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The Possible Useful Effectiveness of Sinapic Acid on Sepsis-Induced Secondary Organ Damage in Rats

Ayhan Tanyeli[1], Fazile Nur Ekinci Akdemir[2], Ersen Eraslan[3], Mustafa Can Guler[1], Saime Ozbek Sebin[1], Selim Comakli[4], Ilhami Gulcin[5]

[1] Atatürk University, Faculty of Medicine, Department of Physiology, Erzurum, Türkiye.
[2] Ağrı İbrahim Çeçen University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Ağrı, Türkiye.
[3] Bozok University, Faculty of Medicine, Department of Physiology, Yozgat, Türkiye.
[4] Atatürk University, Faculty of Veterinary, Department of Patology, Erzurum, Türkiye.
[5] Atatürk University, Faculty of Science, Department of Chemistry, Erzurum, Türkiye.

Correspondence Author: Fazile Nur Ekinci Akdemir
E-mail: fazilenur@yandex.com
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ABSTRACT

Objectives: In this study, we investigated the possible useful effectiveness of Sinapic acid on rat kidney and lung tissues in an experimental cecal ligation puncture (CLP) model.

Methods: CLP model was created for the rats in the CLP group. 20 mg/kg of Sinapic acid was given in the CLP-Sinapic acid group. At the end of the experiment, lung and kidney tissues were collected and biochemical analyzes were evaluated.

Results: For the lung and kidney tissue samples; antioxidant levels decreased, and oxidant levels increased in the CLP group. When the immunohistochemical parameters were evaluated, IL-1β, caspase-3, and TNF-α immunopositivity were severe levels in CLP group. But immunopositivity of these parameters have been observed as attenuated in CLP-Sinapic acid group compared to CLP group.

Conclusion: The results of our study showed that Sinapic acid has useful effectiveness on the sepsis model caused by CLP in the lung and kidney tissues.

Keywords: Cecal ligation puncture, sinapic acid, lung, kidney, rat.

1. INTRODUCTION

Sepsis, a systemic inflammatory response to infection, is a life-threatening health problem (1). Surgery or surgical operations are accepted as one of the most common reasons of sepsis (2). The cecal ligation and puncture (CLP) sepsis model is considered to be the most striking experimental procedure for sepsis-related studies because it is reasonable, repeatable and applicable (3). CLP results in widespread peritonitis leading to contamination of the abdominal area and initiation of the systemic inflammatory response and even sepsis (4). The pathophysiology of sepsis is important for diagnosis, prognosis, and determination of appropriate treatment. Sepsis causes many different physiopathological processes. Basically, free oxygen radicals create damage causing denaturation in cellular proteins, injury to DNA, and peroxidation in membrane lipids (5, 6). Under normal physiological conditions, small amounts of free oxygen radicals have an important function in on cellular activity protecting. However, when the concentrations of these free radicals increased, this leads to fatal damage in the cell (7, 8). Some studies have shown the positive results of antioxidant agents which were applied to relieve the effects of free oxygen radicals in experimental sepsis models (9, 10). The incidence of sepsis-related organ failure is variable due to the definition criteria of organ failure. Respiratory insufficiency is accepted as one of the organ deficiencies at the early stage of sepsis and also, acute renal failure is a common cause of sepsis and worsening prognosis. In addition, coagulopathy, liver, central nervous system and gastrointestinal system pathologies are other situations that can be seen frequently and increase mortality (11, 12).

Phenolic compounds in foods originate from one of the main classes of secondary plant metabolites (13). They act as an antioxidant and protect living plants, and nutrients from oxidative rancidity at a low concentration (14). Sinapic acid (SA) is a hydroxycinnamic acid-derived polyphenol with 3,5-dimethoxy and 4-hydroxyl replacements in the phenyl group of cinnamic acid. SA can be completely acquired from various vegetables, rye and fruits, and it has strong antioxidant, anti-hyperglycemic and anti-inflammatory effects as in vitro and in vivo studies (15-18). Hitherto, it has been proved that SA has protective properties against oxidative damage in a

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large number of experimental animal studies by using different models (17-19). It has not been found any experimental study which researches the effects of SA on kidney and lung in animal experiments with abdominal sepsis. For this purpose, we planned this study to evaluate the effects of SA on lung and kidney in the CLP-induced sepsis model.

2. METHODS

2.1. Laboratory Conditions and Drugs

This study was carried out in Atatürk University Experimental Animal Research and Application Center. University Experimental Animals Local Ethics Committee (27.04.2018-103) has approved the study All rats were kept in a laboratory environment a 12-night/12-day, with a humidity of 55% and a mean temperature of 21 ^{o}C. The experimental animals were fed with standard pellet feed and tap water. However, all rats were starved before 12 hours from the experiment., but free to reach water. Ketamin (Ketalar®, Pfizer, Istanbul), Xylazin (Rompun®, Bayer, Istanbul), and SA (Sigma-Aldrich Co, USA) were used during the experiment.

2.2. Groups and Experimental Model

In this study, 24 Wistar albino male rats (weighing 200±10 g) were used and divided into 3 groups. In the sham-operated group (n=8), anesthesia was applied with a 60/10 mg/kg ketamine/xylazine mixture (20). After the anesthesia, rats' abdomen was shaved, and a vertical midline incision was made in the abdomen through skin and facia, then it was closed with no CLP model. In the CLP group (n=8), a midline laparotomy was done. The cecum was brought outside the body. The cecal ligation was applied to the rats and two through-and-through punctures were made on the antimesenteric face of the cecum with an 18-gauge needle and thus, CLP-induced polymicrobial sepsis model was established. The cecum was replaced into the abdominal cavity and the abdominal incision was closed via 3-0 silk thread. 1% lidocaine solution was applied on the wound for analgesia to the animals. In the CLP+SA group, in addition to the CLP model, 20 mg/kg single dose intraperitoneal (i.p.) SA was given. In this study, the preferred effective dose of SA was selected from the previous studies (21, 22). In the 18th hour after the application of CLP, rats were sacrificed under high dose (23) anaesthesia. Then, the kidney and lung tissues were removed. Tissue samples were stored at – 80 ° C.

2.3. Biochemical Analysis of Kidney and Lung Tissues

After the kidney and lung tissue samples have been homogenized, all biochemical analyses were made for the homogenized tissues. Malondialdehyde (MDA) levels were measured according to the method presented by Ohkawa et. al, to define the lipid peroxidation status (24). The results were given as µmol/g protein. It was analyzed using the superoxide dismutase (SOD) activity specification protocol detected by Sun et al (25). Superoxide dismutase (SOD) activity results in tissue samples were given as U/mg protein. Myeloperoxidase (MPO) activity was measured using a method improved by Bradley et al (26). The results of MPO activity on tissues were presented as U/g protein. Total oxidant status (TOS) measurement was made with the commercially available kit (Rel Assay Diagnostics, Product Code: RL024). Total antioxidant status (TAS) value was evaluated with the commercial kit (Rel Assay Diagnostics, Product Code: RL0017). TAS and TOS results were presented as nmol/L. The ratio of TOS to TAS was accepted as the oxidative stress index (OSI). OSI value was detected as follows: OSI=[(TOS, µmol H_2O_2 equivalent/L)/(TAS, mmol Trolox equivalent/L)×10] (27, 28).

2.4. Immunohistochemical Staining

Detection of kidney and lung tissues from euthanized rats was carried out in neutral formaldehyde solution for 1 day and formaldehyde was removed by washing with tap water. The tissues were blocked in the paraffin through the routine alcohol-xylol follow-up process. After the deparaffinization of the tissues on the polylysine lam, they were kept in 3% H_2O_2 for 10 min to inactivate endogenous peroxidase activity and they were washed in PBS. Later, the samples were stored in antigen retrieval solution for 10 min at 500W to remove antigens and they were washed in PBS again. Sodium citrate buffer (Santa Cruz Biotechnology, Cat. No: sc-294091, 10 mM, pH 6.0) was used as antigen retival solution. Protein block solution was added to prevent nonspecific binding and washed in PBS. Cleaved caspase-3 (Novus Biological, Cat. No: NB600-1235, Dilution:1/100), tumor necrosis factor-alpha (TNF-α) (Novus Biological, Cat. No: NBP1-19532, Dilution:1/100), and interleukin-1 beta (IL-1β) (Bioss, Cat. No: bs-0812R, Dilution:1/100) were applied to the sections as primer antibodies and washed with phosphate buffer solution (PBS). Finally, it was followed the procedure described by the expose mouse and rabbit specific HRP/DAB detection IHC kit (Abcam: ab80436). 3,3'-diaminobenzidine chromogen was used, and contrast stained with hematoxylin. Immunopositivity was examined at 20x magnification in the light microscope according to the severity of positive staining.

2.5. Statistical Analysis

The results obtained from the experiments were given as mean ± standard deviation. *P-values* below 0.05 were considered statistically significant. The comparisons between groups were done according to One-Way ANOVA and Bonferroni test. In the immunohistochemical study, the immunopositivity observed in the kidney and lung tissues were evaluated as severe immunopositivity +++, moderate immunopositivity ++, mild immunopositivity +, and negativity – (29, 30). The Kruskal Wallis test was used to determine the difference among the groups, and the Mann-Whitney U test was used for identification of the groups that produced the differences

3. RESULTS

3.1. Biochemical Results of Kidney and Lung Tissues

The results of this research obviously showed that CLP caused an important increase in the levels of TOS, MDA, OSI values, and MPO activities compared with the Sham group on kidney and lung tissues (*P-values*<0.05) (see Table 1). On the other hand, it was detected that these parameters significantly decreased in the group treated by SA compared with the CLP group (*P-values*<0.05). However, treatment with SA caused significant changes on kidney and lung tissues. TAS values and SOD activities were compared in all groups. TAS values and SOD activities increased due to treatment with SA in comparison with untreated CLP group (see Table 1).

Table 1. *Efficacy of Sinapic acid on kidney and lung, total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI) in sepsis induced by cecal ligation puncture (CLP) in rats.*

		Sham-operated	CLP	CLP-Sinapic acid
Lung	**TAS** (mmol Trolox equivalent / L)	0.61 ± 0.05^{a}	$0.25 \pm 0.01^{a,b}$	0.56 ± 0.06^{b}
	TOS (µmol H_2O_2 equivalent / L)	6.25 ± 0.69^{a}	$8.11 \pm 0.32^{a,b}$	$6.59 \pm 0.42^{a,b}$
	OSI	1.02 ± 0.15^{a}	3.26 ± 0.28^{b}	1.18 ± 0.15^{b}
Kidney	**TAS** (mmol Trolox equivalent / L)	2.12 ± 0.21^{a}	$1.17 \pm 0.17^{a,b}$	2.09 ± 0.20^{b}
	TOS (µmol H_2O_2 equivalent / L)	5.80 ± 0.48^{a}	$7.43 \pm 0.78^{a,b}$	$5.84 \pm 0.53^{a,b}$
	OSI	0.27 ± 0.03^{a}	0.63 ± 0.08^{b}	0.28 ± 0.04^{b}

a(P-values<0.05); Between the Sham-operated and CLP groups statistically significant.
b(P-values<0.05); Between the CLP and CLP – Sinapic acid groups statistically significant.

Table 2. *Quantification of Caspase-3, IL-1β, and TNFα immunopositive cells in the CLP and sinapic acide treated rats in kidney tissue.*

Groups/Immunopositivity	Caspase 3	IL-1β	TNFα
Sham	0.12 ± 0.12^{a}	0.25 ± 0.16^{a}	0.12±0.12
CLP	2.75 ± 0.16^{b}	2.50 ± 0.26^{b}	2.37±0.41
CLP+Sinapic acide	1.62 ± 0.37^{c}	1.25 ± 0.25^{c}	1.12±0.39

Immunopositivity data are expressed as mean ± SEM (n = 8). Different superscript letters(a,b,c) show the difference among groups.

3.2. Immunohistochemical Results of Kidney Tissue

Immunohistochemically, differences between groups were determined in terms of caspase 3, IL-1β and TNFα immunopositivity (p<0.05, Table 2). Immunohistochemical staining for apoptosis did not show caspase-3 immunopositivity in the sham group (Fig. 2A). Caspase-3 immunopositivity was found as the most intensive in tubular epithelial cells and glomeruli in the CLP group (Fig. 2B). In the CLP+SA, Caspase-3 immunopositivity was observed only in the tubular epithelial cells (Fig. 2C). Immunohistochemical staining for inflammatory reaction did not show IL-1β immunopositivity in the sham group (Fig. 3A). IL-1β immunopositivity was most intensively seen in the intertubular area and glomeruli in the CLP group (Fig. 3B and Table 2). In the CLP+SA group, IL-1β immunopositivity was found in the tubular epithelial cells and intertubular area (Fig. 3C and Table 2). TNF-α immunopositivity was not found in the sham group (Fig. 4A). TNF-α immunopositivity was most abundant in the tubular epithelial cells and intertubular area in sepsis (CLP) group (Fig. 4B and Table 2). In CLP+SA group, a mild TNF-α immunopositivity was found in the intertubular area and glomeruli (Fig. 4C and Table 2).

3.3. Immunohistochemical Results of Lung Tissue

Immunohistochemical staining for apoptosis did not show caspase-3 immunopositivity in the sham group (Fig. 5A). Caspase-3 immunopositivity was found as the most intensive in the inflammatory cells of peribronchiolar lymphoid hyperplasia field in the CLP group (Fig. 5B). In the CLP+SA group, there was a mild Caspase-3 immunopositivity around the bronchiole (Fig. 5C). Immunohistochemical staining for inflammatory reaction did not show IL-1β immunopositivity in the sham group (Fig. 6A and Table 3). IL-1β immunopositivity was most intensively seen in the inflammatory cells of peribronchiolar lymphoid hyperplasia field in the CLP group (Fig. 6B and Table 3). In the CLP+SA group, it has been observed that IL-1β immunopositivity decreased although there was peribronchiolar lymphoid hyperplasia intensity (Fig. 6C and Table 3). TNF-α immunopositivity was not found in the sham group (Fig. 7A and Table 3). TNF-α immunopositivity was most abundant in the inflammatory cells of peribronchiolar lymphoid hyperplasia field in the CLP group (Fig. 7B and Table 3). In CLP+SA group, there was a moderate TNF-α immunopositivity in the inflammatory cells around the bronchial (Fig. 7C and Table 3).

Table 3. *Quantification of caspase 3, IL-1β, and TNFα immunopositive cells in lungs of the CLP and sinapic acide treated rats in lung tissue*

Groups/Immunopositivity	Caspase 3	IL-1β	TNFα
Sham	0.00 ± 0.00^{a}	0.12 ± 0.12^{a}	0.12 ± 0.12^{a}
CLP	2.62 ± 0.18^{b}	2.37 ± 0.32^{b}	2.25 ± 0.41^{b}
CLP+Sinapic acide	1.75 ± 0.36^{c}	1.12 ± 0.29^{c}	1.00 ± 0.32^{c}

Immunopositivity data are expressed as mean ± SEM (n = 8). Different superscript letters(a,b,c) show the difference among groups.

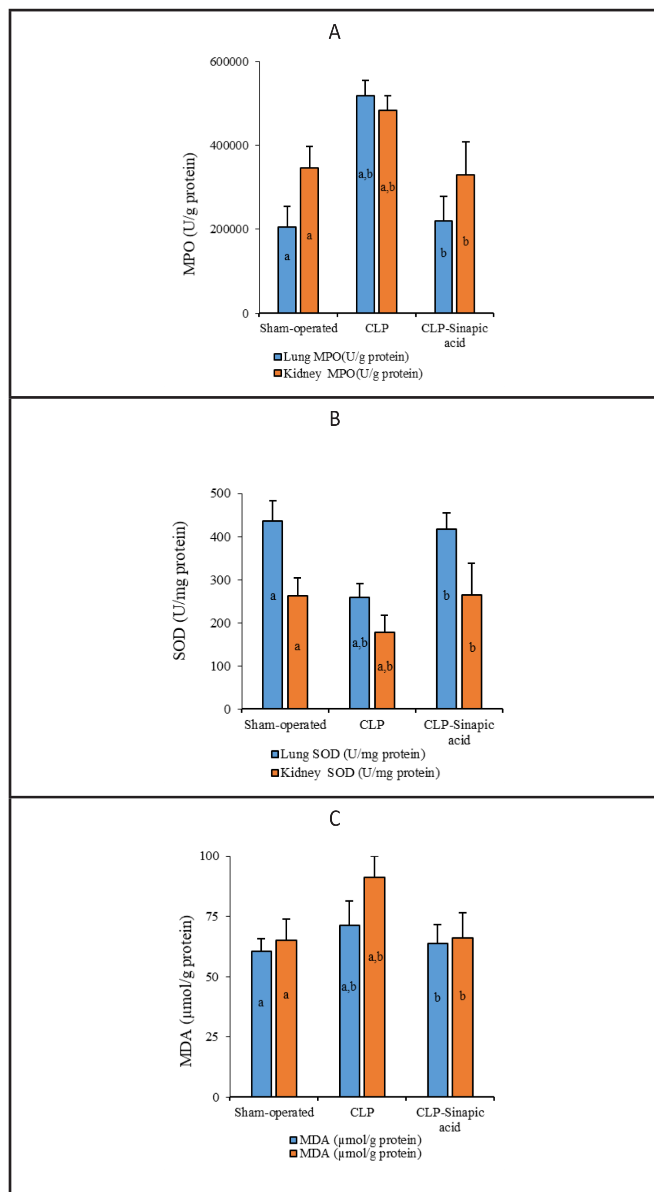

Figure 1. *A) MPO activity in all groups. a (p-values<0.05); Between the sham-operated and CLP groups statistically significant. b (p-values<0.05); Between the CLP and CLP+SA groups statistically significant. B) SOD activity in all groups. a (p-values<0.05); Between the sham-operated and CLP groups statistically significant. b (p-values<0.05); Between the CLP and CLP+SA groups statistically significant. C) MDA levels in all groups. a (p-values<0.05); Between the sham-operated and CLP groups statistically significant. b (p-values<0.05); Between the CLP and CLP+SA – Sinapic acid groups statistically significant.*

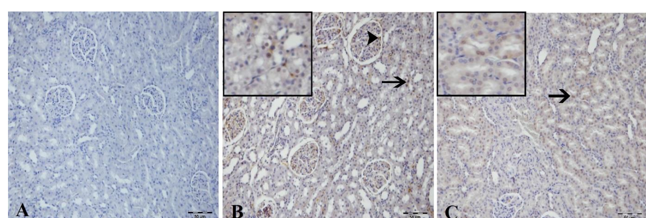

Figure 2. *A) Sham-operated group, B) CLP group, intense caspase-3 immunopositivity in the tubule epithelium (arrow) and glomerular structure (arrow head), C) CLP-Sinapic acid group, caspase-3 immunopositivity in the tubular epithelial cells (arrow).*

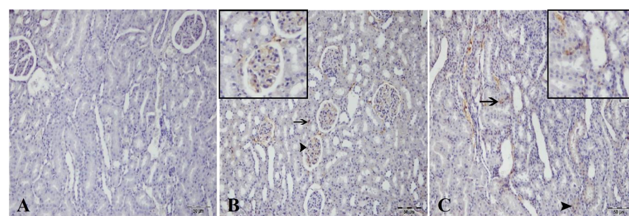

Figure 3. *A) Sham-operated group, B) CLP group, intensive IL-1β immunopositivity in the intertubular area (arrow) and glomerular structure (arrow head), C) CLP-Sinapic acid group, IL-1β immunopositivity in the intertubular area (arrow) and tubule epithelial cells (arrow head).*

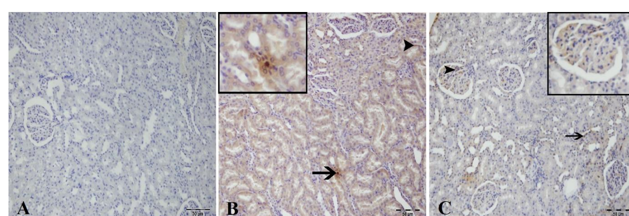

Figure 4. *A) Sham-operated group, B) CLP group, intensive TNF-α immunopositivity in the intertubular area (arrow) and tubule epithelial cells (arrow head), C) CLP-Sinapic acid group, TNF-α immunopositivity in the intertubular area (arrow) and glomerulus (arrow head).*

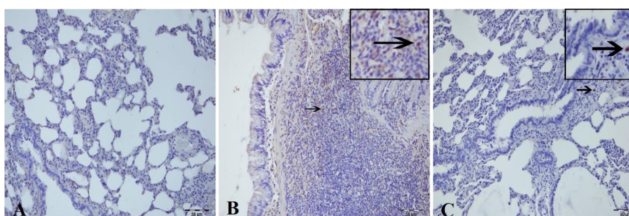

Figure 5. *A) Sham-operated group, B) CLP group, intense caspase-3 immunopositivity in the inflammatory cells of peribronchiolar lymphoid hyperplasia area (arrow), C) CLP-Sinapic acid group, mild caspase-3 immunopositivity in the inflammatory cells around the bronchiole (arrow).*

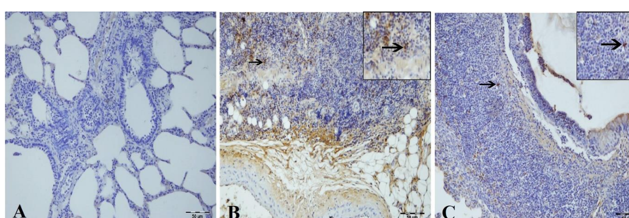

Figure 6. *A) Sham-operated group, B) CLP group, intense IL-1β immunopositivity in the inflammatory cells of peribronchiolar lymphoid hyperplasia area (arrow), C) CLP-Sinapic acid group, decreased IL-1β immunopositivity in the peribronchiolar lymphoid hyperplasia area (arrow).*

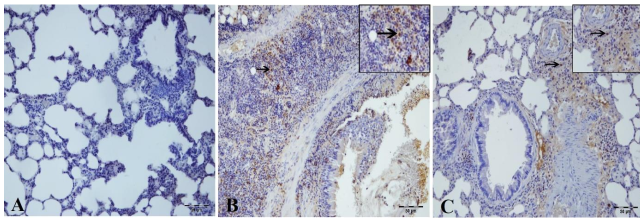

Figure 7. *A) Sham-operated group, B) CLP group, intense TNF-α immunopositivity in the inflammatory cells of peribronchiolar lymphoid hyperplasia area (arrow), C) CLP – Sinapic acid group, mild TNF-α immunopositivity in the inflammatory cells around the bronchiole (arrow).*

4. DISCUSSION

Despite the advances in pathogenesis, pathophysiology, diagnosis and treatment methods, sepsis is a lethal process which still maintains its importance today. The incidence of sepsis, the consequences of which change over time, and having limited information about epidemiology make it a remarkable health problem. It ranks 10th among the causes of death in the USA. It is estimated that 1400 people die every day, and about 500,000 people die per year due to sepsis worldwide (31, 32). The basis of physiopathological events that occur in the sepsis, is an initiation of the immune system response against the toxins and the antigenic structures of the microorganisms entering the body. Sepsis develops if the inflammatory response grows and goes out of control. The inflammatory and procoagulant responses caused by sepsis lead to diffuse endothelial dysfunction, endovascular injury and even multiple organ failure. Factors such as inflammatory-anti-inflammatory, procoagulant-anticoagulant, oxidant-antioxidant, apoptotic-antiapoptotic mechanisms which play a crucial role in maintaining of homeostasis balance, trigger irreversible damage and organ failure in sepsis (33-35). Despite improvements in the treatment of sepsis-induced CLP, the incidence of multiple organ failure and mortality rates are high. It is believed that excessive production of oxygen free radicals, activated by immune system cells, cause oxidative damage and it takes an important role in the pathogenesis of sepsis (36, 37). The lungs are the most affected organs during the multiple organ failure. Poor prognosis in sepsis is often responsible for the lung complications (38). Major systemic and local mediators, neutrophil-endothelium interactions, microvascular thrombosis, renal hypoperfusion and reperfusion injury have been accepted as responsible for the pathogenesis of acute renal failure which is another important organ damage in sepsis. Renal cell death in acute renal failure depends on necrosis as well as apoptosis (39). In the early phase of sepsis, activated phagocytes release large quantities of granular enzymes and produce uncontrolled oxygen free radicals. Goode et al. enounced that oxidative damage is important in the pathogenesis of sepsis and antioxidant therapy can play a protective role against sepsis and its complications (36). The formation of superoxide radical increases depending on a number of factors such as inflammation, radiation, aging, chemical substances and medicines. Superoxide radicals affect all important compounds in cells such as lipids, proteins, DNA, and carbohydrates. Free radicals are highly reactive and short-lived (40, 41). Therefore, it is difficult to measure them directly. To determine the increase in free radical production, measurement of the final products of peroxidation such as MDA, last product of lipid peroxidation, is the most widely used method. In our model, the antioxidant feature is the main protective effect of SA. Inhibition of oxidative stress in the treatment of CLP-induced sepsis model is one of the important mechanisms that prevent organ damage. Other antioxidants such as glutathione (GSH), melatonin, and vitamin E modulate reactive oxygen species (ROS) in cells and inhibit the tissue damage (42, 43). MDA is one of the extremely reactive metabolic products, resulting from lipid peroxidation, which is caused by free oxygen radicals on the tissues (44).]. MDA levels increased significantly on the tissues as a result of lipid peroxidation with liver and kidney toxicity due to CLP, which was given formerly in the literature (9, 45, 46). SOD acts as a supportive antioxidative enzyme that provides protective defence against ROS (47). Viewed incompatible with the finding of Xie et al. (2012), Abd El-Latif et al. (2016) and other studies indicate an important decrease in the activities of SOD in the liver and kidney of CLP-applied animals (9, 48). In our study, MDA level and MPO activity of lung and kidney tissues increased significantly in the sepsis model. However, the SA treatment changed the results markedly and the oxidative stress response reduced. The definition of TOS value provides an important mark of lipid peroxidation and oxidative stress. TAS, as an antioxidant, can maintain the tissue against the oxidative damage through scavenging free radical species. OSI is a parameter that demonstrates whether the oxidant and antioxidant balance is improved on the oxidant side or on the antioxidant side. It is detected by proportioning total oxidants into total antioxidants. The use of OSI is more precious than the use of oxidants and/or antioxidants alone. Increased OSI value due to increased oxidants or reduced antioxidants, initiates uncompensated free radicals, which is lead to peroxidation of lipids, oxidation of proteins and DNA damage (20). In this study, we measured TAS, TOS and OSI values of lung and kidney tissues in the CLP-induced sepsis.

The regulation of apoptosis in cells have conducted by caspases. Until today, 14 different members of the caspase family have been defined, which form two categories. One included in the activation of other caspase family members, caspases such as caspase-1, caspase-2, caspase-4, caspase-5, caspase-8, caspase-9, and caspase-10, and the others mainly interceding apoptosis, involving caspase-3, caspase-6, caspase-7, and caspase-14. Caspase-8 and caspase-9 activate caspase-3 to start apoptosis (49, 50). In this study, as it was in a previous study [39], it was exposed caspase-3 activities and found that CLP promoted caspase-3, indicating that both the programmed cell death receptor and mitochondria-related pathways were involved in apoptosis in the CLP model induced by sepsis of renal and lung cells. Sepsis occurs via a

network of pro-inflammatory cytokines, such as TNF-α and interleukin, which are extremely produced due to the diverse harmful situation, for example, infections. This intensified inflammatory response in the kidney is considered to be a crucial part of the pathophysiology of sepsis (51). Similar to the findings of many studies (52, 53), TNF-alpha and IL-1b levels increased in renal and lung tissues due to sepsis induced by the CLP method. This condition indicates that an intense apoptosis was triggered in kidney and lung tissues. But proinflammatory cytokine levels reduced due to SA treatment and inflammation severity decreased.

5. CONCLUSION

As a conclusion, TAS value declined in lung and kidney tissues but TOS and OSI values increased in the CLP group. On the other side, both TOS and OSI values diminished and TAS value increased due to SA treatment. numerous studies were performed to reduce the complications that may occur during sepsis (4, 9, 54, 55). As a result of these studies, many new drugs have been developed in the treatment of sepsis and it is still debated which drug is more effective. It was detected in many studies in literature that SA protects against oxidative damage of heart tissue in ischemic reperfusion injury, has a protective effect on lysosomal dysfunction in ischemic heart damage caused by isoproterenol, is effective against cisplatin-induced nephrotoxicity, is effective against kainic acid-induced hippocampal neuronal damage, is protective against oxidative kidney damage caused by gentamicin, and also is effective against arsenic-induced toxicity (15-17, 56, 57). In our study, the effects of SA on kidney and lungs were investigated by creating a sepsis model via CLP in rats. This study indicated that SA with antioxidant efficacy may be a potential treatment for sepsis. further researches are imperative through clinical human studies whether SA can be used clinically and to elucidate the mechanisms of the presented therapeutic efficiency of SA.

References

[1] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA. Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. Chest. 1992;101(6):1644-1655.

[2] Newland A, Provan D, Myint S. Preventing severe infection after splenectomy. BMJ. 2005;331(7514):417-418.

[3] Liu MW, Su MX, Wang YH, Wei W, Qin LF, Liu X. Effect of melilotus extract on lung injury by upregulating the expression of cannabinoid CB2 receptors in septic rats. BMC Complement Altern Med. 2014;14:94.

[4] Ritter C, Andrades M, Frota Junior ML, Bonatto F, Pinho RA, Polydoro M. Oxidative parameters and mortality in sepsis induced by cecal ligation and perforation. Intensive Care Med. 2003;29(10):1782-1789.

[5] Bone RC. Gram-negative sepsis – Background, clinical-features, and intervention. Chest. 1991;100(3):802-808.

[6] Otero-Anton E, Gonzalez-Quintela A, Lopez-Soto A, Lopez-Ben S, Llovo J, Perez LF. Cecal ligation and puncture as a model of sepsis in the rat: Influence of the puncture size on mortality, bacteremia, endotoxemia and tumor necrosis factor alpha levels. Eur Surg Res. 2001;33(2):77-79.

[7] Gulcin I. Antioxidant and antiradical activities of L-carnitine. Life Sci. 2006;78(8):803-811.

[8] Gulcin I. Antioxidant properties of resveratrol: A structure-activity insight. Innov Food Sci Emerg. 2010;11(1):210-218.

[9] Abd El-Latif AA, Sayed AA, Soliman AM, Fahmy SR. Exploration of the therapeutic potential effect of Sepia officinalis in animal model of sepsis induced by cecal ligation and puncture. Injury. 2016;47(12):2709-2717.

[10] Gulcin I. Antioxidant activity of caffeic acid (3,4-dihydroxycinnamic acid). Toxicology. 2006;217(2-3):213-220.

[11] Hoste E, Bagshaw S, Bellomo R, Cely C, Colman R, Cruz D. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intens Care Med. 2015;41(8):1411-1423.

[12] Zhai Y, Zhou X, Dai Q, Fan Y, Huang X. Hydrogen-rich saline ameliorates lung injury associated with cecal ligation and puncture-induced sepsis in rats. Exp Mol Pathol. 2015;98(2):268-276.

[13] Gulcin I. Antioxidant activity of food constituents: an overview. Arch Toxicol. 2012;86(3):345-391.

[14] Gulcin I. Antioxidants and antioxidant methods: an updated overview. Arch Toxicol. 2020;94(3):651-715.

[15] Ansari MA. Sinapic acid modulates Nrf2/HO-1 signaling pathway in cisplatin-induced nephrotoxicity in rats. Biomed Pharmacother. 2017;93:646-653.

[16] Ansari MA, Raish M, Ahmad A, Ahmad SF, Mudassar S, Mohsin K. Sinapic acid mitigates gentamicin-induced nephrotoxicity and associated oxidative/nitrosative stress, apoptosis, and inflammation in rats. Life Sci. 2016;165:1-8.

[17] Roy SJ, Stanely Mainzen Prince P. Protective effects of sinapic acid on lysosomal dysfunction in isoproterenol induced myocardial infarcted rats. Food Chem Toxicol. 2012;50(11):3984-3989.

[18] Yun KJ, Koh DJ, Kim SH, Park SJ, Ryu JH, Kim DG. Anti-inflammatory effects of sinapic acid through the suppression of inducible nitric oxide synthase, cyclooxygase-2, and proinflammatory cytokines expressions via nuclear factor-kappaB inactivation. J Agric Food Chem. 2008;56(21):10265-10272.

[19] Silambarasan T, Manivannan J, Priya MK, Suganya N, Chatterjee S, Raja B. Sinapic acid protects heart against ischemia/reperfusion injury and H9c2 cardiomyoblast cells against oxidative stress. Biochem Bioph Res Co. 2015;456(4):853-859.

[20] Fazile Nur Ekinci Akdemir, Ayhan Tanyeri, Mustafa Can Güler, Ersen Eraslan, Emsal Pınar Topdağı Yılmaz, Yunus Emre Topdağı. Brusatol Mitigates Ovarian Tissue Oxidatif Injury Induced by Ovarian Ischemia Reperfusion. Akdeniz Medical Journal. 2021;7(2):206.

[21] Altindag F, Ragbetli MC, Ozdek U, Koyun N, Ismael Alhalboosi JK, Elasan S. Combined treatment of sinapic acid and ellagic acid attenuates hyperglycemia in streptozotocin-induced diabetic rats. Food Chem Toxicol. 2021;156:112443.

[22] Raish M, Ahmad A, Ansari MA, Alkharfy KM, Ahad A, Al-Jenoobi FI. Effects of sinapic acid on hepatic cytochrome P450 3A2, 2C11, and intestinal P-glycoprotein on the pharmacokinetics of oral carbamazepine in rats: Potential food/herb-drug interaction. Epilepsy Res. 2019;153:14-18.

[23] Hilal Kızıltunç Özmen, Fazile Nur Ekinci Akdemir, Ayhan Tanyeli, Serkan Yıldırım, Yasin Bayır, Yılmaz Şahin, Gizem Eser,

Ayşenur Kahramanlar. Thymol May be an Effective Agent in the Treatment of Liver and Kidney Damages Caused by Ionizing Radiation. Turkish Journal of Oncology. 2021;36(1):575-82.

[24] Ohkawa H, Ohishi N, Yagi K. Assay for Lipid Peroxides in Animal-Tissues by Thiobarbituric Acid Reaction. Anal Biochem. 1979;95(2):351-8.

[25] Sun Y, Oberley LW, Li Y. A Simple Method for Clinical Assay of Superoxide-Dismutase. Clin Chem. 1988;34(3):497-500.

[26] Bradley PP, Priebat DA, Christensen RD, Rothstein G. Measurement of cutaneous inflammation: estimation of neutrophil content with an enzyme marker. J Invest Dermatol. 1982;78(3):206-9.

[27] Topdağı Ö, Tanyeli A, Ekinci Akdemir FN, Eraslan E, Güler MC. Barbaloin attenuates oxidative testicular injury induced by ischemia reperfusion via antioxidant effects. Turkish Journal of Science 2020;5(1):28-33.

[28] Topdağı Ö, Tanyeli A, Ekinci Akdemir FN, Güzel Erdoğan D, Güler MC, Eraslan E. The effects of higenamine on testicular damage injured by ischemia reperfusion: A biochemical study. Turkish Journal of Science 2019;4(2):92-99.

[29] Celik H, Kandemir FM, Caglayan C, Ozdemir S, Comakli S, Kucukler S. Neuroprotective effect of rutin against colistin-induced oxidative stress, inflammation and apoptosis in rat brain associated with the CREB/BDNF expressions. Mol Biol Rep. 2020;47(3):2023-2034.

[30] Ozdemir S, Kucukler S, Comakli S, Kandemir FM. The protective effect of Morin against ifosfamide-induced acute liver injury in rats associated with the inhibition of DNA damage and apoptosis. Drug Chem Toxicol. 2020; 22:1-10.

[31] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29(7):1303-1310.

[32] Vincent JL, Abraham E. The last 100 years of sepsis. Am J Respir Crit Care Med. 2006;173(3):256-263.

[33] Almog Y. Statins, inflammation, and sepsis: hypothesis. Chest. 2003;124(2):740-743.

[34] Cohen J. The immunopathogenesis of sepsis. Nature. 2002;420(6917):885-891.

[35] Gao F, Linhartova L, Johnston AM, Thickett DR. Statins and sepsis. Br J Anaesth. 2008;100(3):288-298.

[36] Goode HF, Webster NR. Free-radicals and antioxidants in sepsis. Crit Care Med. 1993;21(11):1770-1776.

[37] Nguyen HB, Rivers EP, Abrahamian FM, Moran GJ, Abraham E, Trzeciak S. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. Ann Emerg Med. 2006;48(1):28-54.

[38] Babayigit H, Kucuk C, Sozuer E, Yazici C, Kose K, Akgun H. Protective effect of beta-glucan on lung injury after cecal ligation and puncture in rats. Intensive Care Med. 2005;31(6):865-870.

[39] Lee HT, Xu H, Siegel CD, Krichevsky IE. Local anesthetics induce human renal cell apoptosis. Am J Nephrol. 2003;23(3):129-139.

[40] Bursal E, Gulcin I. Polyphenol contents and in vitro antioxidant activities of lyophilised aqueous extract of kiwifruit (Actinidia deliciosa). Food Res Int. 2011;44(5):1482-1489.

[41] Gulcin I. Antioxidant activity of eugenol: A structure-activity relationship study. J Med Food. 2011;14(9):975-985.

[42] Ak T, Gulcin I. Antioxidant and radical scavenging properties of curcumin. Chem Biol Interact. 2008;174(1):27-37.

[43] Halliwell B, Gutteridge JM. Role of free radicals and catalytic metal ions in human disease: an overview. Methods Enzymol. 1990;186:1-85.

[44] Kacmaz A, Polat A, User Y, Tilki M, Ozkan S, Sener G. Octreotide improves reperfusion-induced oxidative injury in acute abdominal hypertension in rats. J Gastrointest Surg. 2004;8(1):113-119.

[45] Aksoy AN, Toker A, Celik M, Aksoy M, Halici Z, Aksoy H. The effect of progesterone on systemic inflammation and oxidative stress in the rat model of sepsis. Indian J Pharmacol. 2014;46(6):622-626.

[46] Taner G, Aydin S, Bacanli M, Sarigol Z, Sahin T, Basaran AA, et al. Modulating effects of pycnogenol(R) on oxidative stress and DNA damage induced by sepsis in rats. Phytother Res. 2014;28(11):1692-1700.

[47] Cohen M, Lippman M, Chabner B. Role of pineal gland in aetiology and treatment of breast cancer. Lancet. 1978;2(8094):814-816.

[48] Xie K, Fu W, Xing W, Li A, Chen H, Han H. Combination therapy with molecular hydrogen and hyperoxia in a murine model of polymicrobial sepsis. Shock. 2012;38(6):656-663.

[49] Cheng B, Zhang Y, Wang A, Dong Y, Xie Z. Vitamin C Attenuates isoflurane-induced caspase-3 activation and cognitive impairment. Mol Neurobiol. 2015;52(3):1580-1589.

[50] Nakagawa A, Sullivan KD, Xue D. Caspase-activated phosphoinositide binding by CNT-1 promotes apoptosis by inhibiting the AKT pathway. Nat Struct Mol Biol. 2014;21(12):1082-1090.

[51] Cho SY, Choi JH. Biomarkers of sepsis. Infect Chemother. 2014;46(1):1-12.

[52] Qiu R, Yao W, Ji H, Yuan D, Gao X, Sha W. Dexmedetomidine restores septic renal function via promoting inflammation resolution in a rat sepsis model. Life Sci. 2018;204:1-8.

[53] Wang B, Jiang J, Yang J, Chen J, Zhu Z, Liu J. Pharmacologic studies on ET-26 hydrochloride in a rat model of lipopolysaccharide-induced sepsis. Eur J Pharm Sci. 2017;109:441-445.

[54] Ekinci Akdemir FN, Tanyeli A. The antioxidant effect of Ffaxin against acute organ damage in polymicrobial sepsis model induced by cecal ligation and puncture. Turkish Journal of Science 2019;4:22-29.

[55] Sato Y, Itagaki S, Kurokawa T, Ogura J, Kobayashi M, Hirano T. In vitro and in vivo antioxidant properties of chlorogenic acid and caffeic acid. Int J Pharmaceut. 2011;403(1-2):136-138.

[56] Kim DH, Yoon BH, Jung WY, Kim JM, Park SJ, Park DH. Sinapic acid attenuates kainic acid-induced hippocampal neuronal damage in mice. Neuropharmacology 2010;59(1-2):20-30.

[57] Pari L, Jalaludeen AM. Protective role of sinapic acid against arsenic – Induced toxicity in rats. Chem-Biol Interact. 2011;194(1):40-47.

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