function. In this context, non-usual pharmacological therapies using plants and phytosupplements have already demonstrated antioxidant activity in IRI in experimental studies[6–7].

Curcumin, one of the isolated components of *Curcuma longa* L., a plant belonging to the Zingiberaceae family, distributed in tropical and subtropical regions of the world, has proven anti-inflammatory action and antioxidant action, due to containing natural polyphenol flavonoids isolated from rhizome. Even at low concentrations, curcumin has inhibited hemoglobin oxidation and reduced lipid peroxidation[8].

Studies show that curcumin reduces the release of inflammatory factors involved in AKI; however, the anti-inflammatory mechanism of curcumin is described as mediated by inhibition of expression of the enzyme inducible nitric oxide-synthase (iNOS) and cyclooxygenase (COX-2)[9]. Moreover, a study published in 2020 demonstrated that the antioxidant activity of curcumin was characterized by increased renal activities of superoxide dismutase (SOD) and catalase (CAT), confirming its indirect antioxidant effect[9].

This study aimed to evaluate the effect of curcumin on renal function, hemodynamics, and renal oxidative profile of CKD rats subjected to IRI, under the hypothesis that intervention with the phytodrug curcumin can prevent functional injury determined by IRI and attenuate CKD progression.

METHOD

Type of Study

This is a quantitative experimental study with animal model.

Animals

In the study, 20 male Wistar rats weighing 250–300 g were used, supplied by the Institute of Biomedical Sciences of the University of São Paulo (ICB-USP) and maintained with free access to water and feed, under thermal conditions with alternating day and night cycles.

Local

This study was developed at the Experimental Laboratory for Animal Model (LEMA) of the Escola de Enfermagem da Universidade de São Paulo.

Procedures

Induction of CKD – The animals were anesthetized with 10 mg/kg of xylazine (Anasedan, Vetbrands) and 90 mg/kg of ketamine (Dopalen, Ceva) intraperitoneal (IP) and submitted to the surgical technique of 5/6 renal ablation, which consists of laparotomy followed by right nephrectomy; surgical clamping of two branches of the left renal artery; and suture of the abdominal incision[10]. Curcumin administration: curcumin was administered for 10 days, from the 17th day of the experiment, at a 30 mg/kg/day dose, orally (P.O.), diluted in 0.5% in volume carboxymethylcellulose solution 0.5 mL/100 g[9]. *Induction of acute renal injury by IRI* – The animals were anesthetized, as described, and subjected to laparotomy for unilateral clamping of the renal pedicles for 30 minutes, with non-traumatic vascular clamps. The animals were then evaluated for anesthetic recovery and received analgesia in the postoperative period (Tramadol: 5 mg/kg, IP, 8/8 h, until the third postoperative day) (Figure 1)[7].

Experimental Groups

The animals were distributed in the following groups – Sham (n = 5): rats subjected to simulation of the surgical act of induction of the CKD model on the 1st day of the experiment; CKD (n = 5): rats subjected to the 5/6 renal ablation on the 1st day of the experimental protocol; CKD + IRI (n = 5): rats subjected to the 5/6 renal ablation on the 1st day of the experimental protocol and, on the 26th day, subjected to clamping of the residual renal pedicle for 30 minutes with non-traumatic vascular clamps; CKD + IRI + curcumin (n = 5): rats subjected to the 5/6 renal ablation on the 1st day of the experimental protocol who, on the 17th day of the experimental protocol, received curcumin 30 mg/kg/day, P.O. for 10 days, until the 27th day. On the 26th day, the renal pedicle was clamped for 30 minutes with non-traumatic vascular clamps.

Collection of Biological Samples

The experimental protocols lasted 28 days. On the 27th day, animals were placed in metabolic cages to measure the 24-hour urine volume and collect urine samples for renal function and oxidative stress studies. On the 28th day, the animals were anesthetized as previously described, subjected to procedures for renal function studies, followed by laparotomy for the collection of terminal blood by abdominal aortic puncture, promoting euthanasia, according to ethical standards for the handling of animals in a research laboratory[11]. The right kidney was removed and cooled at −80°C to measure non-protein thiols (Figure 1).

Evaluation of Renal Function

Renal function was evaluated by inulin clearance to estimate the glomerular filtration rate and to measure serum and urine creatinine. The animals were anesthetized, as aforementioned, for catheterization of the jugular vein and inulin infusion at an initial dose of 100 mg/kg, followed by continuous infusion of 10 mg/kg weight for 2 hours, at a speed of 0.04 mL/min. After 30 minutes, urine was collected every half hour by bladder catheterization, and blood samples were collected every 60 minutes, for analysis of inulin concentration by the Anthrone method, the results were expressed in mL/min/100 g[12–13]. The urine and serum creatinine dosage was determined by the Jaffé method and the results expressed in mg/dL[14].

Evaluation of Hemodynamics

The carotid artery was isolated and catheterized with a polyethylene tube to measure mean arterial pressure (MAP) and heart rate (HR)[13]. The left renal artery was isolated and surrounded by an ultrasonic probe to measure renal blood flow (RBF)[13]. Renal vascular resistance (RVR) is calculated using the equation: RVR = MAP/RBF[13].

Evaluation of Oxidative Profile

The oxidative profile was analyzed by measuring oxidative metabolites in a urine sample (peroxides, nitrate, and thiobarbituric acid reactive substances – TBARS) and indirect measurement of the antioxidant thiol reserve in renal tissue analyzed by colorimetric methods in spectrophotometer. The direct measurement of peroxides was performed by the ferrous oxidation-xylenol orange version 2 (FOX-2) and the results were expressed in nmol/gram urine creatinine[15]. Urine nitrate was quantified by the Griess method and the results were expressed in µmol/gram of urine creatinine[16]. The TBARS dosage in urine consisted of the reaction with thiobarbituric acid (0.6% pH 2) in the presence of trichloroacetic acid and the results expressed in nmol/gram of urine creatinine[17]. The quantification of non-protein soluble thiols in renal tissue was performed by the Ellman method and the results were expressed by thiol nmol/mg of total proteins[18].

Ethical Aspects

This quantitative study with animal model was approved by the Research Ethics Committee on the Use of Animals of the Faculdade de Medicina of the Universidade de São Paulo (CEUA – FMUSP) under registration No. 1276/2019. All procedures performed in this study are in accordance with the Ethical Principles of Animal Experimentation adopted by the Brazilian College of Animal Experimentation.

Statistical Analysis

Data are presented as mean value ± standard deviation. The statistical analysis of the results was performed by analysis of variance (ANOVA) and Tukey's multiple comparations as post-test in the statistical program Graph-Pad Prism version-3 for Windows®. The p-values <0.05 were considered significant.

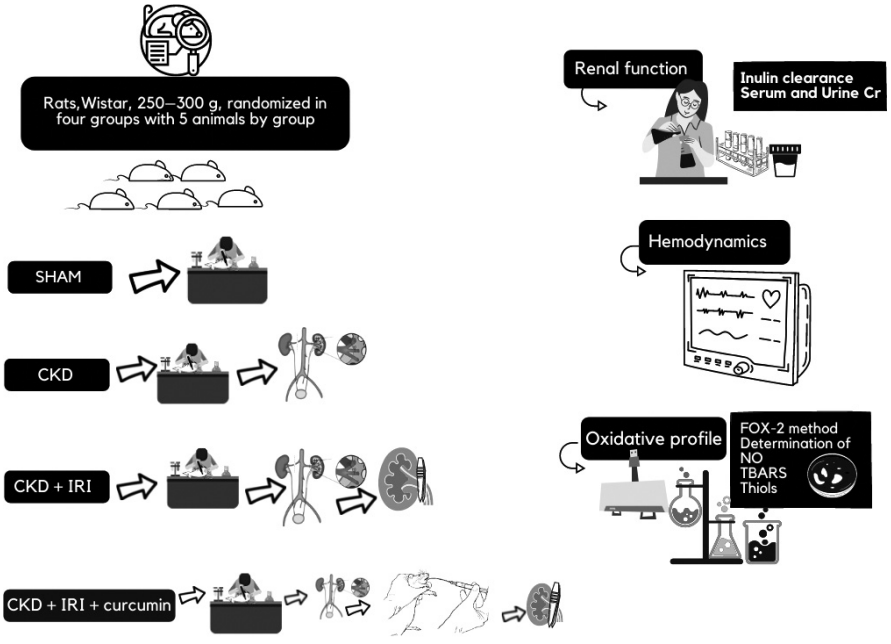

Figure 1 – Schematic design of experimental procedures. São Paulo, SP, Brazil, 2021.
Experimental Laboratory for Animal Models (LEMA) of the Faculdade de Enfermagem of the Universidade de São Paulo 2021.

RESULTS

Renal Function

Table 1 shows results of the evaluation of renal function, performed by the inulin clearance, urine flow, and serum creatinine.

We observed no significant differences between the groups in the pre-intervention period.

Serum creatinine was significantly elevated in the CKD, CKD + IRI, and CKD + IRI + curcumin groups compared with the Sham group. The CKD + IRI group showed an additional increase in this parameter when compared with the CKD group, whereas the CKD + IRI + curcumin group showed a reduction in serum creatinine compared with the CKD + I/R group.

All CKD groups showed significantly reduced inulin clearance when compared with the Sham group. The CKD+IRI group showed a significant reduction in inulin clearance compared with the CKD group, and once again, curcumin treatment in the CKD + IRI + curcumin group increased this parameter compared with the CKD + IRI group.

Global and Renal Hemodynamics

We evaluated global hemodynamics by HR and MAP values, and renal hemodynamics by verifying hemodynamic parameters of HR, MAP, RBF, and RVR (Table 2).

The different groups showed no significantly different values for HR and MAP parameters.

The RBF of the animals CKD, CKD + IRI, and CKD + IRI + curcumin decreased significantly when compared with the Sham group. The induction of IRI in the CKD + IRI group resulted in a significant additional decrease in the RBF compared with the CKD group. The CKD + IRI + curcumin group showed a significant increase in this parameter when compared with the CKD + IRI group.

The RVR of the CKD, CKD + IRI, and DRC + IRI + curcumin groups was significantly higher compared with the Sham group. This parameter increased significantly in the CKD + IRI group when compared with CKD. The CKD + IRI + curcumin group showed a reduction in RVR compared with the CKD + IRI group.

Oxidative Profile

Table 3 presents the oxidative profile evaluated by measuring urine peroxides, TBARS, urine nitrate, and thiols in renal tissue.

Urine peroxide excretion in the CKD+IRI and DRC + IRI + curcumin groups was significantly higher compared with the Sham group. The CKD + IRI group showed a significant increase in peroxides when compared with the

Table 1 – Renal function of Sham, CKD, CKD + IRI, and CKD + IRI + curcumin – São Paulo, SP, Brazil, 2019.

Group	n	Urine flow (mL/min)	Serum creatinine (mg/dL)	Inulin clearance (mL/min)
Sham	5	0.013 ± 0.003	0.20 ± 0.01	0.68 ± 0.05
CKD	5	0.015 ± 0.006	0.91 ± 0.37[a]	0.28 ± 0.06[a]
CKD + IRI	5	0.011 ± 0.002	1.96 ± 0.34[ab]	0.09 ± 0.04[ab]
CKD + IRI + curcumin	5	0.010 ± 0.003	0.96 ± 0.14[ac]	0.44 ± 0.09[abc]

[a]p < 0.05 *versus* Sham; [b]p < 0.05 *versus* CKD; [c]p < 0.05 *versus* CKD + IRI.

Table 2 – Renal hemodynamics of Sham, CKD, CKD + IRI, and CKD + IRI + curcumin – São Paulo, SP, Brazil, 2019.

Group	n	Heart rate (bpm)	Mean blood pressure (mmHg)	Renal blood flow (mL/min)	Renal vascular resistance (mmHg/mL/min)
Sham	5	464 ± 57	101 ± 12	9.28 ± 1.73	11.15 ± 1.62
CKD	5	447 ± 109	129 ± 23	6.13 ± 0.77[a]	20.30 ± 2.78[a]
CKD + IRI	5	523 ± 23	127 ± 22	2.21 ± 0.34[ab]	57.53 ± 7.79[ab]
CKD + IRI + curcumin	5	497 ± 30	117 ± 14	6.03 ± 0.87[ac]	19.69 ± 4.06[ac]

[a]p < 0.05 *versus* Sham; [b]p < 0.05 *versus* CKD; [c]p < 0.05 *versus* CKD + IRI.

Table 3 – Oxidative profile of Sham, CKD, CKD + IRI, and CKD + IRI + curcumin – São Paulo, SP, Brazil, 2019.

Group	n	Urine peroxides (nmol/g urine creatinine)	Lipid peroxidation (nmol/g urine creatinine)	Urine nitrate (µmol/g urine creatinine)	Thiols in renal tissue (nmol/mg of total proteins)
Sham	5	6.61 ± 2.08	0.009 ± 0.003	16.00 ± 5.25	15.74 ± 6.11
CKD	5	7.60 ± 1.90	0.010 ± 0.001	16.40 ± 5.78	11.10 ± 1.74
CKD + IRI	5	13.67 ± 1.48[ab]	0.055 ± 0.008[ab]	42.24 ± 7.09[ab]	6.75 ± 1.45[a]
CKD + IRI + curcumin	5	7.90 ± 1.30[ac]	0.026 ± 0.004[abc]	22.23 ± 8.66[c]	14.51 ± 1.01[c]

[a]p < 0.05 *versus* Sham; [b]p < 0.05 *versus* CKD; [c]p < 0.05 *versus* CKD + IRI.

CKD group, whereas the CKD + IRI + curcumin group showed a significant reduction in peroxide excretion compared with CKD + IRI. Urine TBARS were elevated in the CKD + IRI and DRC + IRI + curcumin groups compared with the Sham group. The IRI insult determined a significant additional elevation in this parameter compared with the CKD group. The CKD + IRI + curcumin group showed a significant reduction in lipid peroxidation compared with the CKD + IRI group. Urine nitrate excretion of the CKD + IRI group showed a significant increase when compared with Sham and CKD groups, whereas the CKD + IRI + curcumin group showed a significant reduction in this parameter compared with the CKD + IRI group.

On the other hand, regarding the endogenous antioxidant reserve, the measurement of thiols in renal tissue in the CKD + IRI group was significantly lower than in the Sham group, whereas CKD + IRI + curcumin was higher than the CKD group.

DISCUSSION

This study confirmed the success of reproducing the experimental model of acute CKD due to IRI, observed by changes in hemodynamic function and renal oxidation. Treatment with curcumin demonstrated a protective effect of function on the mentioned parameters.

CKD is characterized by progressive syndromic reduction of glomerular filtration due to the deterioration of biochemical and physiological functions[19]. The 5/6 renal ablation drastically reduces the glomerular filtration rate and induces CKD[20]. The technique performed by unilateral right nephrectomy and surgical clamping of two branches of the left renal artery results in renal functional impairment, increased kidney weight, and renal hemodynamic alteration[21–22].

The abrupt reduction in the number of nephrons by 5/6 nephrectomy initially promotes an AKI. At this stage, a compensatory phase is detected with increased urine flow by an adaptive glomerular hyperfiltration mechanism that, if maintained, stimulates the production of renin and results in glomerular hypertension, segmental lesion with progressive glomerulosclerosis, and deterioration of renal function[22].

The impairment of renal function evidenced in this study by the decrease of inulin clearance, the glomerular hypertension observed with increased RVR, and the reduction of RBF observed in the animals of the CKD group compared with Sham proved the effectiveness of reproduction of the experimental model for CKD adopted in this study.

The IRI consists of a reversible and sublethal lesion in epithelial and endothelial cells, which contributes significantly to renal tubular dysfunction, with consequent water retention, which culminates in an even more significant decrease in urine flow when CKD is present[23–24].

Both CKD and IRI induce a reduction in glomerular filtration rate, a change that this study shows by changes in serum creatinine and inulin clearance. An important marker for the clinical diagnosis of renal dysfunction is serum creatinine, an endogenous substance whose elevation demonstrates impaired renal function, whereas inulin, an exogenous substance, is a marker considered the gold standard for the experimental determination of glomerular filtration rate[13,25]. In this study, CKD animals showed increased serum creatinine and reduced inulin clearance. When subjected to IRI, serum creatinine had an additional increase accompanied by an exacerbated reduction in inulin clearance.

Partial nephrectomy, renal transplantation, hypovolemia, infections, hypotension, hypertension, renal artery angioplasty, and aortic aneurysm surgery are the mos common causes of reduction of RBF in renal IRI[26–27]. The IRI causes tissue damage during ischemia and after reestablishing blood flow, at reperfusion, exacerbating tissue damage due to reactive oxygen species (ROSs)[6,27].

Curcumin, an active pigment found in *Curcuma longa*, is chemically considered a flavonoid, acting mainly as an electron donor, which gives it an antioxidant activity[28]. The cardioprotective activity of curcumin was demonstrated in *in vivo* and *in vitro* models of myocardial IRI to be associated with the activation of the cell survival protein, SIRT1, resulting in preservation of mitochondrial function by maintaining the redox potential with activation of the endogenous antioxidant enzyme, superoxide dismutase, and decreasing hydrogen peroxide formation[29]. Supplementation with curcumin in rats subjected to coronary IRI resulted in improved functional performance, antiapoptotic effect and antioxidant activity[30].

The study of an IRI model in rats has already demonstrated efficacy of curcumin treatment, with improvement in renal function, associated with decreased inflammatory and apoptotic markers, in addition to ROSs reduction directly and indirectly by inducing antioxidant enzymes[31].

Corroborating the results of the cited studies, this study reaffirms the beneficial effects of pretreatment with this food supplement on renal IRI and highlights its therapeutic role in the presence of CKD, with possible attenuation of its progression.

This study confirmed the beneficial effect of curcumin on CKD + IRI with improved renal function, demonstrated by increased inulin clearance; recovery of renal hemodynamics, demonstrated by increased blood flow and reduction in renal vascular resistance; and tendency of redox rebalancing by reduction of oxidative metabolites (urine peroxides, TBARS, and urine nitrate) accompanied by maintenance of the antioxidant thiol reserve in renal tissue, especially in the CKD + IRI + curcumin group.

Considering that IRI is reversible and treatable, experimental studies that allow isolating non-observable characteristics in humans and correlating with conditions found in clinical practice stimulate the development of studies aimed at the proposition of therapeutic protocols. The outcomes of this study provide elements on pathophysiological mechanisms of CKD and IRI and highlight the beneficial role of curcumin in protecting against the IRI effects, contributing to reduce the morbidity of CKD.

CONCLUSION

The treatment with curcumin preserved the renal function and hemodynamics of animals with CKD subjected to the IRI insult, improving oxidative profile with reduction of oxidants and preservation of antioxidant reserve.

RESUMO

Objetivo: Avaliar o efeito da curcumina na função renal, hemodinâmica e perfil oxidativo renal de ratos com doença renal crônica (DRC) submetidos a isquemia-reperfusão renal (I/R). **Métodos:** Ratos Wistar, 250–300 g, distribuídos em quatro grupos: *Sham (n = 5)*, simulação da DRC; *DRC (n = 5)*, ablação de 5/6 dos rins para indução de DRC; *DRC + I/R (n = 5)*, DRC e clampeamento do pedículo renal por 30 minutos; DRC + I/R + curcumina *(n = 5)* e DRC + I/R, administração de curcumina 30 mg/kg/dia, via oral, por 10 dias. Foram avaliadas a função renal (*clearance* de inulina, fluxo urinário, creatinina plasmática), hemodinâmica (pressão arterial) e perfil oxidativo (peróxidos, TBARS e nitrato urinário, tióis solúveis não proteicos no tecido renal). **Resultados:** O grupo DRC + I/R + curcumina apresentou elevação do *clearance* de inulina e redução da creatinina plasmática, diminuição da RVR e aumento do FSR, diminuição de metabólitos oxidativos na urina e aumento dos tióis no tecido renal quando comparado ao grupo DRC + I/R. **Conclusão:** O tratamento com curcumina preservou a função e hemodinâmica renal dos animais com DRC agudizada, promovendo melhora no perfil oxidativo, com redução de oxidantes e preservação de reserva antioxidante.

DESCRITORES

Insuficiência Renal Crônica; Isquemia; Reperfusão; Curcumina.

RESUMEN

Objetivo: Evaluar el efecto de la curcumina sobre la función renal, hemodinámica y el perfil oxidativo renal en ratas con enfermedad renal crónica (ERC) sometidas a isquemia-reperfusión renal (I/R). **Métodos:** Ratas Wistar, entre 250–300 g, divididas en cuatro grupos: *Sham (n = 5)*, simulación de ERC; *ERC (n = 5)*, ablación de 5/6 de los riñones para inducción de ERC; *ERC + I/R (n = 5)*, ERC y pinzamiento del pedículo renal durante 30 minutos; y ERC + I/R + curcumina *(n = 5)* y ERC + I/R, administración de curcumina 30 mg/kg/día, vía oral, durante 10 días. Se evaluaron la función renal (*clearance* de inulina, flujo urinario, creatinina plasmática), hemodinámica (presión arterial) y el perfil oxidativo (peróxidos, TBARS y nitrato urinario, tioles solubles no proteicos en tejido renal). **Resultados:** El grupo ERC + I/R + curcumina tuvo un aumento en el *clearance* de inulina y disminución de creatinina plasmática, disminución de la RVR y aumento del FSR, disminución de metabolitos oxidativos en orina y aumento de tioles en el tejido renal en comparación con el grupo ERC + I/R. **Conclusión:** El tratamiento con curcumina preservó la función renal y la hemodinámica de los animales con ERC agravada, promoviendo una mejora en el perfil oxidativo, con reducción de oxidantes y preservación de la reserva antioxidante.

DESCRIPTORES

Insuficiencia Renal Crónica; Isquemia; Reperfusión; Curcumina.

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