ORIGINAL ARTICLE

The effect of low-dose Cordyceps on ischemia-reperfusion injury of the kidney in rats

El efecto de dosis bajas de Cordyceps en la lesión por isquemia-reperfusión del riñón en ratas

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Abstract

Objective: *None of studies have been conducted in terms of demonstrating the same effect with the low dose in cordycepin. In our study, we analyzed the histopathological and biochemical changes of low-dose Cordycepin(c) on a rat model in the kidney.* **Materials and methods:** *Twenty-four male Wistar Albino rats were randomly allocated to three groups (n = 8): the sham-control group (Group 1), the renal I/R-untreated (Group 2) group, and the I/R-C-treated (Group 3) group. Cordyceps was administered intraperitoneally at 5 mg/kg twice. Renal histological changes were compared and the relevant parameters of oxidative stress and inflammation were detected.* **Results:** *In blood and tissue biochemistry, it was observed that IL-1 Beta, IL 6, TNF alpha, MDA, TOS, and OSI increased in Group 2 and decreased in Group 3. It was determined that TAS values were increased in Group 3, and decreased in Group 2. In the histopathological evaluation, while Group 1 was evaluated as normal, significant kidney damage was detected in Group 2. It was determined that there was a significant decrease in kidney damage in Group 3.* **Conclusion:** *These results suggest that low dose Cordycepin was as effective as normal dose on renal ischemic reperfusion and reduction of damage.*

Keywords: *Cordyceps. Ischemia-reperfusion injury. Kidney.*

Resumen

Objetivo: *Ninguno de los estudios se ha realizado en términos de demostrar el mismo efecto con la dosis baja de cordicepina. En nuestro estudio, analizamos los cambios histopatológicos y bioquímicos de Cordycepin(c) en dosis bajas en un modelo de rata con isquemia-reperfusión (I/R) inducida en el riñón.* **Materiales y métodos:** *Veinticuatro ratas macho Wistar Albino se asignaron al azar a tres grupos (n = 8): el grupo de control simulado (Grupo 1), el grupo sin tratamiento I/R renal (Grupo 2) y el grupo tratado con I/R-C (Grupo 3). Cordyceps se administró por vía intraperitoneal a 5 mg/kg dos veces. Se compararon los cambios histológicos renales y se detectaron los parámetros relevantes de estrés oxidativo e inflamación.* **Resultados:** *En bioquímica sanguínea y tisular se observó que IL-1 Beta, IL 6, TNF alfa, MDA, TOS y OSI aumentaron en el Grupo 2 y disminuyeron en el Grupo 3. Se determinó que los valores de TAS aumentaron en el Grupo 3, y disminuyó en el Grupo 2. En la evaluación histopatológica, mientras que el Grupo 1 fue evaluado como normal, se detectó daño renal significativo en el Grupo 2. Se determinó que hubo una disminución significativa del daño renal en el grupo 3.* **Conclusión:** *Estos resultados sugieren que la cordicepina en dosis bajas fue tan efectiva como la dosis normal en la reperfusión isquémica renal y la reducción del daño.*

Palabras clave: *Cordyceps. Lesión por isquemia-reperfusión. Riñón.*

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Introduction

One of the most important causes of acute kidney injury (AKI) is the exposure of the kidney to Ischemia-reperfusion (I/R). In clinical practice, AKI may occur in conditions such as systemic hypotension, hypovolemia, cardiac arrest, renovascular surgery, cross-clamping of the aorta, partial nephrectomy, and kidney transplantation[1,2]. Renal ischemia in AKI causes damage and death of kidney cells, but damage may remain in the renal tissue despite reperfusion. The loss of nephrons in the kidney after this damage is significant for the kidney[3,4]. Since short-term ischemia arising after the transplant of a kidney from a living body or a cadaver is correlated with renal transplant rejection and chronic allograft nephropathy, it also gains critical importance for I/R tissue in clinical follow-up[5,6].

After experimental I/R, cytokines such as tumor necrosis factor alpha (TNF-α), IL-1β, and IL-6, which are accepted as inflammatory mediators, are secreted, and these are considered as determinants in the I/R process[7]. In addition, TAS, TOS, and OSI parameters were used to evaluate the total antioxidant capacity in I/R[8].

Cordycepin, which has been used as a medicine for 300 years in China, is an adenosine analog derived from the *Cordycepin militaris* culture and has been reported as a nucleoside antibiotic for the first time[9]. Recently, the importance of Cordycepin in the treatment of various diseases has been increasing due to its different pharmacological effects. Cordycepin has been proven by many studies to be a potent antioxidant and anti-inflammatory agent[10,11]. Moreover, immunomodulatory, antitumor, antiprotease, antimicrobial, hypolipidemic, hypoglycemic, analgesic, and protective effects of Cordycepin on various organs have been reported. Cordycepin has been reported to exert its anti-inflammatory and analgesic effects through inhibition of IL-1*β*, IL-6, TNF-*α*, NF*κ*B, iNOS, and COX-2[9]. These effects are very significant in preventing organ damage after renal I/R. However, some side effects have been observed when used in high doses[12]. Therefore, in our study, we aimed to analyze the histopathological and biochemical changes of intraperitoneally administered low-dose *Cordycepin* in the kidney I/R model created in rats.

Materials and methods

For our study, the decision was made by Dicle University Prof Dr Sabahattin Payzın Health Science Research and Application Center's experimental animals local ethics committee with the protocol number 2021/12. The study was carried out in Dicle University Experimental Study laboratory. 24 male Wistar Albino rats, each weighing 200-250 g, were used in the study. The animals included in the study were randomly divided into three groups. Rats were fed a standard rodent diet and water under appropriate temperature and light conditions.

Preparation, anesthesia, and surgical procedures

General anesthesia was maintained by intramuscular administration of 5-10 mg/kg of Xylazine (Rompun Vet; Bayer AG, Istanbul, Turkey) and 50-70 mg/kg of ketamine hydrochloride (Ketalar; Eczacıbaşı, Istanbul, Turkey) before surgery. The abdomen was cleaned with 10% Povidone-iodine solution after 100 U/kg heparin (intraperitoneal) administration to prevent renal artery thrombosis. The abdomens of the rats were entered with a midline incision. After right nephrectomy, the left renal artery was found to induce I/R, and operations were performed according to the groups.

- Group I (Sham group) (n = 8): All animals underwent left nephrectomy 6 h after right nephrectomy.
- Group II (n = 8): After right nephrectomy, a non-traumatic vessel clamp was placed on the left renal artery for 60 min. Then, the clamp was opened, and the left kidney underwent reperfusion for 6 h. Physiological saline was administered intraperitoneally twice, 30 min after ischemia and just before reperfusion.
- Group III (n = 8): Following the right nephrectomy, a non-traumatic vessel clamp was placed on the left renal artery for 60 min and then reperfusion was applied for 6 h. A total of 5 mg/kg of Cordyceps was administered intraperitoneally twice, 30 min after ischemia and just before reperfusion.

In each stage of the experiment, the animal was prevented from suffering with general anesthesia. No animal perished whereas the experiment was being executed. After 6 h of reperfusion, all rats were sacrificed with high-dose anesthetic agent. The collected blood and a part of each kidney were prepared for the biochemistry laboratory for the biochemical variables IL1, IL6, TNF alpha, total oxidant activity (TOA), and total antioxidant activity (TAA), and the remaining tissue was prepared for the pathology laboratory for histochemical examination.

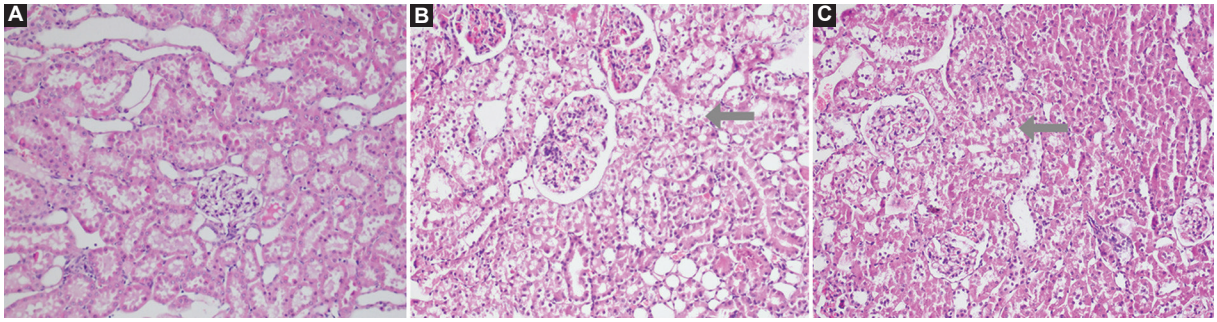

Figure 1. *Representative kidney sections stained with H&E at the end of 6 h' reperfusion.* **A:** *sham-control animals; normal histological characteristic of glomeruli and tubules.* **B:** *rats subjected to renal I/R injury; marked vacuolar changes in tubular epithelium and loss of tubular epithelial cells.* **C:** *rats subjected to renal I/R injury, pretreated with cordycepin: decreased vacuolization of tubule epithelium (H&E, ×200). I/R: Ischemia/reperfusion.*

Biochemical examination

The blood samples obtained were stored in ice and delivered to the Biochemistry Laboratory right after the cardiac puncture. Blood samples were centrifuged at 3000/min for 3 min, serum samples were separated, and IL-6, IL-1β, MDA, TNF-α, TAS, and TOS levels were measured.

The data obtained for tissue biochemistry were processed into a pre-prepared form.

Tissue pieces weighing 0.10-0.22 g were washed with physiological saline several times and dried thoroughly with blotting paper, then placed in Eppendorf tubes and stored at −85 C until the day of examination. The tissues were taken from the freezer and thawed, and then homogenized with an automatic tissue homogenizer when all samplings were completed. IL-6, IL-1β, MDA, TNF-α, TAS, and TOS levels were measured from the collected kidney tissue and blood.

Histopathological examination

Tissue pieces separated for histopathological examination were fixed in 10% formaldehyde solution. Samples that were followed up after fixation were blocked with paraffin. Standard sections with a thickness of 4 μ were prepared for microscopic examination by staining with Hematoxylin-Eosin (HE). All preparations were examined by the same pathologist. Based on the scoring used by Chatterje et al.[13] Scoring was evaluated as Grade 0: no diagnostic change, Grade 1: tubular cell swelling, loss of brush borders, nuclear reduction with up to 1/3 of the tubular profile with nuclear loss, Grade 2: in addition to Grade 1, greater nuclear reduction with up to 2/3 of the tubular profile with nuclear loss, and Grade 3: greater nuclear reduction with more than 2/3 of the tubular profile with nuclear loss.

Statistical analysis

The data were statistically analyzed with SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kruskal-Wallis test was used to compare multiple independent samples. When a significant difference was detected, two independent samples were evaluated by a Mann-Whitney U-test for paired in-group comparison. $p \leq 0.05$ for overall comparisons and $p = 0.017$ for the Bonferroni Corrected Mann-Whitney U test was considered statistically significant.

Results

In blood biochemistry, it was observed that IL-1 Beta, IL 6 TOS, TNF alpha, MDA, and OSI increased in Group 2 and decreased in Group 3. In the comparison between the groups, a statistically significant decrease was observed in IL-1 Beta, IL6, TNF alpha, and OSI values when Group 2 and Group 3 were compared ($p < 0.05$).

In tissue biochemistry, it was observed that IL-1 beta, IL 6, TNF alpha, MDA, TOS, and OSI increased in Group 2 and decreased in Group 3. A statistically significant decrease was determined in IL-1 Beta, IL6, TOS, and OSi values when Group 2 and Group 3 were compared ($p < 0.05$) (Table 1).

Blood and tissue

TAS values increased in Group 1 and Group 3, and decreased in Group 2. In the comparison between the groups, a statistically significant increase was observed

Table 1. Tissue parameters

Groups	IL-β	IL-6	TNF-α	MDA	TAS	TOS	OSİ
Group 1 (S)	551.12 ± 50.7	34.47 ± 2.50	67.02 ± 12.82	8.80 ± 2.24	1.07 ± 0.15	49.15 ± 12.3	45.85 ± 12.1
Group 2 (I/R)	643.50 ± 67.4	38.65 ± 2.75	77.24 ± 12.02	13.89 ± 2.52	0.80 ± 0.09	75.72 ± 11.8	94.42 ± 18.6
Group 3 (C)	554.30 ± 18.9	34.74 ± 2.33	69.06 ± 10.3	12.55 ± 1.45	1.07 ± 0.17	55.68 ± 6.48	52.57 ± 10.8
p	0.002	0.018	0.180	0.178	0.009	0.004	0.003

Meaningful comparison (intergroup) 2-3. C: cordycepin, IL-1β (pg/mL): ınterleukin-1 beta, IL-6 (pg/mL): ınterleukin-6, I/R: ıschemia/reperfusion, MDA (μM): malondialdehyde, OSİ (TOS/TAS): oxidative stress index, S: Sham, TAS (μm Toroxequiv./L): total antioxidant status, TNF-α (ng/L): tumor necrosis factor-alpha, TOS (μm H_2O_2 equiv./L): total oxidative stress

Table 2. Blood parameters

Groups	IL-1β	IL-6	TNF	MDA	TAS	TOS	OSİ
Group 1 (S)	659.94 ± 85.1	59.18 ± 11.9	128.75 ± 23.9	20.15 ± 2.65	0.57 ± 0.18	38.78 ± 3.37	71.71 ± 15.9
Group 2 (I/R)	908.32 ± 99.4	76.08 ± 10.6	209.35 ± 86.4	22.52 ± 3.83	0.39 ± 0.07	40.21 ± 2.76	104.14 ± 18.8
Group 3 (C)	752.15 ± 86.8	66.08 ± 3.61	144.39 ± 28.9	20.86 ± 2.65	0.56 ± 0.19	34.15 ± 7.46	64.57 ± 18.4
p	0.013	0.025	0.025	0.33	0.025	0.142	0.003

Meaningful comparison (intergroup) 2-3. C: Cordycepin, IL-1β (pg/mL): ınterleukin-1 beta; IL-6 (pg/mL): ınterleukin-6, I/R: ıschemia/reperfusion, MDA (μM): malondialdehyde, OSİ (TOS/TAS): oxidative stress index, S: Sham, TAS (μm Toroxequiv./L): total antioxidant status, TNF-α (ng/L): tumor necrosis factor-alpha, TOS (μm H_2O_2 equiv./L): total oxidative stress.

between Group 2 and Group 3 ($p < 0.05$). All biochemical parameters are summarized in table 2.

While no change was detected in Group 1 in the histopathological evaluation, it was observed that six kidneys in Group 2 had Grade 2 and two kidneys had Grade 3 cell and nuclei deterioration (Fig. 1). It was determined that there was a significant decrease in kidney damage in Group 3, which was given Cordycepin, Grade 1 in 6 kidneys, Grade 2 in one kidney and Grade 3 in one kidney. A statistically significant difference was observed when Groups 2 and 3 were compared ($p = 0.007$). Detailed analysis of the findings is summarized in table 3.

Table 3. Histopathological parameters of the all groups

Groups	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Total (%)
Group 1 (S)	8 (100)	0	0	0	8 (100)
Group 2 (I/R)	0	0	6 (75)	2 (25)	8 (100)
Group 3 (C)	0	6 (75)	1 (12.5)	1 (12.5)	8 (100)

Meaningful comparison p = 0.000 (Group 1 vs. 2 and Group 1 vs. 3), p = 0.013 (Group 2 vs. 3). Grade 0: No diagnostic change, Grade 1: tubular cell swelling, loss of brush borders, nuclear reduction with up to 1/3 of the tubular profile with nuclear loss, Grade 2: in addition to Grade 1, greater nuclear reduction with up to 2/3 of the tubular profile with nuclear loss, Grade 3: greater nuclear reduction with more than 2/3 of warm ischemia/reperfusion injury and promotes hepatocyte proliferation. C: Cordycepin, I/R: ıschemia/reperfusion, S: Sham

Discussion

Despite surgical, medical, and pharmacological advances regarding renal vascular injuries, serious problems remain regarding the consequences of short-term I/R after renal vascular surgery, trauma, and transplant[14]. Free oxygen radicals, which are released in large amounts in the ischemic process, occur when they are reperfused, and much more tissue damage occurs[15,16]. Oxidative stress, which plays a role in the pathogenesis of I/R, appears as damage to organs due to an uncontrolled increase in reactive oxygen species (ROS) or a decrease in elimination. Significant damage occurs in the kidney tubules and glomeruli as a result of increased ROS and pro-inflammatory mediators with reperfusion occurring after the ischemic phase[17,18].

Antioxidant capacity and antioxidant agents are used for the treatment of excessive production of free oxygen radicals due to cellular response after renal I/R[19]. In this study, we investigated the histopathological and biochemical parameters of kidney I/R on a rat model of low dose of Cordycepin[10,11], which has been proven by many studies due to its different pharmacological effects such as antioxidant, anti-inflammatory fibrinolytic, antiapoptotic, antioxidant, antimicrobial,

immunomodulator, nephroprotective, and hepatoprotective and has become increasingly important in the treatment of various diseases.

TNF Alpha, IL1B, and MDA are rapidly released after tissue damage and considered as I/R markers[20]. In addition to these, it has been observed that IL6 is also increased as a pro-inflammatory marker in I/R[21]. TAS value is widely used in the determination of total antioxidant capacity, and OSI is a parameter that shows the affinity of oxidant and antioxidants in the oxidant-antioxidant balance[22,23]. Studies have demonstrated that when an anti-inflammatory substance is used, TAS can increase, and its oxidative values are suppressed by decreasing TOS and OSI values[8]. MDA lipid peroxidation, which is also accepted as a broad marker of oxidative stress, occurs as the final production of the enzyme and has been evaluated from many I/R developments[20]. In our study, it was observed that IL-1 Beta, IL 6 TOS, TNF alpha, MDA, TOS, and OSI increased in Group 2 and decreased in Group 3 in biochemistry. In the comparison between the groups, a statistically significant decrease was found in IL-1 Beta, IL6, TNF alpha, TOS, and OSI values when Group 2 and Group 3 were compared ($p < 0.05$). Again, in the biochemical evaluation, the TAS value was increased in Group 1, Group 3, and decreased in Group 2. In the comparison between groups, rat studies were conducted between Group 2 and Group 3, and in these studies, it was determined that cordycepin given orally in different doses on rat kidneys decreased pro-inflammatory cytokine secretion, inflammatory reaction, decreased oxidative stress and was pathologically beneficial[24].

In another study of rats, 10 mg/kg dose of Cordycepin was found to be beneficial on histological and oxidative stress parameters in the group[25]. With such benefits of Cordycepin, it has been reported that severe stomach and diarrhea symptoms occur in high-dose use[12]. Although there is no dose-dependent study in these patients, no side effects were noted in the studies of drugs given 10 mg. The aim of our study is to demonstrate that lower doses can have the same effect and to reduce the possible side effects of high-dose drug use. When we evaluate all these, we see that administering 5 mg/kg intraperitoneally shows the same protective effect as those at higher doses; however, this will become clear with the sharing of larger studies.

As a result, it is observed that low dose cordycepin is a highly nephroprotective agent against renal I/R when given intraperitoneally in diseases that cause I/R in a short time such as organ transplantation, trauma, and sepsis. In this study, it was demonstrated that the nephroprotective effect of cordycepin could be even at half the dose, and the possible side effects of the drug given overdose were reduced depending on the dose, however, different studies comparing more doses are needed for this result.

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Conflicts of interest

The authors report no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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