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Research Article

The effects of lycopene in lung injury associated with cecum ligation and perforation-induced sepsis in rats: An investigative animal experiment study

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ABSTRACT

Background: The primary aim of this study is to evaluate the effect of lycopene on serum interleukin-1ß (IL-1ß) and interleukin-6 (IL-6) levels in rats subjected to sepsis induced by the cecal ligation and perforation (CLP) method, as well as to assess the impact of lycopene on inflammation in the lungs, which is the first organ affected by sepsis.

Methods: Twenty-four male rats were divided into four groups - control (healthy group), sepsis (CLP group), sepsis + lycopene 100 mg/kg (L100 group), and sepsis + lycopene 200 mg/kg (L200 group). Lycopene was administered by gastric lavage at doses of 100 mg/kg to the L100 group and 200 mg/kg to the L200 group. Intracardiac blood samples were collected 18 h after CLP for serum IL-1β and IL-6 level analysis. Lung tissue specimens were also collected for histopathological examination.

Results: IL-1β levels decreased significantly in the L100 and L200 groups compared to the CLP group ($p<0.001$). Both doses of lycopene statistically significantly reduced serum IL-6 levels in the L100 and L200 groups compared to the CLP group. Serum IL-6 levels also decreased significantly in the L200 group compared to the L100 group ($p<0.001$).The degree of inflammation, vascular congestion and edema decreased significantly in the L200 group compared to the CLP group ($p<0.001$).

Conclusion: Use of lycopene in rats with CLP-induced sepsis reduced serum IL-1β and IL-6 levels and inflammation in lung tissue at histopathological examination. Lycopene can be more effective at a dosage of 200 mg/kg.

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1. Introduction

Sepsis is a systemic and irregular inflammatory response to infection that is capable of causing hemodynamic instability, multiple organ dysfunction syndrome (MODS), and even death. Sepsis-related mortality rates may sometimes be very high [1]. Also, it is believed that sepsis is more prevalent than is currently being reported because it causes different clinical manifestations and its reporting is not compulsory in some countries [2]. There are several causes for the high rate of mortality among septic patients. These include intravas-

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cular or urinary catheterization; invasive procedures such as endotracheal intubation, which is done when necessary; antibiotic resistance; and high immune suppression, which is associated with therapeutic protocols [1,3].

The course of a disease when sepsis occurs generally depends on the emergence of sepsis-related MODS. Impaired microcirculation due to endothelial damage and the widespread release of inflammatory mediators can lead to the development of MODS [4,5].

Multiple mediators are involved in the pathogenesis of sepsis—including the inflammatory mediator interleukin (IL), tumor necrosis factor (TNF), arachidonic acid, and platelet-activating factor. Also, monocytes, macrophages, and mast and endothelial cells release cytokines against bacteria and endotoxins. TNF-α, interferon-gamma (IF γ), and IL 1β, IL-6, and IL-8 are involved as proinflammatory cytokines in the pathogenesis of sepsis, while IL 10 serves a basic anti-inflammatory cytokine. The blood levels of these mediators increase in sepsis, and the complex relationship between them is gradually being unraveled [6,7] .

Lycopene is a member of the carotenoid family with a powerful antioxidant property because of its conjugated double bonds [8,9]. Due to its nature as a potent anti-inflammatory and antioxidant molecule, we hypothesized that lycopene might be beneficial in the treatment of sepsis and sepsis-related lung damage.

This study was planned to investigate the effectiveness of lycopene in the treatment of sepsis. This study primarily aimed to evaluate the effect of lycopene on IL-1β and IL-6 levels in rats induced with sepsis using the cecum ligation and perforation (CLP) method and assess the level of inflammation in the lungs, which is the first organ affected in sepsis. The secondary aim of the study was to compare the effects of different doses of lycopene on inflammation.

2. Materials and Methods

2.1. Animal models

Atatürk University Animal experiments were carried out with the decision of the local ethics committee dated 27.12.2018, number 13, decision number 235. Twenty-four male albino Wistar rats weighing 220–250 g obtained from the University Medical Experimental Application and Research Centre Laboratory were used for the experiment, which was conducted in the same laboratory. During the experiment, rats were allowed ad libitum access to water and chow (complete mouse and rat feed: raw protein 23%, raw ash 8%, raw cellulose 7%, and raw fat 3%; Bil-yem, Ankara, Turkey). Before the experiment, the animals were housed in the laboratory in groups in standard cages with sawdust flooring at normal room temperature (22–25 °C) and in a 12 h light/12 h dark cycle. Access to water alone was permitted 12 h before and after the experiment.

Polymicrobial sepsis was induced in healthy rats using the CLP model. For that purpose, the rats were anesthetized with a combination of 75 mg/kg ketamine and 5 mg/kg xylazine. The rats were placed in the supine position while the abdominal region was shaved and cleansed with a 10% povidone-iodine solution. A two cm abdominal midline incision was first made. Then the cecum was located and explored through the anterior muscles of the abdominal wall. The cecum was ligated with 3/0 silk distally to the ileocecal valve in such a way as not to impair blood flow or intestinal circulation. Four holes were made in the cecum (one from one side and one from the opposite side) with the help of an 18-gauge needle, and one part of the cecum content was exteriorized. The abdomen was washed with one ml saline solution and then closed with a 3/0 synthetic absorbable sterile suture.

2.2. Study design

The rats were randomly assigned into groups containing six animals each.

1. Control group (group healthy; n=6): No procedure was performed on the animals in this group to determine the investigated parameters in normal healthy animals. Intracardiac blood and lung tissue specimens were collected immediately after sacrificing the rats.
2. Sepsis group (CLP group; n=6): CLP was performed on this group to induce intra-abdominal sepsis.
3. Sepsis + lycopene 100 mg/kg group (L100 group; n=6): Lycopene (100 mg/kg) was administered by gastric lavage.
4. Sepsis + lycopene 200 mg/kg group (L200 group; n=6): Lycopene (200 mg/kg) was administered by gastric lavage.

The rats were sacrificed 18 h after the induction of sepsis and intracardiac blood and lung tissue specimens were collected immediately after the sacrifice group CLP, L100 and L200.

2.3. Chemicals

Lycopene (DSM, RedivivoTM [lycopene] 10% fluid suspension, Basel, Switzerland) was administered by gastric lavage at dosages of 100 mg/kg and 200 mg/kg to the rats in the L100 and the L200 groups, respectively.

2.4. Serum IL-1β and IL-6 level measurement

Approximately 4–6 cc of blood was collected to measure IL-1β and IL-6. The blood specimens were centrifuged for 10 min at 4000 rpm to separate the serum. The serum specimens were then placed in Eppendorf tubes and stored at -80°C until the day they were analyzed. Serum IL-1β and IL-6 levels were determined using rat IL-1β enzyme-linked immunosorbent assay (Invitrogen, USA; Code: KRC0011) and IL-6 ELISA (Invitrogen, USA; Code: KRC0061) kits, respectively. Unit values were expressed as pg/ml.

2.5. Histological procedures

The lungs of the rats were removed by opening the diaphragm. They were then placed in 10% neutral formaldehyde and sent to the pathology laboratory for his-

topathological examination. All the conventional light microscopy procedures were carried out at the Atatürk University Medical Faculty Pathology Department laboratory. At the end of the experiment, the lung tissues were fixed in 10% formalin solution for 48–55 h. The tissues were dehydrated by passing them through increasing alcohol series and then cleared with xylene series. Following the histopathological procedures, the tissues were embedded in paraffin and cut into five nm-thick sections using a microtome (Leica RM2235, Leica Instruments, Nussloch, Germany) with single-use microtome blades (Leica 819, Leica Instruments, Nussloch, Germany). The tissues were then stained with hematoxylin and eosin and examined under a light microscope. Photomicrographs were also taken.

Inflammation was evaluated using two different methods when the histopathological examination was performed:

For the first inflammation score, sections were obtained systematically and randomly. The degree of inflammation in the perivascular area was then scored in a double-blinded manner by two independent pathologists as shown below [9]:

0: No inflammatory cells;
1: A few inflammatory cells;
2: Several inflammatory cells in the peripheral regions of the perivascular region;
3: Numerous inflammatory cells in the perivascular area.

The second inflammation score was designed based on the presence of values indicating inflammation during the histopathological examination: Polymorphonuclear leukocytes (PMNL): Present/Absent, Vascular congestion (VC): Present/Absent, Edema: Present/Absent

2.6. Statistical analysis

Numerical values obtained from the groups were expressed as mean ± standard deviation. Numerical data obtained from biochemical analyses were assessed using one-way ANOVA and Tukey tests, and p-values <0.05 were regarded as significant. Data yielded by histopathological examinations were analyzed using the Kruskal-Wallis and the Fisher–Freeman–Halton tests, and p-values < 0.05 were regarded as significant. All statistical analyses were performed on IBM SPSS-20 software.

3. Results

3.1. Biochemical findings

Serum IL-1β levels in the CLP group increased significantly compared to the healthy control group ($p<0.001$). In addition, serum IL-1β levels decreased significantly in the L100 and L200 groups compared to the CLP group ($p<0.001$). Although a numerical decrease was observed in serum IL-1β levels in L100 and L200 groups, the difference was not statistically significant ($p>0.05$) (Fig. 1).

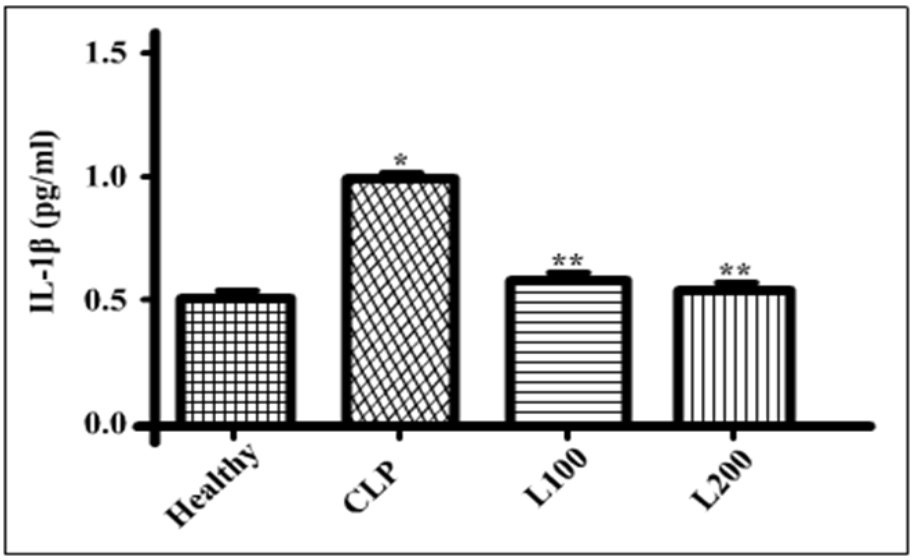

Fig. 1. Group healthy, Group ÇLP, Group L100, Group L200 IL-1β values in pg/ml.
* $p<0.001$ for the CLP group compared with the healthy group.
** $p<0.001$ for the CLP group compared with the L100 and L200 groups.

Serum IL-6 levels in the CLP group increased significantly compared to the healthy control group ($p<0.001$). The administration of both doses of lycopene in the L100 and L200 groups reduced serum IL-6 levels significantly compared to the CLP group ($p<0.001$). Serum IL-6 levels were also statistically significantly lower in the L200 group compared to the L100 group ($p<0.01$) (Fig. 2).

3.2. Histopathological findings

Light microscopic examination revealed that pulmonary tissues from the rats in the healthy control group were within physiological limits: no inflammation, edema, nor congestion was observed (Fig. 3a). However, marked interstitial expansion and inflammation, diffuse conges-

tion, and edema were observed in the CLP group (Fig. 3b). The degree of Inflammation and congestion decreased while edema improved in the L100 group compared to the CLP group (Fig. 3c). Furthermore, we observed that the pulmonary tissue from the L200 group exhibited a morphology close to that of the healthy controls (Fig. 3d).

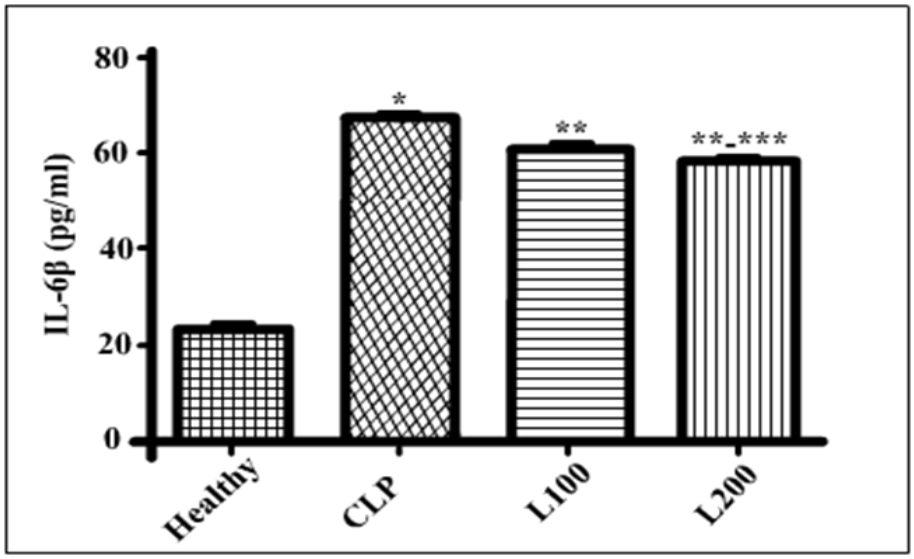

Fig. 2. Group healthy, Group CLP, Group L100, Group L200 IL-6 values in pg/ml.
* p<0.001 for the CLP group compared with the healthy group.
** p<0.001 for the CLP group compared with the L100 and L200 groups.
*** p<0.001 for the L200 group compared with the L100 group.

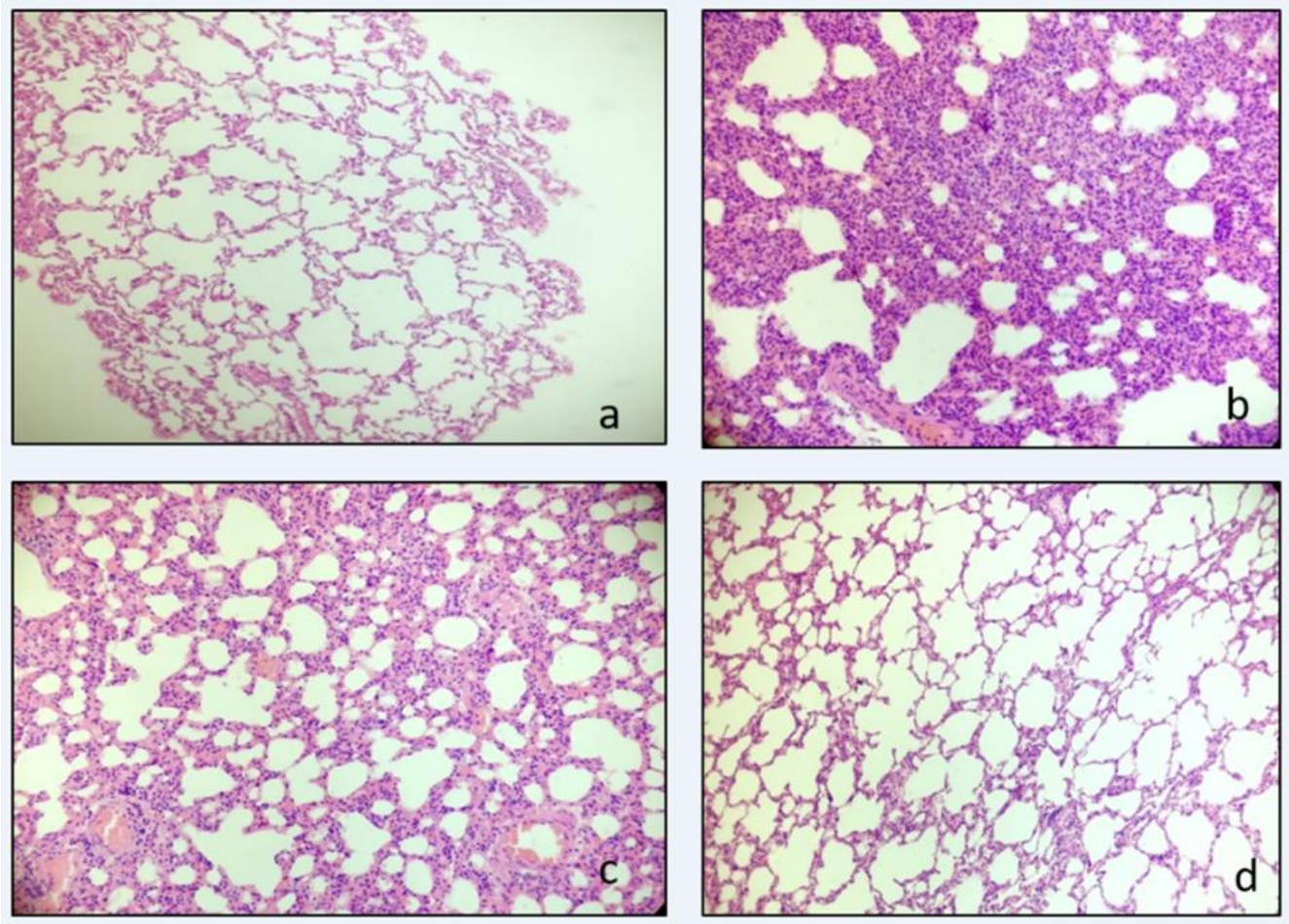

Fig. 3. Histopathological findings: (a) Healthy group; (b) CLP group; (c) L100 group; (d) L200 group.

3.3. Histopathological changes in lung tissues

Histopathological inflammation scores in the study groups were produced for PMNL, VC, and edema (Table 1). We found that the degree of inflammation in the CLP group increased compared to the healthy control group, while it decreased in the L100 group compared to the CLP group and decreased more markedly in the L200 group compared to the CLP group.

Statistical analysis was performed using the Kruskal-Wallis test with the assumption that the variables were gradually increasing or decreasing ordinal variables. Analyzed in terms of PMNL, VC, and edema, the degree of inflammation in the CLP group increased significantly compared to the healthy control group ($p<0.001$). Assessed in terms of PMNL, VC, and edema, the degree of inflammation in the L200 group was significantly lower than in the CLP group ($p<0.001$). Again, assessed in terms of PMNL, VC, and edema, the degree of inflammation was also lower in the L100 group than in the CLP group, although the difference was not statistically significant ($p>0.05$). Similarly, although a numerical decrease in the degree of inflammation was observed in the L200 group compared to the L100 group, the difference was not statistically significant ($p>0.05$) (Table 2).

Table 1. A comparison of graded inflammation findings in lung tissue among the study groups.

		Healthy group (n=6)	CLP group (n=6)	L100 group (n=6)	L200 group (n=6)
PMNL	0	3 (50%)	0 (0%)	0 (0%)	1 (16.7%)
	1	3 (50%)	0 (0%)	3 (50%)	5 (83.3%)
	2	0 (0%)	0 (0%)	3 (50%)	0 (0%)
	3	0 (0%)	6 (100%) [a]	0 (0%)	0 (0%) [b]
VC	0	2 (33.3%)	0 (0%)	0 (0%)	5 (83.3%)
	1	4 (66.7%)	0 (0%)	5 (83.3%)	1 (16.7%)
	2	0 (0%)	2 (33.3%)	1 (%16.7)	0 (0%)
	3	0 (0%)	4 (66.7%) [a]	0 (0%)	0 (0%) [b]
Edema	0	5 (83.3%)	0 (0%)	2 (33.3%)	6 (100%)
	1	1 (16.7%)	0 (0%)	4 (66.7%)	0 (0%)
	2	0 (0%)	6 (100%) [a]	0 (0%)	0 (0%) [b]

All data are expressed as number (percentage).
Kruskal Wallis test
CLP: Cecum ligation and perforation; PMNL: Polymorphonuclear leukocyte; VC: Vascular congestion.
[a] $p<0.001$ for the CLP group compared with the healthy groups.
[b] $p<0.001$ for the CLP group compared with the L200 groups.

Table 2. Comparison of graded inflammation findings in lung tissue among the groups.

		Healthy group (n=6)	CLP group (n=6)	L100 group (n=6)	L200 group (n=6)
PMNL	Median	0.50 (0-1)	3.00 (3-3) [a]	1.50 (1-2)	1.00 (0-1) [a]
VC	Median	1.00 (0-1)	3.00 (2-3) [b]	1.00 (1-2)	0.00 (0-1) [b]
Edema	Median	0.00 (0-1)	2.00 (2-2) [c]	1.00 (0-1)	0.00 (0-0) [c]

Results were presented as mean ± standard deviation.
Kruskal Wallis test
CLP: Cecum ligation and perforation; PMNL: Polymorphonuclear leukocyte; VC: Vascular congestion.
[a] $p < 0.001$ for the CLP group compared with the healthy and L200 groups.
[b] $p < 0.001$ for the CLP group compared with the healthy and L200 groups.
[c] $p < 0.001$ for the CLP group compared with the healthy and L200 groups.

No statistically significant difference was observed between the groups when the presence or absence of PMNL in the lung tissues was used as a marker of inflammation ($p>0.05$). When the presence or absence of VC was evaluated as a marker of inflammation in the study groups, a significant decrease in inflammation was observed in the L200 group compared to the CLP group ($p<0.001$). VC was also significantly lower in the L200 group compared to the L100 group ($p<0.001$). When the presence or absence of edema was used as a marker of inflammation, a significant increase in edema was observed in the CLP group compared to the healthy control group ($p<0.001$). In addition, edema decreased in the L100 group compared to the CLP group, but this was not statistically significant ($p>0.05$). However, edema decreased significantly in the L200 group compared to the CLP group ($p<0.001$) (Table 3).

Table 3. A comparison of inflammation findings in lung tissue among the groups.

		Healthy group (n=6)	CLP group (n=6)	L100 group (n=6)	L200 group (n=6)
PMNL	(Yes/No)	3/3	0/6	0/6	1/5
VC	(Yes/No)	2/4	0/6 [a]	0/6 [b]	5/1
Edema	(Yes/No)	5/1 [c]	0/6 [a]	2/4	6/0

Results were presented as number.
Fisher–Freeman–Halton test
CLP: Cecum ligation and perforation; PMNL: Polymorphonuclear leukocyte; VC: Vascular congestion.
[a] $p<0.001$ for the CLP group-L-200 group
[b] $p<0.001$ for the L100 group -L200 group
[c] $p<0.001$ for the healthy group-CLP group

4. Discussion

In our study, IL-1β and IL-6 levels were significantly decreased in both lycopene groups compared to the cecal ligation perforation group. When we look at our study in terms of histopathological findings, inflammation findings were decreased in both lycopene groups compared to the cecal ligation perforation group. A statistically significant decrease in inflammation was found in the L 200 group compared to the other groups.

Despite the variation in the incidence of sepsis and septic shock in the last 10 years, significant reductions have been observed since consensus decisions have been adopted for the treatment of severe sepsis in patients presenting to intensive care, leading to lower mortality rates. The reasons for this include early diagnosis, more conscious emergency treatment, and earlier initiation of antibiotic therapy [10]. However, there is still no reliable and specific parameter that can be used to promptly identify septic patients [11].

Models frequently employed for inducing experimental sepsis include intravascular lipopolysaccharide injection, induction of peritonitis by applying feces or bacteria into the peritoneal cavity, abscess creation with infected material, opening an intestinal segment, ascending colon stent peritonitis, and CLP [12]. CLP, a simple model that can be applied in clinical settings and can be used in all animal species to induce intra abdominal sepsis, has become a widely employed method in experimental studies. We, therefore, employed a CLP sepsis model in the present study.

In polymicrobial sepsis, cytokines such as IL-1β, IL-6, and TNF-α are released from intestinal epithelial cells. These cytokines have been proved to play an important role in the inflammatory response [13,14]. An increase in IL-6 levels has been identified as a marker of poor prognosis and linked to severe inflammatory complications [15]. Parameters such as IL 1β and IL-6 were therefore investigated in animals with CLP-induced sepsis in the present study. Several studies have reported significant increase in IL-1β, IL-6, and TNF-α levels due to the inflammatory response in induced sepsis models [15]. This is consistent with the findings of the present research and supports the model used to induce sepsis. Similar to previous literature, we found significantly higher IL-1β and IL-6 levels in the sepsis group than in the control group. Thus, we believe that IL-1β and IL-6 values can represent important parameters in the treatment of sepsis [16,17].

The present study employed lycopene, a hydrocarbon with known antioxidant, anticarcinogenic, and anti-inflammatory effects, and hypothesized that it might be beneficial in the treatment of sepsis. While our scan of the literature revealed that the antioxidant and anticarcinogenic effects of lycopene have been widely studied, there has been insufficient research on its anti-inflammatory effects in sepsis. We, therefore, investigated the anti inflammatory effect of lycopene in rats with induced sepsis. Lycopene suppresses inflammation by reducing the synthesis of the proinflammatory molecules—prostaglandin, prostacyclin, thromboxane, and leukotriene, and regulating cyclooxygenase and lipo oxygenase activities [18].

There is a known interaction between oxidative stress and inflammation. Nuclear factor Kappa-B is one of the protein complexes that control transcription in DNA and it is co present with inhibitor factor Kappa-B, which is generally found in the passive form in cytoplasm and becomes activated when it separates from inhibitor factor kappa-B through phosphorylation. According to Huang et al., lycopene can act as an anti-inflammatory molecule by inhibiting the binding activity of nuclear factor Kappa-B [19].

Chung et al. [21] determined that smoking increased IL-1β levels in smokers' saliva and phlegm [20]. Simone et al. exposed macrophages to cigarette smoke and showed that the increase in IL-8 synthesis reached a level that is close to that of the control group approximately 3 h after lycopene treatment. The authors thus determined that oxidative stress and inflammation were suppressed as a result of lycopene treatment.

The anticarcinogenic effect of lycopene observed in animal studies may be associated with the antioxidant activity of lycopene, stimulation of gap junctions providing intercellular signaling, induction of detoxification enzymes, and cellular proliferation inhibition. Studies have shown that lycopene may protect lipids, nucleic acids, and proteins against oxidative stress that is capable of resulting in cancer, and it has been suggested as potentially useful in the treatment of cancer [22,23].

Research has also demonstrated that lycopene can reduce the effects of toxic agents when administered together. Jamshidzadeh et al. [24] investigated the effects of tomato extract on pulmonary, hepatic, and renal tox-

icity induced in rats with amiodarone, acetaminophen, and cyclosporine, respectively, and reported biological and histopathological improvement in the groups in which lycopene was administered together with the toxic substances. A review study published by Petyaev [25] reported that, in studies on chronic vascular diseases using various animal models, lycopene led to increased endothelial nitric oxide synthase activity, which returned nitric oxide levels to normal, and improved endothelial function, as well as the weakening of inflammatory damage and inhibition of cholesterol biosynthesis.

Lycopene has been shown to exhibit beneficial effects in models of hypertension and diabetes [26,27]. Hyperglycemia is an important clinical parameter in the pathogenesis of sepsis and develops due to various causes. The use of lycopene in rats with induced sepsis in the present study is, therefore, particularly valuable. The effect of lycopene on sepsis-related hyperglycemia may be a subject deserving of investigation.

Colitis is not yet fully understood. Genetic and environmental factors, micro-organisms or their antigens, and immune system disorders have been implicated in the etiopathogenesis of colitis [28]. Reifen et al. [29] studied colitis in rats following iron supplementation and showed that lycopene reduced oxidative stress and inflammation. They also observed that lycopene had an anti-inflammatory effect.

Lung tissue is one of the organs that is affected in cases of sepsis. Cadirci et al. [9] evaluated lung damage in rats with sepsis that is induced using a CLP model. Their histopathological examination showed significantly greater PMNL infiltration, VC, and edema in the sepsis group than in the other study groups. A study investigating the protective effect of lycopene in a lung disease model induced in rats with oleic acid showed less neutrophilic infiltration and perivascular and alveolar edema in the lycopene group [30]. Lung damage is one of the principal pathologies that develop in sepsis and the main cause of secondary Acute Respiratory Distress Syndrome. In the present study, we investigated pulmonary histopathology using lycopene in rats with induced sepsis and detected a positive anti-inflammatory effect after the treatment.

Hua et al. [31] investigated acute lung damage as a result of induced sepsis in rats. The changes detected after histopathological analysis of the septic lung included pulmonary edema, breakdown of pulmonary alveolar structures, and inflammatory cell infiltration.

Demir et al. [32] performed a histopathological examination of the lungs of rats with CLP induced sepsis and observed mononuclear cell infiltration in lung tissue, increased capillary permeability, alveolar edema, diffuse alveolar injury, and increased numbers of alveolar macrophages. In light of the studies cited above, which showed that the lung is affected in sepsis, we believe that lycopene administration can be used to prevent pulmonary inflammation in a sepsis model.

As limitations of our study; CRP, Procalcitonin, platelet and leukocyte values in the blood should not be checked and only the lung should be evaluated histopathologically. These include not examining tissues that can be easily affected by sepsis-related inflammation, such as the liver, brain and kidney. A more comprehensive study could be conducted by increasing the number of rats.

5. Conclusions

In this study documenting in terms of serum IL-1β and IL-6 levels and changes occurring in lung tissues in a CLP-induced model of sepsis in rats, we believe that the use of lycopene in sepsis will be beneficial. In addition, we found that the 200 mg/kg lycopene dosage exhibited more positive effects than a dosage of 100 mg/kg in the treatment of sepsis in our CLP-induced model.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets created and/or analyzed during the current study are not publicly available, but are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Atatürk University. Animal experiments were carried out with the decision of the local ethics committee dated 27.12.2018, number 13, decision number 235. Written informed consent was obtained from the participants. All methods were performed in accordance with relevant guidelines and regulations.

Author Contributions

Sumeyra Zeren: *investigation, methodology, data curation, writing – original draft.*
Ozgur Ozmen: *conceptualization, supervision, writing – review & editing, project administration.*
Zekai Halici: *methodology, resources, pharmacological oversight.*
Sare Sipal: *histopathological analysis, visualization.*
Betul Gundogdu: *histopathological analysis, validation.*
Kamber Kasali: *formal analysis, statistical analysis, software.*
Nazim Dogan: *methodology, animal experimentation support.*
Husnu Kursad: *data curation, writing – review & editing.*

REFERENCES

1. Rhodes A, Ewans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. **2017**;43:304–377.
2. Bone RC, Grodzin CJ, Balk RA. Sepsis: A new hypothesis for pathogenesis of the disease process. *Chest*. **1997**;112:235–243.
3. Zilbelberg MD, Shorr AF, Micek ST, et al. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. *Crit Care*. **2014**;18:596.

4. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. **2001**;344:699–709.
5. Pool R, Gomez H, Kellum JA. Mechanisms of organ dysfunction in sepsis. *Crit Care Clin*. **2018**;34:63–80.
6. Karakike E, Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: a distinct entity leading to early death in sepsis. *Front Immunol*. **2019**;10:55.
7. Bozza FA, Salluh JI, Japiassu AM, et al. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. *Crit Care*. **2007**;11:R49.
8. Bhuvaneswari V, Nagini S. Lycopene: a review of its potential as an anticancer agent. *Curr Med Chem Anticancer Agents*. **2005**;5:627–635.
9. Cadirci E, Ugan RA, Dincer B, et al. Urotensin receptors as a new target for CLP induced septic lung injury in mice. *Naunyn Schmiedebergs Arch Pharmacol*. **2019**;392:135–145.
10. Herrán-Monge R, Muriel-Bombín A, García-García MM, et al. Grecia network epidemiology and changes in mortality of sepsis after the implementation of Surviving Sepsis Campaign guidelines. *J Intensive Care Med*. **2019**;34:740–750.
11. Yébenes JC, Ruiz-Rodriguez JC, Ferrer R, et al. Epidemiology of sepsis in Catalonia: analysis of incidence and outcomes in a European setting. *Ann Intensive Care*. **2017**;7:19.
12. Poli-de-Figueiredo LF, Garrido AG, Nakagawa N, et al. Experimental models of sepsis and their clinical relevance. *Shock*. **2008**;30:53–59.
13. Ding LA, Li JS, Li YS, et al. Intestinal barrier damage caused by trauma and lipopolysaccharide. *World J Gastroenterol*. **2004**;10(16):2373–2378.
14. Yang S, Koo DJ, Chaudry JH, et al. The important role of the gut in initiating the hyperdynamic response during early sepsis. *J Surg Res*. **2000**;89:31–37.
15. Zhang H, Slutsky AS, Vincent JL. Oxygen free radicals in ARDS, septic shock and organ dysfunction. *Intensive Care Med*. **2000**;26:474–476.
16. Qin X, Jiang X, et al. Micheliolide inhibits LPS-induced inflammatory response and protects mice from LPS challenge. *Sci Rep*. **2016**;6:23240.
17. Huang H, Tu L. Expression of S100 family proteins in neonatal rats with sepsis and its significance. *Int J Clin Exp Pathol*. **2015**;8(2):1631–1639.
18. Pruthi RS, Derksen E, Gaston K. Cyclooxygenase-2 as a potential target in the prevention and treatment of genitourinary tumors: a review. *J Urol*. **2003**;169:2352–2359.
19. Huang CS, Fan YE, Lin CY, et al. Lycopene inhibits matrix metalloproteinase-9 expression and down-regulates the binding activity of nuclear factor-kappa B and stimulatory protein-1. *J Nutr Biochem*. **2007**;18:449.
20. Chung KF. Cytokines as targets in chronic obstructive pulmonary disease. *Curr Drug Targets*. **2006**;7:675–681.
21. Simone RE, Russo M, Catalano A, et al. Lycopene inhibits NF-kB-mediated IL-8 expression and changes redox and PPARγ signalling in cigarette smoke–stimulated macrophages. *PLoS One*. **2011**;6:e19652.
22. Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. *J Natl Cancer Inst*. **1999**;91(4):317–331.
23. Kuçuk O, Sarkar H, Sakr W, et al. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. *Cancer Epidemiol Biomarkers Prev*. **2001**;10:861–868.
24. Jamshidzadeh A, Baghban M, Azarpira N, et al. Effects of tomato extract on oxidative stress induced toxicity in different organs of rats. *Food Chem Toxicol*. **2008**;46:3612–3615.
25. Petyaev IM. Lycopene deficiency in ageing and cardiovascular disease. *Oxid Med Cell Longev*. **2016**;2016:3218605.
26. Osinska AN, Begier-Krasinska B, Rzymski P, et al. The influence of adding tomato extract and acetylsalicylic acid to hypotensive therapy on the daily blood pressure profiles of patients with arterial hypertension and high cardiovascular risk. *Kardiochir Torakochir Pol*. **2017**;14:245–252.
27. Li W, Wang G, Lu X, et al. Lycopene ameliorates renal function in rats with streptozotocin-induced diabetes. *Int J Clin Exp Pathol*. **2014**;7:5008–5015.
28. Dieleman LA, Goerres MS, Arends A, et al. Lactobacillus GG prevents recurrence of colitis in HLA-B27 transgenic rats after antibiotic treatment. *Gut*. **2003**;52:370–376.
29. Reifen R, Nissenkorn A, Matas Z, et al. 5-ASA and lycopene decrease the oxidative stress and inflammation induced by iron in rats with colitis. *J Gastroenterol*. **2004**;39:514–519.
30. Turkoglu S, Muz MH, Özercan R, et al. Effects of lycopene on the model of oleic acid induced acute lung injury. *Tuberk Toraks*. **2012**;60:101–107.
31. Hua S, Liu X, Lv S, et al. Protective effects of Cucurbitacin B on acute lung injury induced by sepsis in rats. *Med Sci Monit*. **2017**;23:1355–1362.
32. Demir M, Taylan M, Kaya H, et al. Histopathological and biochemical effects of Ecballium elaterium on sepsis-induced lung injury. *J Investig Surg*. **2016**;29:302–308.