Original Research Article

Ipragliflozin protect from acute pulmonary injury induced by endotoxemia in mouse model via NF-KB pathway

Noor Adnan Najm¹, Ekhlas Sabah Hassan^{1,*}

¹Department of Pharmacology & Therapeutics, Faculty of Medicine, University of Kufa, Najaf, Iraq

Corresponding author:* Ekhlas Sabah Hassan, Department of Pharmacology & Therapeutics, Faculty of Medicine, University of Kufa, Najaf, Iraq, *E-mail: ekhlass.khazaal@uokufa.edu.iq* **DOI: 10.22034/HBB.2024.06

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ABSTRACT

Sepsis is now more commonly regarded as an uncontrolled inflammatory and immune response throughout the body, triggered by microbial invasion and resulting in high mortality rate from organ damage. This study aimed to demonstrate the protective impact of ipragliflozin on lung damage induced in mice by Cecal Ligation and Puncture (CLP). The levels of lung tissue inflammatory & oxidative stress markers (IL-1 β , IL-6, TNF- α , NF-KB & MDA) were significantly elevated in the sepsis in comparison to the sham. On other hand, mice treated with ipragliflozin had a significant reduction in the level of these mediators. Histological examination revealed significant lung tissue damage in mice undergo sepsis which significantly reduced after ipragliflozin treatment. Ipragliflozin shows promise in reducing pulmonary dysfunction in male mice with sepsis.

Keywords: Endotoxemia, Ipragliflozin, NF-KB

INTRODUCTION

Sepsis is characterized as a microbial infection causing fever (or low body temperature), increased heart rate, rapid breathing, and alterations in blood leukocyte levels. However, sepsis is now more commonly regarded as an uncontrolled inflammatory and immune response throughout the body, triggered by microbial invasion and resulting in organ damage [1].

Sepsis can affect individuals of all age groups & it is particularly significant in Intensive Care Units (ICUs), affecting around 30 % of patients, although the prevalence varies across different regions. A study conducted in the United States, involving more than 170,000 sepsis cases, found that 55 % of these cases admitted in ICU [2]. Endotoxemia is referred to sepsis that caused by gram negative bacteria. They contain endotoxins in their outer membrane. Endotoxins. large Lipopolysaccharides (LPS) that are heat stable, can enter the bloodstream causing this condition [3].

The high mortality rate of sepsis resulted from multi organ damage including the lungs. Acute Lung Injury (ALI) is a serious pulmonary condition described by uncontrollable oxidative stress release, inflammation. pulmonary edema & infiltration of neutrophils [4]. The more severe damage to lungs occur during Acute Respiratory Distress Syndrome (ARDS) which regarded as a life-threatening illness manifested by profound inflammation & destruction of the general architecture of the lung alveoli resulting in insufficient oxygen supply and abrupt onset of symptoms [5].

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Sepsis immediately up regulates pattern recognition receptors (PRRs) and activates signal transduction cascades including key inflammatory mediators like TNF-α, IL-1 & IL-6 in addition to specific antiinflammatory mediators, such as IL-4, IL-10 and transforming growth factor $-\beta$ that work counteract to intense pro inflammatory response, aiming to restore immunology. Maintaining a well-regulated equilibrium in the mediators network and anti-inflammatory mediators, is vital for effectively eliminating invading pathogens while preventing excessive and tissuedamaging inflammation [6].

Ipraglflozin inhibits Sodium-Glucose cotransporter 2 enzyme (SGLT2) which is primarily accountable for reabsorption of filtered glucose and sodium in tubules of kidney. It is used for treating type 2 diabetes. Repeated administration of this drug over four weeks, improved obesity, hepatic steatosis, and hyperlipidemia [7].

Ipragliflozin lowers blood glucose independently of insulin secretion & action, which reduces the risk of hypoglycemia [8]. It has been observed that it can induce a daily excretion of approximately 50 to 80 grams of urinary glucose, depending on the dose [9].

The oral bioavailability of ipragliflozin is reported to be 90 % and the majority of it in the plasma (94.6-96.5 %) is bound to plasma proteins, mainly albumin. Despite this, it is extensively distributed outside the blood plasma and its terminal half-life is approximal 10-15 hours. Ipragliflozin is largely metabolised through glucuronidation and biliary excretion may contribute to its clearance [9]. Leg and foot amputation, bone fracture, cancer, genital and urinary tract infection, and diabetic ketoacidosis are the main adverse effects that reported for ipragliflozin [10].

Previous studies suggested that ipragliflozin reduced the inflammatory marker levels [11] and oxidative stress biomarkers in kidneys [12] & in liver [13]. Only one research discussed the impact of ipragliflozin on sepsis- induced acute lung injury and no work deals with its effect on oxidative markers in this serious condition, this expressed the novelty of this study in dealing with that subject. Aim of this research was to demonstrate the protective impact of ipragliflozin on lung damage induced by sepsis.

MATERIALS AND METHODS

Time and site of research

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The study began on 1- 3- 2023, and ended on 1-9-2023 at Pharmacology Department, Faculty of Medicine, University of Kufa. The project obtained approval from the local Bioethical Committee (ethical approval number 6014, on February 2, 2023). The study adhered to the recommendations of the Committee during its whole course.

Animal research and experimental design A total of 24 adult Albino Swiss mice, weighing between 20 and 35 grams on average, and achieving maturity within a period of 9 to 14 weeks (source: Animal Resources Centre in Faculty of Science, University of Kufa). The mice were housed in a controlled environment regarding temperature (25 °C), humidity (60 % - 65 %) & a light-dark cycle of 12 hours. The mice were segregated into four groups, with each group including six mice:

- Sham: subjected to anesthesia through laparotomy surgery without CLP.
- 2. Sepsis (CLP): underwent CLP procedure.
- DMSO-Vehicle group: received a daily oral administration of an equivalent volume of (DMSO+corn oil) seven days before CLP.

 Ipragliflozin: The pure powder of drug was obtained from Med Chem Express, USA, and was made by diluting it in a solution containing 5 % DMSO and Corn Oil. Mice received ipragliflozin (5 mg/kg/day orally) for 7 days before CLP [13].

Experimental procedure

Sepsis in mice induced surgically by a standard procedure called cecal ligation and puncture. The mice were anaesthetized by administering an intraperitoneal dose of 100 mg/kg of ketamine (obtained from Bremer Pharma GMB, Germany) & 10 mg of xylazine (from V.M.D, Belgium). At the midpoint of the abdomen, small surgical incision measuring approximately 1-2 cm was made to find the cecum, ligated it below the ileocecal valve & punctured twice with a G-20 needle. Then incision was closed using a 5.0 surgical suture. After the therapy, the mice were carefully monitored for any signs of disease at 4-hour intervals over a 24-hour period before being put back in their habitat [14,15].

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Tissue Preparation for ELISA to Measure (*IL-1B*, *IL-6*, *TNF-a*, *NF-KB & MDA*)

The lung was rinsed with a 0.9 % Nacl solution to eliminate any red blood cells or clots. Then preserved at -80 °C till utilization. The lungs were homogenized using a high-intensity ultrasonic liquid processing method with solution 1:10 [weight/volume] composed of phosphate buffer saline [16]. The lysates were subsequently subjected to centrifugation at 10,000 rpm at a temperature 4 °C for 10 minutes. The supernatants were then used to quantify the markers using tissue ELISA kits specific for mice (supplied from according Bioassay, china) to the recommendation of the manufacturer.

Tissue histopathology

The remaining portion of the lung tissue was submerged in a solution of 10% formalin, subjected to dehydration using several types of alcohol, treated with xylene to remove impurities, and finally placed within a paraffin block for preservation. The tissue sectioned & stained with Hematoxylin and Eosin dye (H&E) according to standard procedure. Afterward, they are sent to а histopathologist for histological evaluation

[17]. Competent pathologists blindly evaluated lung tissue injury by examining four randomly chosen regions. The portions were evaluated using a scale designed to assess the extent of lung damage [17]: score 0: no damage, score 1,2,3,4 referred to tissue damage 25 %, between 25 % - 50 %, between 50 % - 75 % & between 75 % - 100 %, respectively.

Statistical 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 regularly distributed data, while the Kruskal Wallis test was used to compare results for histopathological data with more than three means. Both tests were conducted at a significance level of α <0.05. Ipragliflozin protect from acute pulmonary

RESULTS

Effect of ipragliflozin on pro-inflammatory cytokines

Concentrations of IL-1B, IL-6, TNF-A, & NF-KB in lungs were elevated in both vehicle and sepsis groups as compared to sham. Furthermore, administration of ipragliflozin significantly reduced the levels of these cytokines in the treated group, with a significant statistical difference (p<0.05), Table 1.

Effect of Ipragliflozin on oxidative stress

The levels of oxidative stress marker (MDA) was notably elevated in the lung tissue of mice belonging to both the CLP and vehicle groups. However, the group that received pre-treatment with ipraglflozin exhibited a substantial reduction in the level of this mediator in the lung tissue, Table 1.

Inflammatory	Sham	CLP	DMSO-	Ipragliflozin	p value
and oxidative			vehicle		
stress					
markers					
IL-1B	1330.32±8.646	1651.07±18.154	1696.37±25.979	1419.75±9.442	*0.00001
					**0.107
					***0.00001
IL-6	58.02±1.834	84.18±1.356	83.84±77.445	65.36±0.993	*0.00001
					**0.087
					***0.00001
TNF	413.46±11.490	615.08±4.981	621.71±8.704	541.95±15.301	*0.00001
					**0.709
					***0.00001
NF-KB	37.03±1.976	76.53±1.798	74.76±2.457	53.26±1.463	*0.00001
					**0.528
					***0.00001
MDA	3.55±0.127	5.06±0.1766	4.98±0.194	4.17±3.781	*0.00001
					**0.763
					***0.00001
		1	1		1

Table 1: Inflammatory & oxidative stress biomarkers in pulmonary tissue of mice

*Comparison of CLP versus sham, ** comparison of CLP versus vehicle, *** comparison of CLP versus ipragliflozin groups. The data were reported as mean ± standard error of mean.

Effect of ipragliflozin on lung histopathology

The control group displayed histological characteristics typical of healthy lung tissue, showing no discernible alterations in the walls of alveoli, interstitum, or bronchioles. In addition, there are no indications of lung inflammation, such as edoema and hyperemia Figure 1A. Conversely, the CLP group, consisting of mice who were subjected to sepsis, exhibited significant lung damage. The condition was distinguished by the invasion of macrophages and neutrophils to the alveoli, congested blood arteries, increased blood flow, and swelling in the interstitial space, leading to the most elevated histopathological score (Figure 1B). The examination of the lung tissue sections of DMSO group showed several

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aberrant histological alterations, such as the presence of macrophages within the alveoli, neutrophils, notable inflammation around blood vessels, increased blood flow, and swelling in the interstitial space (Figure 1C).

An enhancement in the histological features of the lung was reported in the received group that ipragliflozin treatment. The histopathological score of sepsis shown a notable decrease in comparison to both the CLP and DMSO groups. Lungs showed a less intense inflammation, which was characterized by a little buildup of macrophages and neutrophils in the alveoli, along with localized increased blood flow and vascular congestion (Figure1D).



Figure 1. The histological sections of lung tissue. A: Sham group (400X), no abnormalities were identified. B: The CLP group (100X) had a significant presence of inflammatory cells, specifically neutrophils & macrophages, covered 50 % of the investigated lung tissue. Furthermore, signs of hyperemia, congestion (shown by black arrow), and haemorrhage were clearly observable. C: DMSO-vehicle group (400X) showed lung tissue with a moderate level of inflammation within the air sacs, characterised by a high presence of neutrophils and macrophages. This inflammation affected 40 % of the lung tissue that was analyzed (black arrow). Additionally, there was evidence of increased blood flow around the blood vessels D: The group treated with Ipragliflozin (100X) had lung tissue characterized by a combination of focal inflammation in the interstitial and intra-alveolar regions (shown by the black arrow), which accounted for 10 % of the tissue analyzed.

DISCUSSION

Sepsis, is a critical condition characterized by the body's disproportionate response to an infection, resulting in the sudden malfunction of essential organs like the brain [18,11], heart [19], and kidneys [20]. Among these organs, the lungs are most susceptible to sepsis, since over 50 % of sepsis patient progress to ALI or severe RDS. The significance of acute lung injury

in the mortality of individuals affected by this condition [21].

The results of our study demonstrate that sepsis caused by CLP triggers acute pulmonary injury in mice. This is supported by the observation of elevated levels of inflammatory mediators (TNF- α , IL-1 β , IL-6, & NF-KB) in the lung homogenates of the sepsis group. According to Arslan et al., the pulmonary IL-6 level of the sepsis group were significantly elevated when investigating the anti-inflammatory effects of Ecballium elaterium in rats [22]. A further investigation conducted by Speer et al. in 2020 confirmed our findings, showed high levels of the inflammatory mediators (TNF- α , IL-1 β , & IL-6) in the lungs of mouse models following CLP [23].

Furthermore, in the study conducted by Wang *et al.* in 2019, it was discovered that IL-1B, IL-6 & TNF- α levels in mice subjected to CLP were markedly elevated in both bronchoalveolar lavage fluid and sera [24].

The levels of the inflammatory markers those measured in our research showed a significant reduction in the lungs of mice that received pre-treatment with ipragliflozin. These findings suggest that ipragliflozin has strong anti-inflammatory

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properties in the context of ALI. According to our knowledge, at this time no published research investigate the effect of ipragliflozin on lung injury induced by sepsis and our work is novel 2023 found .Mohammad.*et* al that Ipragliflozin has the potential to reduce cerebral impairment in male mice with polymicrobial sepsis induced by CLP through downstream TLR4. STAT3 signaling pathways reduced so inflammatory mediators like IL-1B, IL-6, TNF-alpha [25].

Abd Uljaleel *et al* Investigation revealed, the mice that received ertugliflozin treatment showed markedly reduced levels of inflammatory cytokines in lung [26]. In another study Dapagliflozin appeared to reduced PAI-1 and TNF- α in patient received this drug, thus lowering the risk of cardiovascular events [27].

Wang *et al* Observation disclosed that empagliflozin reduced IL-6, and TNF-Alpha after their increament in the group undergo ischemia-reperfusion [28]. Empagliflozin shown the capacity to reduce acute kidney injury in mice during sepsis generated by CLP. This effect was achieved via altering TLR4, TNF- α , IL-6,

and the downstream signalling pathway of NF-κB cascades [29].

The cause behind the protective effect of ipragliflozin for lung may be due to decreasing an excessive build-up of a variety of signaling molecules, including IL-6, IL-1 β , TNF- α , which increased in lung injury after CLP [30]. Cytokines are molecules that control the immune response to infection and have a crucial function in controlling inflammation and damage. There are two distinct categories of cytokines. Pro-inflammatory cytokines promote widespread inflammation, while anti-inflammatory cytokines suppress inflammation and promote recovery [31].

In the recent study, a significant rise in level of MDA (malondialdehyde) was observed in lung homogenates after CLP, as compared to sham group. The similar results were achieved by other studies [32,33].

Sang *et.al* showed that MDA marker reduced by quercetin after its increment by CLP [34]. ROS can induce oxidative stress in the lung's epithelial cells, which in turn triggers endoplasmic reticulum stress and leads to mitochondrial damage, ultimately resulting in apoptosis. This stress is reflected to have crucial role in the

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pathogenesis of septic ALI [34,35]. A substantial reduction in the MDA marker had been occurred in lung samples of mice within the ipragliflozin pre-treated group versus the sepsis group. According to our knowledge, no previous research deals with this work and our study is a novel in researching the effect of ipragliflozin on markers of oxidative stress in acute lung injury. Previous studies found that, ipragliflozin reduced the excessive production of ROS in kidney of mice [8], in liver [36]. Empagliflozin can and mitigate heightened oxidative stress in diabetic mice [37].

SGLT2 inhibitors have showcased evident cardiovascular advantages in Diabetic Kidney Disease, potentially due to their role in establishing a favorable balance between mechanisms that produce oxidants and those that offer antioxidant protection [38,39].

This effect for Ipragliflozin in reducing the excessive production of ROS [8] and effective detoxifying most mitochondrial ROS [36] had important role in reducing acute lung injury in mice that treated by this drug [26].

This investigation revealed significant histopathological alterations in the lungs 24

hours post CLP induced sepsis. The observed alterations included widespread infiltration of inflammatory cells, swelling in both, the interstitium and alveolar spaces, occasional bleeding and hyaline thickening of the walls between the alveoli.

Following the administration of LPS (lipopolysaccharide), Zhu et al. (2018) similarly observed distinct and identifiable pulmonary pathological alterations as a result of sepsis [40]. According to Yang et al. (2016), they detected pulmonary histological abnormalities after performing the cecal ligation and puncture technique. These changes included alveolar haemorrhage and the presence of neutrophils infiltrating the tissue [41].

Lung tissues were collected from mice after ipragliflozin treatment expressed substantial improvement in the lung injury score. Taksua et al investigated that Ipragliflozin successfully prevented left ventricular hypertrophy & fibrosis in nondiabetic rats, and this occurred without any impact level of plasma glucose. These results imply that SGLT2 inhibitors may offer cardiac protection for non-diabetic individuals suffering from cardiomyopathy [42]. Ipragliflozin improved kidney health *Ipragliflozin protect from acute pulmonary* by reducing endoplasmic reticulum (ER) stress and apoptosis [43].

Ipragliflozin has the ability to reduce cerebral injury score in mice with CLP induced polymicrobial [25]. Canagliflozin additionally demonstrate antiinflammatory effects by inhibiting glucose intracellularly, causing a reduction in the production of inflammatory factors in macrophages induced by LPS. Canagliflozin, an analogue of SGLT2 inhibitors, exhibited a lung with a regular appearance and a lower lung pathological score in the LPS+Cana as compared to the LPS group alone [44].

The lower pathological score observed in CLP+ipraglflozin groups due the to improve Alveoli function, decrease bleeding & fluid inside the alveolar space reduced infiltration and the of inflammatory cells, implies that this medication may have the potential to protect the lungs [45].

CONCLUSION

Ipragliflozin shows promise in reducing pulmonary dysfunction in male mice with sepsis. This is achieved by decreasing the concentrations of inflammatory &

oxidative stress indicators in the lung tissue.

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