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Reno-Protective Effects of 6-Shogaol on Kidney Tissue in Cecal Ligation and Puncture-Induced Polymicrobial Sepsis Rat Model

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Abstract: Sepsis is a life-threatening syndrome that may lead to multiple organ dysfunction with high mortality. A deformation or puncture in the intestinal barrier plays an important role in sepsis-induced multiple organ failure. The protective effects of 6-Shogaol (6-SHO) on renal injury caused by cecal ligation and puncture (CLP) was investigated. Experimental animals were divided into 4 groups and planned as follows; sham, CLP, CLP+DMSO, and CLP+6-SHO. In CLP + 6-SHO group, 20 mg/kg 6-SHO was administered intraperitoneally before the CLP model. The levels of antioxidant molecules (total antioxidant status (TAS) and superoxide dismutase (SOD)), oxidant molecules (total oxidant status (TOS), malondialdehyde (MDA) and myeloperoxidase (MPO)) and proinflammatory cytokines (tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β)) were measured by homogenizing in collected kidney tissues. Statistical analyzes were performed via ANOVA. In CLP groups, antioxidant molecule levels decreased while oxidant molecule values elevated. Similarly, proinflammatory cytokine levels were found high in CLP groups. In CLP+6-SHO group, oxidant molecules, MPO, and proinflammatory cytokine levels diminished, and antioxidant molecules increased. 6-SHO application has been shown to be effective against oxidative renal injury caused by the CLP-induced polymicrobial sepsis model.

Keywords: 6-Shogaol, Cecal ligation and puncture, Inflammation, Kidney, Oxidative stress.

Çekal Ligasyon ve Delmeye Bağlı Polimikrobiyal Sepsis Sıçan Modelinde 6-Shogaol'ün Böbrek Dokusu Üzerine Renoprotektif Etkileri

Öz: Sepsis, yüksek mortalite ile çoklu organ disfonksiyonuna ilerleyebilen hayatı tehdit eden bir sendromdur. Bağırsak bariyerinde gerçekleşen bir deformasyon veya delinme sepsise bağlı çoklu organ yetmezliğinde önemli bir rol oynar. 6-Shogaol'ün (6-SHO) çekal ligasyon ve delmeye (CLD) bağlı böbrek hasarındaki koruyucu etkileri araştırıldı. Deney hayvanları 4 gruba ayrıldı ve şu şekilde planlandı; sham, CLD, CLD + DMSO ve CLD + 6-SHO. CLD + 6-SHO grubunda, CLD'den önce 6-SHO enjekte edildi (20 mg/kg, intraperitoneal). Toplanan böbrek dokuları homojenize edilerek antioksidan moleküller (total antioksidan kapasite (TAS) ve süperoksit dismütaz (SOD)), oksidan moleküller (total oksidan kapasite (TOS), malondialdehit (MDA) ve myeloperoksidaz (MPO)) ve pro-inflamatuar sitokinlerin (tümör nekroz faktör-α (TNF-α) ve interlökin-1β (IL-1β)) düzeyleri ölçüldü. İstatistiksel analizler ANOVA ile yapıldı. CLD gruplarında antioksidan moleküller; seviyeleri azalırken oksidan molekülerin seviyeleri yükseldi. Benzer şekilde pro-inflamatuar sitokin seviyeleri de CLD gruplarında yüksek bulundu. 6-SHO ile tedavi edilen grupta oksidan moleküllerin ve proinflamatuar sitokin seviyelerinin azaldığı ve antioksidan moleküllerin seviyeleri yüksek bulundu. 6-SHO uygulamasının CLD ile indüklenen polimikrobiyal sepsis modeli tarafından üretilen oksidatif böbrek hasarına karşı etkili olduğunu gösterilmiştir.

Anahtar Kelimeler: 6-Shogaol, Böbrek, Çekal ligasyon ve delme, İnflamasyon, Oksidatif stres.

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INTRODUCTION

Sepsis is a common health condition worldwide, and infections underlie the etiology. With a 30 million annual number, it is a frequent complication resulting from infection, trauma, shock, and various illnesses (1). In half of the patients that survive after sepsis, in long-term, psychological and physiological effects of sepsis remain (2). Acute kidney injury (AKI) causes a sudden decline in renal function within hours or days. Often severe infections are among the most common causes of AKI (3). Various developments were achieved about enlightening sepsis mechanism, but it is still hard to treat its complications (4). Antioxidant systems prevent oxidative damage in tissues generated by oxidant mechanisms leading to lipid peroxidation (5). Reactive oxygen species (ROS) can decrease glutathione (GSH) and superoxide dismutase (SOD) (6). Lipid peroxides, ROS, malondialdehyde (MDA), reactive nitrogen species, and several oxidative products constitute total oxidant status (TOS) (7). TOS and Total antioxidant status (TAS) indicate the oxidation and antioxidation balance. TAS is a summary of entire antioxidant activity but TOS is restricted via ROS reflection (8). Cecal ligation and puncture (CLP)-induced sepsis is a common experimental method used in the sepsis model (9). Some proinflammatory cytokine levels increase in the CLP-induced sepsis model (10). Myeloperoxidase (MPO) is released by neutrophils (11) and it indicates neutrophil infiltration.

Ginger (*Zingiber officinale* var. Roscoe) has been preferred in traditional herbal medicine for centuries. Shogaol is a main class of gingerol derivates. 6-Shogaol (6-SHO) has several properties such as anti-inflammatory (12), antioxidative (13), and neuroprotective (14) activities. 6-SHO mitigates neuroinflammatory and cognitive deficits (15). Here, it was planned to examine the effects of 6-SHO against CLP-induced polymicrobial sepsis in rats.

MATERIALS and METHODS

Laboratory Conditions and Drugs

The present study was carried out in Atatürk University Experimental Animal Research and Application Center. It has also been approved (Protocol number: 07.11.2019-204) by Atatürk University Experimental Animals Local Ethics Committee. All rats were kept in a laboratory environment a 12-night/12-day, with a humidity of 55% and a mean temperature of 21 degrees. The experimental animals were given standard pellet feed and tap water. However, all rats were starved 12 hours prior to the experiment. Ketamine (Pfizer, Turkey), Xylazine (Bayer, Turkey) were used during sacrification. 6-SHO and Dimethyl sulfoxide (DMSO) were supplied by Sigma-Aldrich Co, USA.

Experimental Animals and Experimental Design

For the current experiment, 24 healthy Sprague Dawley male rats (230-260 gr) were randomly assigned to 4 groups (n=6). All experimental procedures were performed under ketamine-xylazine (50-10 mg/kg) anesthesia conditions. The anesthetic dose was preferred from a previous study (16). In all groups, the abdominal regions were disinfected with povidone-iodine after being shaved. Analgesic lidocaine solution was applied to the suture areas in order to prevent pain stress to remove the error margin. The rats in the sham group (group I) had a 2 cm incision at the abdominal area to reach the peritoneum, and it was closed with a 3.0 silk suture without any procedure. The rats in the CLP group (group II) had their cecum isolated after reaching their peritoneum through a 2 cm incision. Following that, the ileocecal valve was ligated up to 2 cm distally and pierced by an 18-gauge needle (4 holes). After all, the cecum was placed back, and the abdomen was closed with a 3.0 silk suture. The rats of the CLP+DMSO group (group III) were applied 0.3 ml DMSO (3.6% DMSO in saline) intraperitoneally (i.p.) (17) 30 minutes before the CLP model application as described in group II. The rats of CLP+6-Shogaol (SHO 20 mg/kg, group IV) were

administered at the dose of 6-SHO 20 mg/kg i.p. (17) 30 minutes before the same CLP model in the CLP group. In all groups, the abdominal regions were washed with povidone-iodine after being shaved. Analgesic lidocaine solution was applied to the suture areas to prevent pain stress of the rats to remove the error margin. As postoperatively, the rats had no food but were free to reach water for 18 hours until they were sacrificed.

Biochemical Analysis

Renal tissue specimens, 100 mg weighing each, was subjected to homogenization with 2 mL of phosphate buffer solution (PBS). Following the homogenization (5000 rpm, +4°C, and 20 minutes), the supernatants were put into microcentrifuge tubes and run at -80°C. The compound occurring due to the reaction of MDA with thiobarbituric acid forms the principle of MDA measurement (18). TAS and TOS values were determined using ELISA kits (Rel Assay Diagnostics, Turkey). Oxidative stress index (OSI), TOS to TAS ratio, was gauged as: OSI= [(TOS, µmol H_2O_2 eq/L) / (TAS, mmol trolox eq/L)X10].

OSI indicates oxidative stress. It has been proposed that OSI may demonstrate oxidative status more correctly than TOS (19). MPO activity measurement is based on the reaction of MPO and o-dianisidine (20). Formazan dye levels are used on superoxide dismutase (SOD) enzyme measurement (21). Determination of TNF-α and IL-1β levels was done according to the manufacturer's instructions (Elabscience, China).

Statistical Analyses

Firstly, one-way ANOVA test was chosen for the biochemical data, and then Duncan test for multiple comparisons. The results were given as Mean ± Standard Deviation (SD). Statistical significance level was considered when p-value below 0.05.

RESULTS

Biochemical Parameters Results

In kidney tissues TOS and OSI values increased while TAS values decreased in CLP and CLP+DMSO groups compared to the sham group. However, it has been observed that TAS value increased, but TOS and OSI values significantly reduced due to SHO 20 mg/kg treatment (Table 1).

When the CLP and CLP+DMSO groups compared to the sham group, SOD level decreased, while MPO, MDA levels increased. When the SHO 20 group compared to the CLP and CLP+DMSO groups, SOD values increased, but MPO, and MDA levels decreased (Table 2).

Table 1. Effects of SHO treatment on TAS, TOS and OSI levels in CLP-induced kidney injury.
Tablo 1. CLP ile indüklenen böbrek hasarında SHO tedavisinin TAS, TOS ve OSI düzeyleri üzerine etkileri.

Parameters/Groups	TAS (mmol/mg)	TOS (µmol/mg)	OSI (arbitrary unit)
Sham	234.56 ± 23.43	95.25 ± 10.33	0.04 ± 0.00
CLP	133.06 ± 9.34*	177.11 ± 8.10*	0.13 ± 0.01*
CLP+DMSO	137.73 ± 7.44*	179.31 ± 6.87*	0.13 ± 0.01*
SHO 20mg/kg	216.10 ± 20.80#	95.37 ± 7.74#	0.04 ± 0.00#

TAS; Total antioxidant status, TOS; Total oxidant status, OSI; Oxidative Stress Index. All data were presented as mean±SD. *P<0.05 compared to sham group. #P<0.05 compared to CLP group and CLP+DMSO group.

Table 2. Effects of SHO treatment on SOD, MPO and MDA levels in CLP-induced kidney injury.
Tablo 2. CLP kaynaklı böbrek hasarında SHO tedavisinin SOD, MPO ve MDA düzeyleri üzerindeki etkileri.

Parameters/Groups	SOD (U/mg protein)	MPO (U/g protein)	MDA (µmol/g protein)
Sham	2.09 ± 0.08	5.44 ± 0.77	0.21 ± 0.02
CLP	0.91 ± 0.04*	10.47 ± 0.72*	1.07 ± 0.09*
CLP+DMSO	0.85 ± 0.05*	10.53 ± 1.26*	1.23 ± 0.10*
SHO 20mg/kg	2.07 ± 0.20#	5.91 ± 0.50#	0.31 ± 0.04#

SOD; Superoxide dismutase, MPO; Myeloperoxidase, MDA: Malondialdehyde. All data were presented as mean±SD. *p < 0.05 compared to sham group. #p< 0.05 compared to CLP group and CLP+DMSO group.

Results of Pro-inflammatory Cytokines

In CLP and CLP+DMSO treated groups, there was a significant increase in proinflammatory mediators (tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β)) as compared with the sham group. The 6-SHO 20 mg/kg group showed marked improvement with a significant decrease in these parameters compared with CLP and CLP+DMSO groups (Figure 1).

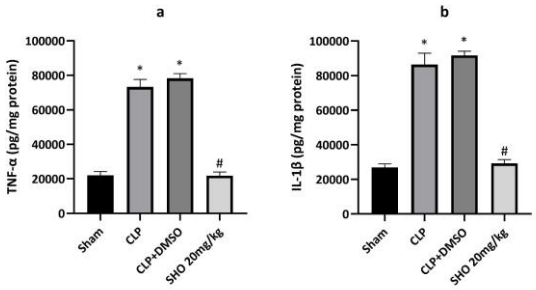

Figure 1. The results of proinflammatory cytokines (a)TNF-α and (b) IL-1β levels in CLP-induced kidney injury. All data were presented as mean±SD. *P<0.001 compared to the sham group. #P<0.001 compared to the CLP and CLP+DMSO groups.
Şekil 1. CLP'nin neden olduğu böbrek hasarında pro-inflamatuvar sitokinlerin (a) TNF-a ve (b) IL-1β düzeylerinin sonuçları. Tüm veriler ortalama ± SD olarak sunuldu. *P<0.001 sham gruba kıyasla. #P<0.001, CLP ve CLP+DMSO gruplarına kıyasla.

DISCUSSION and CONCLUSION

Sepsis occurs as an answer to infections, but it damages the organism and leads to organ failure and even death (22). About half of the whole acute kidney injuries (AKI) arise from systemic infections (23). Following AKI, various organ damages exist, resulting in multiple organ dysfunction syndrome (MODS). Infection based AKI fatality constitutes about 70% of all AKI related deaths, and this is higher than the other reasons (24). Current therapeutic approaches are confined to early antibiotic administration and supportive care due to the absence of therapies specific to microvascular dysfunction (25). In addition, antioxidants and anti-inflammatory molecules regulate inflammation and tissue damage caused by sepsis (26). CLP is a common experimental model in sepsis research (27).

Excessive proinflammatory cytokine formation triggers sepsis, which ends up with organ injury and even death (28). ROS is a keystone in sepsis-related hemodynamic corruption and organ failure. It induces cytotoxicity in organs and causes changes in cell signal pathways (29). ROS initiates a series of the reaction of chemicals (such as cytokines and chemokines) (30) and could cause damage to renal tubular epithelial cells (31). In the renal tissues of the current study, while TAS and SOD levels decreased, the levels of TOS and MDA were found to be high in sepsis model created with CLP. The deterioration of the balance between this oxidant/antioxidant systems in the kidneys enhances the damage. 6-SHO elevated the level of antioxidant molecules while decreasing the activity of oxidant molecules. 6-SHO increases the expression of nuclear factor (erythroid-derived 2)-like 2 (Nrf2), which regulates the expression of antioxidant enzymes (32). Nrf2 induces the expression of a number of genes such as glutathione-S-transferase, HO-1, and NADPH kinin oxidoreductase 1 (33). In this study, 6-SHO increased SOD expression while inhibiting MDA formation. In addition, changes in TAS and TOS levels may be associated with Nrf2 (34). From this point of view, the protective effects of 6-SHO on kidney damage may be related to the recovery of antioxidative enzyme levels through activation of Nrf2.

Many factors stimulate nuclear factor kappa B (NF-κB) activation, such as cytokines, growth factors, pharmaceuticals, bacterial products, viral infections, and oxidative stress (35). Neutrophils in infection and distant areas contribute to organ damage in sepsis by producing reactive products and proinflammatory cytokines (36). Neutrophils can also be an essential source for NF-κB-dependent cytokines (TNF-α, IL-1β, and IL-6) and chemokines (37). The neutrophils release reactive oxygen intermediates (ROI) such as MPO with strong oxidant activity. MPO is secreted from neutrophils during severe sepsis. It reveals antibacterial effect and increases the neutrophil

levels (38). A relationship was observed between MPO expression and infection level in a previous study (9). Current results represent that 6-SHO administration may be a potential renoprotective agent against sepsis-induced renal injury through decreasing MPO levels. Detrimental situations, including sepsis, result in the production of IL-1, TNF-α, and many other cytokines by neutrophils (10,39). IL-1β, TNF-α, IL-6, and other various members of proinflammatory cytokines play a role in the formation of septic clinic table (40). In a sepsis-induced lung injury, TNF-α and IL-1β levels increased in the polymicrobial sepsis group (41). In the current study, proinflammatory cytokine levels increased due to CLP induction, but 6-SHO treatment has been shown to be effective in alleviating tissue inflammatory response. The molecular mechanism underlying the renoprotective effects of 6-SHO appears to be related to the inhibition of NF-κB activity. This suggests that 6-SHO can prevent sepsis-induced kidney damage.

In conclusion, 6-SHO prevented kidney injury resulting from CLP-induced sepsis. It may be why 6-SHO declines sepsis-associated renal injury is 6-SHO alleviates oxidative injury and inflammation. However, further microbial and histological studies are required to state these effects clearly.

Conflict of interest

The authors declare that they have no conflict of interest.

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