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# Mitigation of acute lung injury by semaglutide: role of inflammatory and oxidative stress pathways.

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## Abstract

Endotoxic disease Increased production of pro-inflammatory cytokines during bacterial infection is caused by high endotoxin levels, the protective effect of semaglutide on endotoxemia-induced acute lung injury was investigated in this research. twenty-four adult mice of the Swiss-Albano strain, aged 8-14 weeks and weighing between 25- 40 grams, were randomly divided into four groups. The groups were as follows: control (undergoing laparotomy without cecal ligation and puncture), endotoxemia (undergoing cecal ligation and puncture), vehicle (receiving normal saline for 1 week), and treatment (receiving semaglutide at a dose of 0.06mg/kg once daily subcutaneously for 1 week prior to cecal ligation and puncture). The scarification of animals was done 24 hours following the CLP treatment, and their lung tissues were utilized for histological investigation as well as the assessment of inflammatory mediators (IL-6, TNF-α, IL-1B, and NF-KB) and oxidative markers (MDA). The levels of lung tissue, inflammatory mediators, and oxidative stress were considerably elevated ($P<0.05$) in both the endotoxemia and vehicle groups compared to the control group. The treatment group exhibited significantly reduced levels of inflammatory and oxidative stress mediators compared to the endotoxemia and vehicle groups, with a statistical significance of $P<0.05$. Microscopically, mice in the endotoxemia and vehicle groups exhibited pronounced lung tissue damage. However, this damage was significantly ($P<0.05$) mitigated in the group treated with semaglutide. Semaglutide had the capacity to alleviate acute lung damage in male mice exposed to endotoxemia generated by CLP through a decrease in pro-inflammatory cytokines (such as interleukin-1β, interleukin-6, TNF-alpha, and NF-KB) as well as oxidative stress marker (MDA) inside the lung tissue.

**Key words**: endotoxemia, semaglutide, CLP.

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**Introduction**

Endotoximia Increased production of pro-inflammatory cytokines during bacterial infection is caused by high endotoxin levels, which can cause cellular damage, shock, and possibly multiple organ damage [1]. The high rates of mortality and morbidity associated with sepsis, along with the substantial financial burden it places on society, make it a global public health priority study that uncovered concerning worldwide data, projecting 48.9 million sepsis diagnoses and 11.0 million fatalities associated with sepsis in 2017 [2,3].

Acute lung injury (ALI) One typical type of organ failure that arises in sepsis caused by Gram-negative bacteria [4]. Bacterial endotoxin released into the bloodstream is one of the mechanisms underlying acute lung injury (ALI). This process initiates inflammatory mechanisms within the lungs, ultimately leading to pulmonary impairment. Endotoxins can induce changes in hemodynamic parameters by the stimulation of inflammatory cytokine release and the generation of an excessive quantity of free radicals and other oxidant mediators [5].

In the end, when lung function is compromised, it results in the occurrence of lung failure, in the form of acute respiratory distress syndrome (ARDS) [6] which is a severe and potentially lethal (30–40% in most studies) [7] described by widespread lung inflammation, resulting in poor oxygen supply [8,9]. The disorder is associated with damage to the structure of alveoli and tiny blood arteries at a microscopic level. This damage leads to the accumulation of protein-rich inflammatory fluid in the alveolar sacs [7].

The inflammation in lungs triggered when sepsis stimulate toll like receptor- 4 signaling pathway (TLR-4) (important cell surface receptor for pattern recognition of pathogens) [10], this will translocate nuclear factor-kappa B (NF-KB) to modulate the expression of inflammatory genes, including IL-1β, TNF-α, and IL-6[11,12]. These mediators are also elevated in lung disorders induced hypoxia as high altitude [13]. NF-κB is persistently activated in various inflammatory conditions, including sepsis, cardiovascular disorders, inflammatory bowel disease and arthritis [14]. Oxidative stress is defined as an imbalance between heightened levels of reactive oxygen species (ROS) and insufficient performance of antioxidant mechanisms. Elevated levels of oxidative stress can lead to cellular structural damage and potentially inflict injury on tissues. ROS, or reactive oxygen species, are essential for maintaining cellular homeostasis and facilitating mitochondrial energy generation [15]. Continuous NF-κB activity in inflammatory cells can drive the generation of reactive oxygen species (ROS), hence causing damage to the DNA of neighboring epithelial cells [14].

Cecal ligation and puncture in mouse model was used by many researches as an situation greatly mimic endotoxemia in order to explore beneficial effect of hypothesized drugs [16, 17,18,19].

Semaglutide drug Glucagon-like peptide-1 is a hormone that has a diverse spectrum of pharmacological potential and exerts various effects on metabolism. An important impact of GLP-1 is its capacity to induce the release of insulin in response to glucose levels [20]. Furthermore, it decreases the rate at which the stomach empties, inhibits hunger, stimulates the excretion of sodium and water, and controls the growth of β-cells in rodents. GLP-1 exhibits cardioprotective and neuroprotective properties, diminishes inflammation and cellular apoptosis, and has consequences for cognitive processes like learning and memory, reward-seeking behaviour, and taste preference. GLP-1 receptor agonists have been effectively used in clinical settings to treat type-2 diabetes by making

biochemical alterations that increase their strength and extend their duration of action [20].

In 2017, the US Food and Drug Administration (FDA) approved semaglutide, a GLP-1 receptor agonist, as a once-weekly injectable medication for the treatment of type 2 diabetes (T2D). In 2018, the European Medicines Agency authorised the use of semaglutide for the same purpose, allowing doses of up to 1.0 mg. Semaglutide is a long-acting GLP-1 analogue. It demonstrates a 94% sequence homology with human GLP-1 and specifically attaches to the GLP-1The configuration of semaglutide enables it to attach to albumin and hinder its breakdown by DPP-4, leading to a decrease in excretion via the kidneys. Consequently, semaglutide has a significantly extended half-life (about 7 days) in comparison to liraglutide and native GLP-1. This enables the administration of subcutaneous doses once a week without diminishing its efficacy [22].

Semaglutide not only impacts insulin and glucagon, but also facilitates weight loss by decreasing energy intake without dramatically altering energy expenditure. It stimulates GLP-1 receptors in the hindbrain and hypothalamus, affecting neuronal circuits that are responsible for controlling appetite and regulating food consumption [21].

The liver potentially plays a role in the elimination process of semaglutide breakdown products, as they are expelled through urine and feces after being metabolized [22]. Semaglutide use is associated with some adverse effect as hypoglycemia, gastrointestinal upset, pancreatitis, thyroid cancer, cholelithiasis and cardiovascular events [23].

In previous studies, GLP-1 agonists had beneficial effect against sepsis induced inflammatory and oxidative pathways in kidney [24], brain [25] and lungs [26]. The effect of semaglutide on lung injury that occur during sepsis in not thoroughly investigated.

So this research aimed to examine the beneficial role of semaglutide against endotoxemia - induced acute lung injury.

**Methods**

The research accomplished in the Pharmacology Department/ Faculty of Medicine/ University of Kufa (approved by the local Committee for Bioethics) at period 5-2-2023 to 1-9-2023.

**Animals and study design**

A total of 24 Albino Swiss mice, classified as adults, were obtained from the Animal Resources Centre at the University of Kufa-Faculty of Science. These mice had an average weight ranging from 25 to 40 grams and reached maturity between 8 to 14 weeks. The mice were housed in a regulated environment with a constant temperature of 25°C, a humidity level of 60-65%, and a light/dark cycle of 12 hours. The mice were classified into four groups, with each group consisting of six animals.

1- Control group: laparotomy surgery without CLP.
2- Endotoxemia group: CLP was performed.
**3-** Vehicle group: The mice were administered normal saline subcutaneous (SC) daily for 1 week before CLP.
**4-** Treatment group: mice received semaglutide in a dose of 0.06 mg/kg/day SC for 1 week before CLP [27,28].

**Experimental procedure of CLP:**

The mice were anesthetized by intraperitoneal administration of 10 mg of xylazine (V.M.D; Belgium) and 100 mg/kg of ketamine (Bremer Pharma GMB; Germany). The lower abdomen was shaved and a 1-2 cm incision was made in the abdominal area to find the cecum.

Subsequently, the cecum was securely fastened below the ileocecal valve and pierced twice with a G-20 needle before being repositioned to its original state. The abdominal incision was sutured with a 5.0 medical suture. Afterwards, the mice were observed for different signs of disease every 4 hours within a 24-hour timeframe before being returned to their cages [29,30].

**Prepration of semaglutide**

The pen was acquired from Novo Nordisk Germany and mixed with its vehicle (normal saline). The mice were then administered semaglutide at a dosage of 0.06 mg/kg per day for one week via subcutaneous injection before the cecal ligation and puncture procedure.

**Measurement of inflammatory and oxidative stress mediators**

The excised lung was rinsed with a normal saline solution to eliminate any traces of blood. Afterward, the lung was conserved by subjecting it to freezing at a temperature of -80°C. The lung section was subsequently pulverized using a pestle and mortar in a phosphate-buffered saline solution at a ratio of 1:10 (weight/volume). The solution comprised of 1% Triton X-100 and a protease inhibitor mixture. In order to further break down the homogenate, an ultrasonic cell disrupter was used for sonication [31].

The supernatant required for the measurement of IL-1β, IL-6, TNF-α, NF-KB, MDA, and TAS was obtained by centrifuging the homogenate according to the technique provided by the bioassay technology laboratory.

**Tissue preparation for histopathology**

The extracted lungs from the mice that killed rinsed with a saline solution to eliminate erythrocytes and clots. Subsequently, the cleaned lungs were immersed in a 10% formalin solution for preservation, to later undergo processing and embed in paraffin. To eliminate any residual water or formalin, the specimens underwent a dehydration process by submerging them in ethanol solutions with several concentrations (70%, 80%, 90%, and 100%) for around two hours each. Following that, xylene, an organic solvent, was employed to remove the alcohol from the samples and facilitate their immersion in paraffin wax, which served as an embedding agent. To evaluate the extent of lung damage, histological slices from all groups were examined under magnification ranging from X100 to X400. The results were scored as follows [32]:

- Zero score:no damage.
- One Score: under 25% damage (mild).
- Two Score 2: 25% - 50% of damage (moderate).
- Three Score: 50% - 75% of damage (severe).
- Four Score: 75% -100% of damage (highly severe).

**Quantitative data analysis**

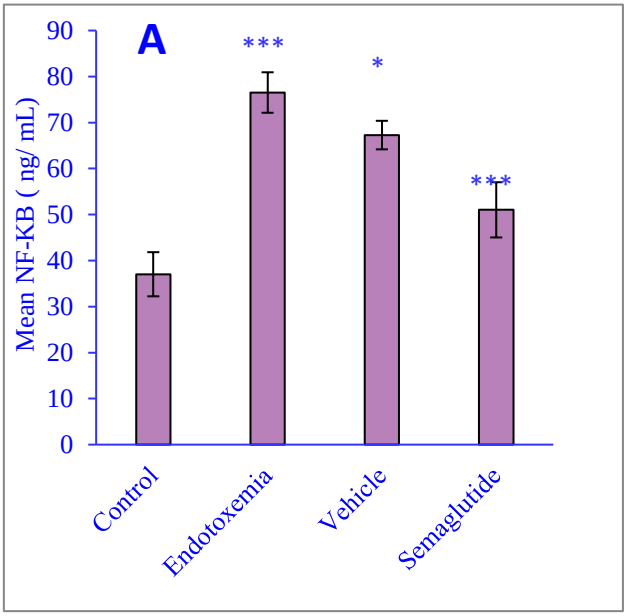
The normality of the data in SPSS was evaluated using the Kulmogorov-Smirnov and Shapiro tests. The ONE-way ANOVA test was used to compare results for normally distributed data, while the Kruskal-Wallis test was employed for histopathological data that is non-parametric. Both tests were conducted to compare more than three means, with a significance threshold of $P<0.05$.

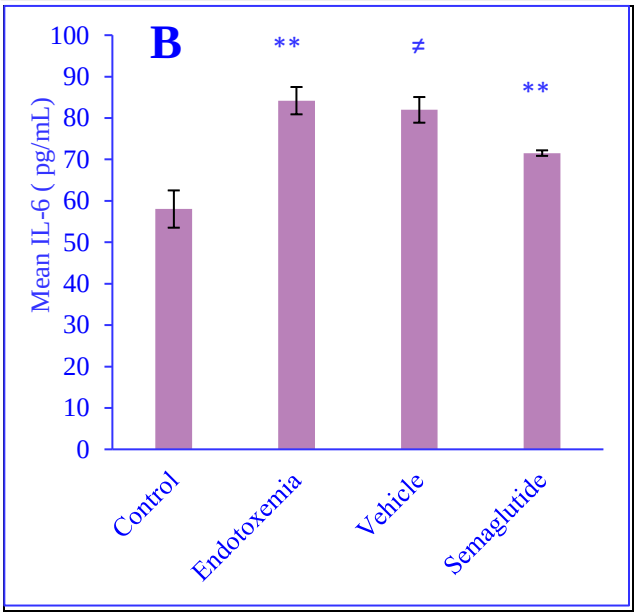
**Results**

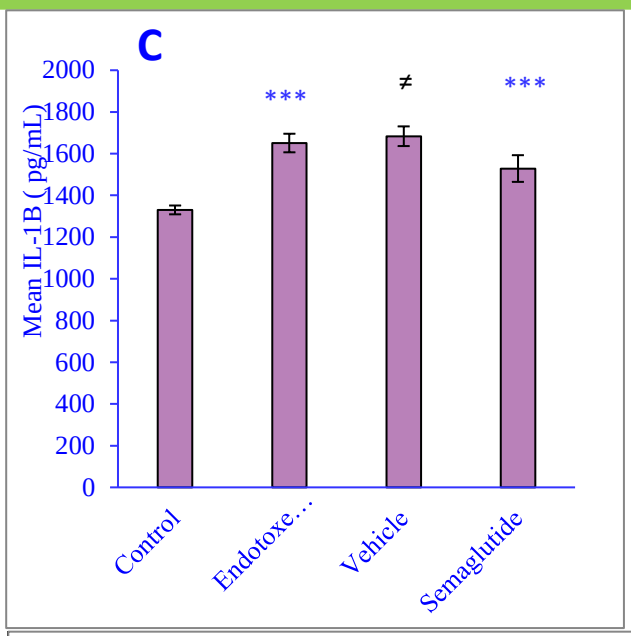
**1-Effect of semaglutide on pro-inflammatory mediators**

The levels of NF-KB, IL-6, IL-1β, and TNF-α in lungs of both endotoxemia and vehicle groups were significantly higher than levels in the control group. These cytokines levels were

significantly ($p<0.05$) reduced after treatment with semaglutide, figures (1 A-D).





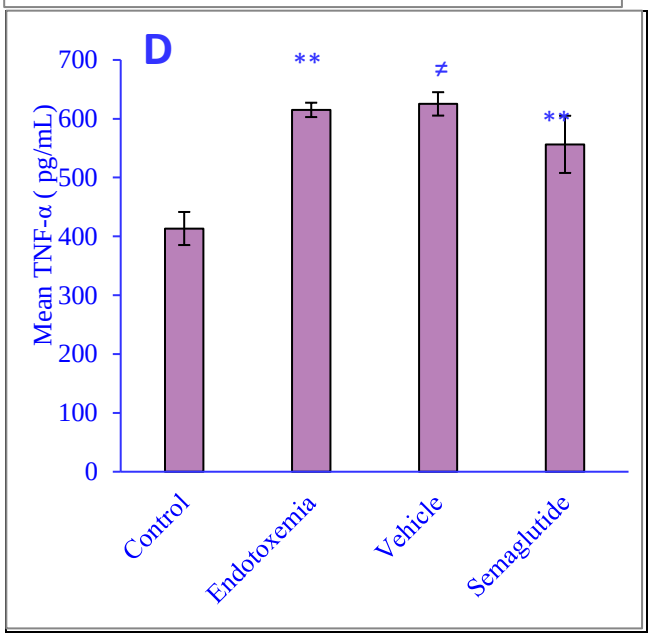




**Figure 1**: Effect of semaglutide on inflammatory cytokines of lung tissue including (A) NF-KB (B) IL-6 (C) IL1β (C) TNF-α. The data are presented as mean ± SD. ≠ P> 0.05 indicates non-significant differences while (*P < 0.01, ** P < 0.001, and ***P < 0.0001,) indicate significant differences in comparison with the endotoxemia group.

**2-Effect of semaglutide on oxidative stress markers:**

The (MDA) oxidative stress significantly high levels in lung tissue of mice endotoxemia and vehicle groups. The amount of these markers dramatically lowered in the lung tissue treated by semaglutide (figure 2).

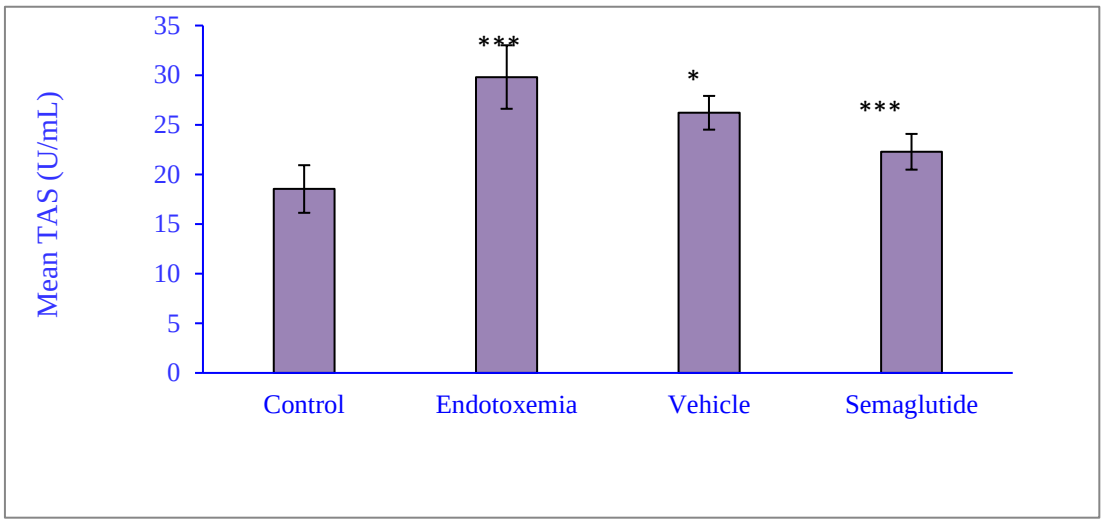



**Figure 2**: Effect of semaglutide on oxidative stress marker (MDA) in lung tissue. The data are presented as mean ± SD. ≠ P> 0.05 indicates non-significant differences while [*P < 0.01, ** P < 0.001, and ***P < 0.0001,] indicate significant differences in comparison with the endotoxemia group.

**3-Effect of semaglutide on lung histopathology**

Microscopic examination that done for lung tissue of mice in the control group revealed normal histological architecture with score zero, as illustrated in figure 3A. The endotoxemia- exposed mice exhibited extensive lung injury, with inflammatory cells infiltration as macrophages and neutrophils which observed within the alveoli, formation of hyaline membranes, and thickening of the interalveolar septa. Moreover, the blood vessels in the lung tissue exhibited congestion, resulting in the occurrence of hyperemia and interstitial edema. Furthermore, the presence of leaked red blood cells (RBCs) was observed in both the air sacs and the surrounding tissue, leading to the highest histopathological score of 2., figure 4B. These histopathological changes were also clearly observed in saline –vehicle group, score 2 also, figure 3C. Lung sections of semaglutide treated group revealed improvement in the histological architecture of the tissue. A mild form of inflammation was appeared, with few foci of macrophages and neutrophils accumulation in the alveoli with vascular congestion and focal areas of hyperemia, score 1, figure 3D. The percent of histopathological damage in lung tissue illustrated in figure 3E, with highest percent in mice with endotoxemia and lowest percent of damage in control group. Semaglutide treatment caused reduction in percent of damage.

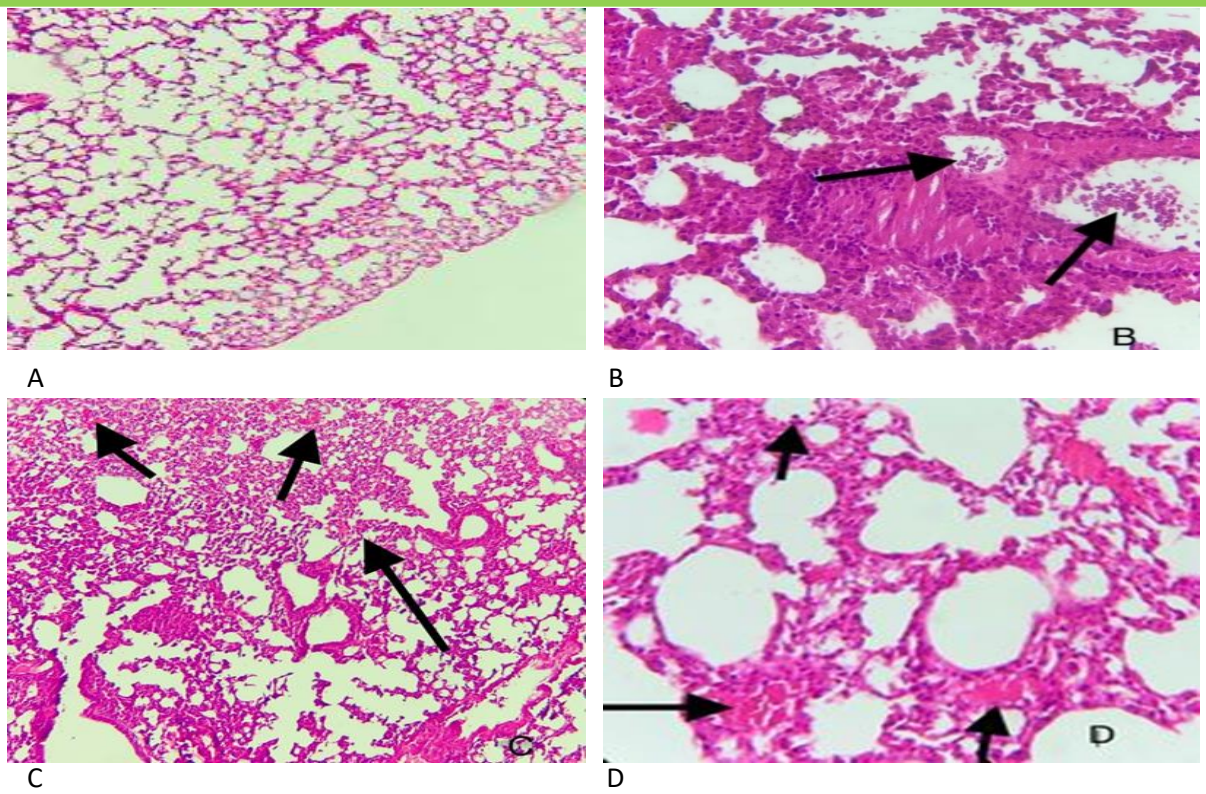



**Figure 3:** Histological cross sections of lung tissue stained by H& E. (A) control group (100X), normal histology with score zero (B) The endotoxemia group had a significant infiltration of mixed inflammatory cells, including neutrophils and macrophages, affecting 45% of the analyzed lung tissue, with a severity score of 2. The black arrows indicate hyperemia, congestion, and hemorrhage at a magnification of 400X. (C)In the saline vehicle group the lung tissue shows interstitial, perivascular, and intra-alveolar mixed inflammation, represented by a black arrow, affecting 40% of the examined tissue with a score of 2 at a magnification of 100X.( D)In the treatment group the lung tissue of mice exhibits focal interstitial and intra-alveolar mixed inflammation, indicated by a black arrow, involving 25% of the examined tissue with a score of 1 at a magnification of 400X. The histopathological damage percentage, expressed

as mean± SEM, shows significant differences (P <0.001) compared to the endotoxemia group.

**Discussion**

Sepsis is a potentially fatal disorder resulting from an abnormal response of the body to an infection, which causes rapid failure of essential organs such as the liver, lungs, brain, and kidneys. The lung is highly vulnerable to the impacts of sepsis, with around 50% of sepsis patients advancing to acute lung injury (ALI) and severe acute respiratory distress syndrome (ARDS) [33].

The findings of our study indicate that the administration of CLP resulted in acute lung injury in mice, as evidenced by increased levels of pro-inflammatory cytokines (, IL-6, IL-1β, NF-Kβ, and TNF-α) in the lung homogenate of the endotoxemia group.

The findings contradicted the findings of Hu et al. (2020), who reported that pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 were elevated in lung tissue and played a crucial role in the early phases of acute lung injury generated by the CLP challenge [34].

A recent study examined the effects of continentalic acid on the lungs of mice. The researchers found that the levels of cytokines stated earlier were significantly increased in the lung homogenates of the sepsis group, indicating a heightened state of inflammation [35]. In addition, a study conducted by Cinar and Sirin in 2019 discovered that the levels of IL-6 and NF-KB were higher in the group of rats with sepsis following the CLP process [36].

Recent research observed a significant elevation in the levels of MDA in lung homogenates in the endotoxemia group compared to the control group.

The results of this investigation align with the findings of Zolali *et al*, who observed a significant rise in oxidative stress markers in lung tissues when exposed to endotoxemia produced by LPS treatment [37]. Lingaraju *et al*. conducted a study to examine the elevated levels of oxidative stress in the lungs following cecal ligation and puncture (CLP) [38].

According to our results, the histological alterations in the lung appear 24 hours after the CLP surgery. The observed findings encompassed significant and extensive infiltration of inflammatory cells, accumulation of fluid in both the alveolar spaces and interstitium, occasional bleeding, thickening of the walls separating the alveoli, and the development of hyaline membranes Zhu *et al.* (2018) and Akpinar *et al*. (2022) observed significant and distinctive lung pathological alterations following LPS [39, 40]. According to Yang et al. (2016), pulmonary histological changes such as alveolar hemorrhage and infiltration of neutrophils were observed in lung tissue following CLP [41].

The research findings a significant decrease in the levels of pro-inflammatory mediators in the pulmonary tissues of the group treated with semaglutide, as compared to the group subjected to CLP.

The study conducted by Li et al. also confirmed the advantageous effects of semaglutide, as it resulted in a reduction in the levels of NF-κB, TNF-α, and IL-1β expression [43] Jiang et.al demonstrated that pretreatment with semaglutide resulted in a significant reduction in IL-6, TNF-α, and lung damage in rats [42]. Shnaien *et al*. (2023) discovered that Semaglutide reduced the levels of inflammatory cytokines, specifically in brain tissue of male mice, following polymicrobial sepsis [25]. The NF-κB signaling system is crucial for regulating inflammatory responses and biological activities such as cell proliferation and apoptosis. Inhibiting the NF-κB signaling pathway is an efficient strategy to protect against acute lung injury (ALI) generated

by lipopolysaccharide (LPS). Semaglutide can alleviate the damage inflicted on human pulmonary artery endothelial cells (HPAECs) by LPS by deactivating the NF-κB signaling pathway, resulting in reduced levels of inflammatory cytokines [42].

In this study, the level of oxidative stress was shown to be higher in the group with endotoxemia, while it was lower in the treatment group. Semaglutide protected HPAECs from the suppressive impact of LPS on cell growth, as well as the increase in pro-inflammatory cytokines and cell death. The inhibition of Histone Deacetylase 5 (HDAC5) expression led to the attainment of this protection [30]. In a study conducted by Li *et al*. in 2020, it was shown that Semaglutide reduced oxidative stress and cardiac damage in rats [43]. Semaglutide has the potential to reduce inflammation and oxidative stress in the heart. The study found that in mice with obesity, the treatment resulted in a significant decrease in body weight and also had anti-inflammatory and antioxidant effects [44]. Lung tissues were collected from mice that received semaglutide treatment exhibited substantially decreased infiltration of inflammatory cells into the lungs, as well as reduced hyperemia, edema, congestion, and another pathological abrasion resulting by endotoxemia with the reduction in overall lung injury score.

Wang *et al*. found that semaglutide, GLP-1 receptor agonists, mitigated airflow restrictions, airway damage and fibrosis as well as enhanced the well-being of individuals with chronic obstructive air way disease [45]. Other recent study observed that tissues extracted from mice that received semaglutide displayed notably reduced cellular damage with suggestion that semaglutide has the potential to safeguard against sepsis avert brain impairment [25]. Abd Uljaleel *et al* showed that dulaglutide showed effectively decreased histopathological lesions in lung challenged with LPS and reduced lung injury [26]. This improvement in lung tissue architecture was clearly attributed to ability of semaglutide on reduction of inflammatory mediators and oxidative stress markers as explained above in this study.

**Conclusion:** Semaglutide has the capacity to alleviate acute lung damage in male mice exposed to endotoxemia generated by CLP through a decrease in pro-inflammatory cytokines (such as interleukin-1β, interleukin-6, TNF-alpha, and NF-KB) as well as oxidative stress markers (MDA and TAS) inside the lung tissue

**Ethical clearance:** The study was approved by the Bioethical Committee of the University of Kufa, as well as its representative in the Faculty of Medicine (number 6014, dated 2/2/2023).

References

[1] Jawad, A. S., Hassan, E. S. & Mohammad, A. R. Protective Effect of Empagliflozin from Acute Renal Injury During Endotoxemia in Mice Model. Lat. Am.J. Pharm. 2022; 41 (2): 463-71. https://www.latamjpharm.org/resumenes/41/2/LAJOP_41_2_1_23.pdf.

[2] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock. Intensive Care Med. 2021;47(11):1181–247.

[3] Abd Uljaleel A, Hassan E. Protective Effect of Ertugliflozin against Acute Lung Injury Caused by Endotoxemia Model in Mice. Iran J War Public Health 2023; 15 (1) :67-75. URL: http://ijwph.ir/article-1-1307-en.

[4] Hamza RT, Majeed SA, Ghafil FA, Hassan, E. S. and Hadi, N. R. Nephroprotective Effect of Melatonin in

Sepsis Induces Renal Injury : CLP Mice Model. Lat Am J Pharm. 2022;41(3):589–96. https://www.latamjpharm.org/resumenes/41/3/LAJOP_41_3_1_12.pdf.

[5] Gokcinar D, Ergin V, Cumaoglu A, Menevse A, Aricioglu A. Effects of ketamine, propofol, and ketofol on proinflammatory cytokines and markers of oxidative stress in a rat model of endotoxemia-induced acute lung injury. Acta Biochimica Polonica. 2013;60 (3).

[6] Ware LB. Pathophysiology of acute lung injury and the acute respiratory distress syndrome. Semin Respir Crit Care Med. 2006;27(4):337-49.

[7] Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, et al. Acute respiratory distress syndrome. Nature Reviews Disease Primers. 2019;5(1):18.

[8] Diamond M, Peniston HL, Sanghavi DK, Mahapatra S. Acute Respiratory Distress Syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.

[9] Vassiliou AG, Kotanidou A, Dimopoulou I, Orfanos SE. Endothelial damage in acute respiratory distress syndrome. International journal of molecular sciences. 2020;21(22):8793.

[10] Mohammad, A. R. , Hadi, A.R. and Hassan, E. S. Potential Protective Effect of Ibrutinib from Acute Brain Injury During Endotoxemia in Mice . Lat. Am. J. Pharm. 2022; 41 (2): 472-80. https://www.latamjpharm.org/resumenes/41/2/LAJOP_41_2_1_24.pdf.

[11] Jiang Q, Yi M, Guo Q, Wang C, Wang H, Meng S, et al. Protective effects of polydatin on lipopolysaccharide-induced acute lung injury through TLR4-MyD88-NF-kappaB pathway. Int Immunopharmacol (2015) 29(2):370–6. doi:10.1016/j.intimp.2015.10.027

[12] Hussein S N, Majeed S A, Ghafil F A, Hassan E S, Abdulkadim A H, Alaa Ghazi, et al. Nephroprotective effect of Celastrol in an experimental model of Endotoxemia. Bulletin of national institute of health, 2022; 140 (6): 2865-74.https://www.healthsciencesbulletin.com/volume/BNIHS/140/06/nephroprotective-effect-of-celastrol-in-an-experimental-model-of-endotoxemia-6334125c1eabb.pdf.

[13] Song TT, Bi YH, Gao YQ, Huang R, Hao K, Xu G, et al. Systemic pro-inflammatory response facilitates the development of cerebral edema during short hypoxia. J Neuroinflammation (2016) 13(1):63. doi:10.1186/s12974-016-0528-4.

[14] Park, M. H. and J. T. Hong (2016). "Roles of NF-κB in cancer and inflammatory diseases and their therapeutic approaches." Cells 5(2): 15.

[15] Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiological reviews. 2014;94(3):909-50.

[16] Hussein S N, Majeed S A, Ghafil F A, Hassan E S & Hadi N R. Toll-like receptors 4 antagonist, Ibudilast, ameliorates acute renal impairment induced by sepsis in an experimental model. Bulletin of national institute of health, 2022; 140 (7): 2900-09.

[17] Mohammad A R, Shnaien A A, Alabsawy S K, Hassan E S. Protective Effect of Ipragliflozin in Acute Brain Injury Induced by Endotoxemia in Mice. Iran J War Public Health 2023; 15 (3) :225-231. URL: http://ijwph.ir/article-1-1328-en.html.

[18] Ghafil FA, Hassan ES, Aziz ND, Salim MM, Majeed SA, Rasheed SMH , Mardan HW. Cardioprotective Potential of Celastrol In Sepsis-induced Cardiotoxicity: Mouse Model of Endotoxemia. Iran J War Public Health 2023; 15 (4). https://ijwph.ir/article-1-1344-en.html.

[19] Mohammad AR, Hassan ES and Majeed SA. PI3K/AKT and STAT3 pathways mediate the neuroprotective effect of dasatinib from acute cerebral injury in endotoxemic mice. Research in pharmaceutical sciences; 2024; 19 (1).

[20] Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide 1 (GLP-1). Molecular Metabolism. 2019;30:72-130.

[21] Lau DC, Batterham RL, le Roux CW. Pharmacological profile of once-weekly injectable semaglutide for chronic weight management. Expert Review of Clinical Pharmacology. 2022;15(3):251-68.

[22] Jensen L, Helleberg H, Roffel A, van Lier JJ, Bjørnsdottir I, Pedersen PJ, et al. Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species. European Journal of Pharmaceutical Sciences. 2017;104:31-41.

[23] Smits MM, Van Raalte DH. Safety of semaglutide. Frontiers in endocrinology. 2021;12:645563.

[24] Hassan, E. S., Jawad, A. S. & Mohammad, A. R. Protective Effect of Liraglutide from Acute Renal Injury During Endotoxemia in Mice Mode. Lat. Am. J. Pharm. 2022; 41 (2): 428-36. https://www.latamjpharm.org/resumenes/41/2/LAJOP_41_2_1_19.pdf.

[25] Shnaien A, Mohammad A, Hassan E. Neuroprotective Effects of Semaglutide in Endotoxemia Mouse Model. Iran J War Public Health 2023; 15 (2) :199-205.URL: http://ijwph.ir/article-1-1327-en.html

[26] Abd Uljaleel AQ, Hassan ES, Mohammad AR, Hadi NR. Protective Effect of Dulaglutide on Lung Injury in Endotoxemia Mouse Model. Iran J War Public Health 2023; 15 (1):35-42. URL: http://ijwph.ir/article-1-1289-en.html.

[27] Zhang L, Zhang L, Li L, Hölscher C. Neuroprotective effects of the novel GLP-1 long acting analogue semaglutide in the MPTP Parkinson's disease mouse model. Neuropeptides. 2018;71:70-80.

[28] Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. Journal of medicinal chemistry. 2015;58(18):7370-80.

[29] Drosatos K, Khan RS, Trent CM, Jiang H, Son N-H, Blaner WS, et al. Peroxisome proliferator-activated receptor-γ activation prevents sepsis-related cardiac dysfunction and mortality in mice. Circ Heart Fail. 2013;6(3):550–62.

[30] Wellington D, Mikaelian I, Singer L. Comparison of ketamine-xylazine and ketamine-dexmedetomidine anesthesia

and intraperitoneal tolerance in rats. J Am Assoc Lab Anim Sci. 2013;52(4):481-7.

[31] Najm NA, Hassan ES. Ipragliflozin protect from acute pulmonary injury induced by endotoxemia in mouse model via NF-KB pathway. Health Biotechnology and Biopharma (2023), 7(4): 98-113.

[32] Zahran R, Ghozy A, Elkholy SS, El-Taweel F, El-Magd MA. Combination therapy with melatonin, stem cells and extracellular vesicles is effective in limiting renal ischemia reperfusion injury in a rat model. Int J Urol. 2020;27(11):1039-49.

[33] Jensen JK, Binderup T, Grandjean CE, Bentsen S, Ripa RS, Kjaer A. Semaglutide reduces vascular inflammation investigated by PET in a rabbit model of advanced atherosclerosis. Atherosclerosis. 2022;352:88-95.

[34] Hu Q, Wang Q, Han C, Yang Y. Sufentanil attenuates inflammation and oxidative stress in sepsis-induced acute lung injury by downregulating KNG1 expression. Molecular Medicine Reports. 2020;22(5):4298-306.

[35] Ali, H., Khan, A., Ali, J., Ullah, H., Khan, A., Ali, H., et al. Attenuation of LPS-induced acute lung injury by continentalic acid in rodents through inhibition of inflammatory mediators correlates with increased Nrf2 protein expression. BMC Pharmacol Toxicol. 2020; 21: 81.

[36] Cinar I, Sirin B, Aydin P, Toktay E, Cadirci E, Halici I, et al. Ameliorative effect of gossypin against acute lung injury in experimental sepsis model of rats. Life sciences. 2019;221:327-34.

[37] Zolali E, Asgharian P, Hamishehkar H, Kouhsoltani M, Khodaii H, Hamishehkar H. Effects of gamma oryzanol on factors of oxidative stress and sepsis-induced lung injury in experimental animal model. Iranian journal of basic medical sciences. 2015;18(12):1257.

[38] Lingaraju MC, Pathak NN, Begum J, Balaganur V, Bhat RA, Ram M, et al. Betulinic acid negates oxidative lung injury in surgical sepsis model. J Surg Res. 2015;193(2):856-67.

[39] Zhu T, Li C, Zhang X, Ye C, Tang S, Zhang W, et al. GLP-1 analogue liraglutide enhances SP-A expression in LPS-induced acute lung injury through the TTF-1 signaling pathway. Mediators of inflammation. 2018;2018.

[40] Akpinar E, Kutlu Z, Kose D, Aydin P, Tavaci T, Bayraktutan Z, et al. Protective effects of idebenone against sepsis induced acute lung damage. Journal of investigative surgery. 2022;35(3):560-8.

[41] Yang L, Li D, Zhuo Y, Zhang S, Wang X, Gao H. Protective role of liriodendrin in sepsis-induced acute lung injury. Inflammation. 2016;39:1805-13.

[42] Jiang Z, Tan J, Yuan Y, Shen J, Chen Y. Semaglutide ameliorates lipopolysaccharide-induced acute lung injury through inhibiting HDAC5-mediated activation of NF-κB signaling pathway. Human & Experimental Toxicology. 2022;41:09603271221125931.

[43] Li Q, Tuo X, Li B, Deng Z, Qiu Y, Xie H. Semaglutide attenuates excessive

exercise-induced myocardial injury through inhibiting oxidative stress and inflammation in rats. Life sciences. 2020;250:117531.

[44] Pan X, Yang L, Wang S, Liu Y, Yue L, Chen S. Semaglutide ameliorates obesity-induced cardiac inflammation and oxidative stress mediated via reduction of neutrophil Cxcl2, S100a8, and S100a9 expression. Molecular and Cellular Biochemistry. 2023:1-15.

[45] Yaribeygi H, Maleki M, Sathyapalan T, Jamialahmadi T, Sahebkar A. Anti-inflammatory potentials of incretin-based therapies used in the management of diabetes. Life Sci. 2020;241:117152. doi: 10.1016/j.lfs.2019.117152.