Effect of Alpinia officinarum Aqueous Extract on Lipopolysaccharide - Induced Acute Lung Injury in Rats

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Abstract:

The objective of this study was to assess the effect of Alpinia officinarum aqueous extract (AOAex) on Lipopolysaccharide (LPS)-induced ALI. 50 adult albino male rats Sprague-Dawley strain weighting (180±10 g) were divided randomly into two groups: First main group 9 rats received a baseline diet served as negative control group. Second main group 41 rats, LPS were injected at a dose of 50 mg/kg into the rats to cause ALI, after that 5 rats from LPS groups were slaughtered to confirm ALI. Then, rats reclassified into 4 equal groups (9 rats each) as following: Group 1 served as the control positive group and 3 treated rat groups were fed basal diets and given oral doses of AOAex (100, 150, and 200 mg/kg) for 28 day. The results revealed that in the all rat groups treated by different levels of AOAex, pro-inflammatory cytokines (IL-1β, IL-6, IL-10, TNF-α) and oxidative stress decreased. Also, neutrophil infiltration, lymphocytes, monocytes and IgE level reduced. Correspondingly, hematological parameters (Hb, HCT, RBCs, WBCs) and antioxidant enzymes (SOD, CAT, GSH and GPX) were improved dramatically in serum, lung tissues and bronchoalveolar lavage fluid. Additionally, there were significant improvements in the histological examination of ALI brought on by LPS. It can be recommend that the consumption of Alpinia officinarum aqueous extract (AOAex) have antioxidant and anti-inflammatory effects and that play significant safer role from treatment of acute lung injury and inhibit of inflammatory and complications in rats.

Keywords: Alpinia officinarum, acute respiratory distress syndrome, pulmonary fibrosis, proinflammatory cytokines, lipopolysaccharide, rats.

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Introduction

Acute lung injury (ALI) is a serious condition with a multifactorial pathophysiology that is primarily characterised by dysregulation of the inflammatory response, disruption of the pulmonary endothelium and epithelial barriers **(Cen *et al.*, 2021)**. Globally, ALI is a life-threatening disease and a complex disease that is closely correlated with inflammatory processes and immunological responses **(Karki *et al.*, 2021)**.

Lipopolysaccharide (LPS) is the primary contributor to Gram-negative bacterial infections which appear to be the main cause of ALI, which happens 4-48 h after pathogen exposure **(Gabarin *et al.*, 2021)**. LPS are also known as endotoxins and it is a critical component of the bacterial outer membrane that can cause acute lung injury by overproducing numerous pro-inflammatory cytokines and accelerating cell infiltration in lung tissues. This is accompanied by acute hypoxic respiratory insufficiency, interstitial or alveolar oedema, and diffuse pulmonary edoema **(Li *et al.*, 2021)**. As a result, novel treatments that are very effective and safe are required to improve ALI, such as the use of natural plants.

Alpinia officinarum Hance (*A. officinarum*) lesser galangal is a crucial member of the Zingiberaceae family **(Saboo *et al.*, 2014)**. Galangal rhizome resembles ginger in appearance and flavour and grows in Asian countries **(Akbar, 2020)**. The rhizomes of *A. officinarum* are widely used as a food ingredient and herbal medicine. It has been used in drinks, flavours, spices, drinks **(Lim, 2016)**. *A. officinarum* represent an invaluable natural source of many bioactive components. It is known to exhibit a beneficial effect for anti-inflammatory and anti-oxidant **(Yoo *et al.*, 2021)**. *A. officinarum* extract was an effective treatment for particulate matter-induced lung injury in mice, through reversing cell membrane damage, decreasing oxidative stress, and inflammation **(Zhao *et al.*, 2019)**. The common cold, bronchial catarrh, throat infections, viral disorders, inflammation , microbial infection are just a few of the conditions that the rhizome is frequently used to treat **(Jantan *et al.*, 2023)**. Therefore, this study was carried out to

evaluate the possible effects of *Alpinia officinarum* aqueous extract on against acute lung injury in rats by lipopolysaccharide.

Material and method

Material

- **Chemicals**: Basal diet, Casein, cellulose, vitamins and minerals were purchased from the General Company for Commerce and Chemicals, Cairo, Egypt.
- **Kits** for determination of all hematological, antioxidant parameters, Lipopolysaccharide (LPS) (*Escherichia coli*) and cytokines from enzyme-linked immunosorbent assay (ELISA) were purchased from Sigma-Aldrich for use in analysis.
- **Plant**: Rhizomes of *A. officinarum* were purchased from a market for herbs in Port Said, Egypt.
- **Animals:** 50 Sprague-Dawley albino rats weighing (180±10g) were purchased from the National Organisation for Drug and Control Research in Giza, Egypt.

Method

Preparation of *A. officinarum* Aqueous extract (AOAex): Fresh rhizomes were rinsed under the tap to remove the soil and debris. The rhizomes were subsequently cut into slices, baked in an oven at 40 ºC, and ground for 10 min to create a fine powder. Dried *A. officinarum* (1 kg) was extracted in 10 L (1/10, w/v) (g/mL) of distilled water under circumfluence for 3h at 100 ± 2 °C and its filtration (53 µm mesh) to constitute 100, 150 and 200 mg/kg doses of AO then its kept at -20 °C until further use **(Song *et al*., 2021)**.

Chemical analysis

A. officinarum was examined using conventional techniques for moisture, protein, fat, ash, and crude fibre according to **AOAC, (2010)**. By using the differential, total carbohydrates were computed.

Total phenolic content (TPC)

The Folin-Ciocalteu technique was used to determine the TPC using common gallic acid **(El-shiekh *et al*., 2019)**.

Total flavonoids content (TFC)

The total flavonoid content was found utilising a conventional quercetin aluminium chloride colorimetric technique **(Chatatikun and Chiabchalard, 2013).**

Determination of DPPH radical scavenging activity

Methanol solution of DPPH was used as a reagent for the spectrophotometric assay with slightly modifications **(Mensor *et al.*, 2001)**. Percent inhibition was calculated using the following expression **(Singh *et al.*, 2008)**.

% Inhibition = ($\mathbf{A}_{\text{blank}} - \mathbf{A}_{\text{sample}} / \mathbf{A}_{\text{blank}}$) x 100

Biological Experiment

50 male rats (180±10g bw) were fed on a basal diet for 7 days. According to **Reeves *et al.*, (1993)**, the basal diet (AIN-93M) was created to provide rats with the suggested amounts of nutrients.

Ethical approval: The study received approval from the research ethics committee of the nursing faculty of Port Said University, code number: NUR (7-5-2023) (25).

After acclimatization, rats were randomly divided into two groups: First main group 9 rats received a baseline diet served as negative control group. Second main group 41 rats, Lipopolysaccharide (LPS) was injected at a dose of 50 mg/kg to cause ALI according to **Lee *et al.*, (2019)**. Plasma and lung tissues were collected for the purpose of analyzing inflammatory cytokines 24 h after the LPS injection, 5 rats from LPS groups were slaughtered to confirm ALI. Then, rats reclassified into 4 equal groups (9 rats each) as following: Group 1 was supplied only the basal diet as (LPS) rats positive control, and the three other groups were fed standard diets and given oral doses of AOAex (100, 150, and 200 mg/kg), respectively for 28 day.

After the experiment was completed, blood samples from the orbital plexus were collected and centrifuged at 3000 rpm to extract the sera, which were then stored in a deep freezer at -80°C until they were analyses.

Biological Evaluation

The amount of food intake (FI) was recorded daily, while rat's weight was measured once a week to identify body weight gain. Body weight gain (BWG%) and feed efficiency ratio (FER) calculate according to **Chapman *et al*., (1959)** using the following equation:

$$\mathbf{BWG\%} = \frac{\text{Final body weight} - \text{Initial body weight}}{\text{Initial body weight}} \times 100$$

$$\mathbf{FER} = \frac{\text{weight Gain (g)}}{\text{Feed intake (g)}}$$

Collection of Bronchoalveolar Lavage Fluid (BALF)

Rats were euthanized and their thoraxes were opened. Then, a cannula was placed into the trachea, and the right lung lobe was rinsed five times with 1 mL of saline each time. The obtained (BALF) was centrifuged for 10 minutes at 4°C at 2500 rpm to separate supernatants **(Dikmen *et al*., 2021)**. Protein analysis in the acquired supernatants was performed using the bicinchoninic acid (BCA) test **(Redinbaugh and Turley, 1986)**. The counts of neutrophils, lymphocytes, and monocytes were performed in accordance with the literature **(Saadat *et al*., 2019)**.

Measurement of lung water content

After the rats were anaesthetized, the right lung lobes were extracted and weighed to determine moist weight. The same tissues were then placed in an incubator at 60°C for 72 h and their dry weights were determined. The lung wet-to-dry (W/D) weight ratio was calculated according to **Su *et al*.,(2023)** the following formula.

$$\text{Lung water content} = \frac{\text{wet lung weight dry lung weight}}{\text{wet lung weight}} \text{ X } 100$$

Biochemical analysis:

Haemoglobin (Hb) and Hematocrite (Hct) were measured depending on the method of **Bain *et al*., (2016)**. Red blood cells (RBCs) and white blood cells (WBCs) were measured depending on the method of **Fischbach,**

(2015). For assessing lipid peroxidation, the plasma level of Malondialdehyde (MDA) was determined according to **Draper and Hadley, (1990)**. Superoxide dismutase (SOD) activity was assessed according to **Spitz and Oberley, (1989)**. Catalase (CAT) was measured by **Aebi, (1984),** serum glutathione (GSH) levels and Glutathione peroxidase (GP_X) were measured methods by **Habig *et al*., (1974) and Moin, (1986)** respectively. The ELISA kit (Bioassay Technology Laboratory (BT Lab)) was used to measure serum cytokines such as interleukin (IL-1β, IL-6, IL-10) and tumor necrotic factor-α (TNF-α) levels in tissue, serum, and BALF according to **Dikmen *et al*., (2021)**.Serum immunoglobulin E (IgE) levels were measured according to **Kim *et al*., (2002)**.

Histopathological analysis

The lung tissue was perforated with and fixed in formalin solution and embedded in paraffin. Hematoxylin and eosin (H&E)-stained lung slices (4m thick) were seen under a microscope (Leica Microsystems, Germany) at 100X and 200X magnifications **(Nagaraju *et al*., 2022)**.

Statistical analysis

Results were provided as mean ± Standard Error (SE). The SPSS programme was used to statistically analyse the data using one-way ANOVA and post hoc multiple comparisons (**Snedecor and Cochron, 1989)**.

Results and Discussion

Table (1) displayed the chemical composition *A. officinarum* powder which found AO had higher content of carbohydrate, crude fiber and moisture (59.94, 17.27 and 11.76) respectively. However, moderate amounts of crude protein lower in fat and ash were observed (5.56, 2.23 and 3.24) respectively. These results agreement with **Negm and Ragheb, (2019) and Alasmary *et al*., (2019)** observed carbohydrate had the largest percentage of active ingredients seen, whereas fat had the lowest percentage (2.79), and protein had the highest percentage (5.11) of other constituents.

Table (1): Chemical composition of *A. officinarum* powder (g/100 g dried).

Nutrients	Crude Protein	Crude Fat	Ash	Carb.	Moisture	Crude Fiber
A. officinarum	5.56	2.23	3.24	59.94	11.76	17.27

Tabulated data in table (2) presented the mean value of TPC, TFC and antioxidant (46.51± 0.40 mg/GAE100g, 30.97±1.85 mg/QE100g and 3.05±0.26%), respectively. These results support those of **Elspeiy *et al.*, (2022); Eid *et al.*, (2022) and Li *et al.*, (2021)** reported that *A. officinarum* contains more bioactive substances, including flavonoids, phenolic acids, and alkaloids, as well as flavones like galangin, quercetin, curcumin, and kaempferol, which are believed to have antioxidant effects, an anti-inflammatory, and promote health benefits.

Table (2): Total phenol, Flavonoid contents and Antioxidant activity of AOAex.

Sample / Parameters	*Alpinia officinarum*
Total phenols* (GAE/g extract)	**46.51 ± 0.40**
Total flavonoids* (QE/g extract)	**30.97±1.85**
Antioxidant activity** (DPPH %)	**3.05±0.26**

* Values are presented as mean SD. GAE: gallic acid equivalent;

QE: quercitin equivalent. ** Expressed as Ascorbic acid equivalent.

Results in table (3) discovered that LPS groups had a significant decrease in IBW, FBW, FI, BWG% and FER when comparison to negative control rats. LPS observes that ALI caused loss of appetites may be brought on by an increase in oxidative stress and pro-inflammatory cytokines. Whereas, oral administration aqueous extract of *A. officinarum* (100, 150 and 200 mg/kg) caused a significant increase in IBW, FBW, FI, BWG% and FER when in comparison to LPS group, may be as a result of AO anti-

inflammatory and antioxidant properties. These results are consistent with **Pirzadeh *et al*., (2021)** showed that 100 and 300 mg/kg doses of AO extract administration significantly increased animal body weight compared to control groups. Similar, **Heidari *et al*., (2021)** observed that AO (200 and 500 mg kg^{-1}) significantly raised body weight in contrast to the diabetes control group, due to the antioxidant potential of the compound.

Table (3): Effect of *A. officinarum* aqueous extract (AOAex) on BWG%, FI and FER for LPS induced acute lung injury.

Parameters / Groups	IBW (g)	FBW (g)	BWG %	FI (g/day)	FER
Control (-ve)	**189.03±1.64^{a}**	**215.20±1.60^{a}**	**13.84±1.13^{a}**	**16.00**	**0.058±0.05^{a}**
LPS	**181.82±1.73^{a}**	**173.19±1.44^{d}**	**-4.75±1.80^{e}**	**10.00**	**-0.031±0.07^{e}**
AOAex 100 mg/kg	**184.05±1.13^{a}**	**186.64±2.62^{c}**	**1.41±1.62^{d}**	**12.00**	**0.008±0.06^{d}**
AOAex 150 mg/kg	**187.65±1.24^{a}**	**197.76±2.41^{b}**	**5.39±1.06^{c}**	**15.00**	**0.024±0.07^{c}**
AOAex 200 mg/kg	**188.44±0.60^{a}**	**202.54±3.54^{b}**	**7.48±0.56^{b}**	**14.00**	**0.036±0.03^{b}**

Initial body weight (IBW), Final body weight (FBW), Body weight gain (BWG %), food intake (FI) and feed efficiency ratio (FER). Results are expressed as mean ± SE. Values in each column which have different letters are significantly different at ($P \leq 0.05$).

Results in table (4) observed that the lung W/D ratio was significantly increased in lung weight and total protein by the LPS group compared to negative control group. These results are consistent with **Sadiq and Zalzala, (2021) and Su *et al*., (2023)** showed that administering LPS to rats results in a significant rise in the wet/dry ratio when comparison to the negative control group. Conversely, oral aqueous extract of AO (100, 150, and 200 mg/kg) dramatically reduces lung edema in LPS-induced ALI and causes a considerable drop in lung weight when comparison to the positive control group, due to its anti-inflammatory and antioxidant effects. It does not show any statistical significance among both groups of AO at doses

(150 and 200 mg/ kg). Furthermore, the amount of BALF protein concentration rose in the current study with the administration of LPS and then reverted to normal levels with the administration of AO. These findings are in line with **Lee *et al*., (2019) and Dikmen *et al*., (2021)** observed that there was a significant increase in total protein of the LPS group-induced ALI compared to the negative control group. One of the signs of pulmonary edoema and inflammation is an increase in the BALF protein concentration brought on by protein extravasation **(Müller *et al*., 2014)**.

Table (4): Effect of *A. officinarum* aqueous extract (AOAex) on lung weigh and total protein in BALF for LPS induced acute lung injury.

Parameters / Groups	Lung weight (g)	Total Protein (mg/ml)
Control (-ve)	1.05 ± 0.07^{d}	0.05 ± 0.04^{e}
LPS	2.78 ± 0.14^{a}	0.83 ± 0.15^{a}
AOAex 100 mg/kg	1.87 ± 0.13^{b}	0.42 ± 0.10^{b}
AOAex 150 mg/kg	1.61 ± 0.08^{bc}	0.34 ± 0.16^{c}
AOAex 200 mg/kg	1.23 ± 0.10^{cd}	0.23 ± 0.09^{d}

Results are expressed as mean ± SE.

Values in each column which have different letters are significantly different at ($P\leq0.05$).

The results in table (5) observed that there was a significant reduced ($p\leq0.05$) of hematological parameters (Hb, HCT, RBCs, WBCs) in the group receiving LPS comparison with negative group. LPS are the finest option to cause immune system diseases and the inflammatory process in rats **(Li and Zou, 2020)**.WBCs are an indicator of the health of the immune system and the measurement of high WBC counts in peripheral blood is a common way for determining an infection or inflammation **(Kany *et al*., 2019)**. The abnormal changes in the blood indices that indirectly affect feed and water intake and weight loss may be the cause of the surge in pro-

inflammatory cytokines and increased oxidative stress causing fast catabolism and lethargy **(Vanitha *et al*., 2022)**.

Conversely, the treated groups showed a significant reversal in their values, which, when rats were given an oral dose of an aqueous extract of AOAex along with LPS, haematological measures significantly increased ($p \leq 0.05$) in comparison to LPS group. The groups treated with the AOAex seem normal levels in hematological parameters (Hb, HCT, RBCs, WBCs) compared to control negative in a dose dependent manner. The haemoprotective impact of AO may result from increased free radical scavenging activity, antioxidant capabilities, and anti-inflammatory efficiency **(Li *et al*., 2021)**.

Our findings are supported by **Abbas *et al*., (2023)** indicated that mice given galangin at a dose of 80 mg kg-1 body weight experienced changes in the median characteristics of haematological measures. Similar, **Elspeiy *et al*., (2022)** discovered that *Alpinia galanga* administration may improve the blood parameters, immunity, and oxidative condition. **Rajendiran *et al*., (2018)** observed that rats treated with hexane extract of *A. officinarum* (HEAO) had significantly increased in the levels of haematological markers (Hb, HCT and RBC). This demonstrates that the rats treated with HEAO did not exhibit any symptoms of anemia.

Table (5): Effect of *A. officinarum* aqueous extract (AOAex) on some hematological parameters in BALF for LPS induced acute lung injury.

Parameters / Groups	Hb (g/dl)	HCT (%)	RBCs (10^6/µL)	WBCs (10^3/µL)
Control (-ve)	15.98±0.72^a	46.25±0.04^a	5.46±0.15^a	12.47±0.03^a
LPS	8.87±0.75^d	21.49±0.21^d	3.11±0.04^d	7.91±0.03^d
AOAex 100 mg/kg	11.60±0.68^c	36.36±0.14^c	4.50±0.57^c	9.35±0.06^c
AOAex 150 mg/kg	13.18±0.46^b	41.50±0.16^b	4.89±0.43^b	10.76±0.05^b
AOAex 200 mg/kg	14.45±0.44^a	45.73±0.09^a	5.25±0.76^a	11.87±0.04^a

Hemoglobin (Hb), Hematocrit (HCT), red blood cell (RBC), and white blood cells (WBCs). Results are expressed as mean ± SE. Values in each column which have different letters are significantly different at ($P \leq 0.05$).

The findings in table (6) showed that the LPS group had considerably higher neutrophil, lymphocyte, and monocyte counts than the control group. After 4-48 hours after LPS treatment, a crucial indicator of the later stage acute lung inflammation is the progressive concentration of neutrophils and lymphocytes in BALF **(Trivedi *et al*., 2020)**. The buildup of leukocytes is a major factor in the deterioration of the lungs and worsening of ALI **(Kellner *et al*., 2017)**. Our findings are consistent with **Sadiq and Zalzala, (2021)** observed that a considerable increase in neutrophils and lymphocytes in the LPS model group at a dosage of 50 mg/kg in comparison to healthy group.

Conversely, oral administration of AO (100, 150 and 200 mg/kg) demonstrated a substantial decrease in the serum differential cell percentage of neutrophils, lymphocytes, and monocytes in comparison to LPS group. There was significant difference in serum differential cell percentage (neutrophils and monocytes), with the exception of the lymphocyte findings did not differ among all groups treated with AO. Interestingly, we found that AO extract significantly reduces neutrophil recruitment and activity as measured by an increase in WBC relative to the LPS group. These findings are consistent with **Ni *et al*., (2022)** demonstrated that treatment with a water-soluble polysaccharide (AOHP) obtained from *A. officinarum* greatly decreased lymphocyte proliferation. Also, **Rajendiran *et al*., (2018)** observed that hexane extract of *A. officinarum* (HEAO) was successful in lowering lymphocyte, neutrophil levels and raising hematocrit levels, both of which indicated its antioxidant properties.

Table (6) Effect of *A. officinarum* aqueous extract (AOAex) on differential cell percentage in BALF for LPS induced acute lung injury.

Parameters / Groups	Neutrophils %	Lymphocyte %	Monocytes %
Control (-ve)	3.94±0.04^{d}	75.82±0.82^{c}	2.90±0.36^{e}
LPS	8.80±0.03^{a}	90.66±0.52^{a}	7.83±0.33^{a}
AOAex 100 mg/kg	5.76±0.07^{b}	84.70±0.93^{b}	5.14±0.21^{b}
AOAex 150 mg/kg	4.33±0.05^{c}	80.54±1.02^{b}	4.78±0.24^{c}
AOAex 200 mg/kg	2.87±0.02^{e}	75.24±0.90^{bc}	3.80±0.41^{d}

Results are expressed as mean ± SE.

Values in each column which have different letters are significantly different at (P≤0.05).

As shown in table (7) the results indicate that there was a significant reduction (p≤0.05) of serum parameters (SOD, CAT, GSH and GPX) but a significant increasing MDA in the group receiving LPS comparison with negative group, this has the potential to compromise lung immunological function. Inflammation and oxidative stress are recognised to play important roles of lung injury **(Kim *et al.*, 2018)**.These outcomes are in line with **Zhang *et al.*, (2019)** demonstrated that levels of CAT, SOD, and GSH were found to be inversely connected with LPS-induced acute lung damage, while levels of MDA were found to be positively correlated. Likewise, **Dikmen *et al.*, (2021)** found that MDA levels increase while antioxidant activity decrease in LPS-induced ALI. All of these studies confirm and support our results.

On the other hand, the findings of our study indicated that different levels (100, 150, and 200) mg/kg of AOAex provides high protection against oxidative damage, as (SOD, GSH, GPX) levels and CAT activity significantly increased (P≤0.05) while MDA significantly reduced (P≤0.05) in all the protected groups in comparison to LPS group. The outcomes indicated that oral administration of *A. officinarum* considerably reduced oxidative stress brought on by LPS. It is possible to the conclusion that the antioxidant properties of *A. officinarum*, which contains substances like polyphenols and flavonoids that scavenge reactive oxygen species, are

responsible for the significant modulation of antioxidant enzymes and oxidative stress. Many studies in this field showed the effectiveness of extracts of this plant against oxidative stress, **Khashan *et al.*, (2023)** suggests that *A. officinarum* extract is helpful in mitigating the negative consequences of elevated oxidative stress, which observed to increase in CAT activity and GSH levels in the protected group. These outcomes are in line with **Elspeiy *et al.*, (2022)** showed that using *A. officinarum* galanga supplements significantly increased CAT, GSH, and SOD levels compared to the control group. Similarly, **Bebars *et al.*, (2021)** demonstrated that *A. officinarum* rhizome extract decreased oxidative stress in the form of increased SOD level and decreased MDA level. Likewise, **Zhao *et al.*,(2019)** found that oxidative stress markers were dramatically reduced while, increased SOD levels after mice were administered with AO extract.

Table (7): Effect of *A. officinarum* aqueous extract (AOAex) on antioxidant enzymes and oxidative stress in lung tissues for LPS induced acute lung injury.

Parameters / Groups	MDA (nmol/ml)	SOD (U/L)	CAT (U/L)	GSH (U/L)	GPX (U/L)
Control (-ve)	185.70±3.50^{d}	16.42±0.82^{a}	6.50±0.06^{a}	22.42±1.73^{a}	18.50±0.50^{a}
LPS	310.34±6.30^{a}	8.33±0.52^{d}	3.06±0.05^{d}	12.73±0.95^{d}	9.40±0.30^{c}
AOAex 100 mg/kg	225.81±1.40^{b}	12.42±0.93^{c}	4.52±0.02^{c}	16.72±0.98^{c}	13.96±0.02^{b}
AOAex 150 mg/kg	205.54±1.20^{c}	14.63±1.02^{b}	5.43±0.07^{b}	19.64±1.05^{b}	14.93±0.21^{b}
AOAex 200 mg/kg	190.32±0.60^{d}	15.90±0.90^{a}	6.13±0.02^{a}	21.70±1.28^{a}	17.30±0.12^{a}

Malondialdehyde (MDA), Superoxide dismutase (SOD); Catalase (CAT), Glutathione (GSH) and Glutathione peroxidase (GPx). Results are expressed as mean ± SE. Values in each column which have different letters are significantly different at ($P \leq 0.05$).

As shown in table (8) results showed that LPS significantly increased in serum proinflammatory cytokines (IL-1β, IL-6, IL-10, TNF-α) and IgE in lung tissue comparison with negative control group. These results are consistent with **Sadiq and Zalzala (2021) and Shokry *et al.*, (2022)** found that proinflammatory cytokines increased by LPS treatment. Similar, **Lee *et al.*, (2019)** observed that LPS stimulates macrophages to

secrete proinflammatory cytokines and activates the inflammatory cascade by increasing the migration and infiltration of immune cells involved in inflammation, and increases in proinflammatory cytokines are thought to play a role in the pathophysiology of ALI and acute respiratory distress syndrome (ARDS).

Conversely, oral of aqueous extract of *A. officinarum* a doses of (100,150 and 200mg/kg) had a significant reduction in these pro-inflammatory cytokines and IgE as compared with LPS group, indicating that AO has anti-inflammatory effect against ALI. The findings revealed that the rat group given AO orally once a day at a dose of 200 mg/kg had the lowest level of cytokines and was nearly as healthy as the control group. These findings are in line with **Li *et al*., (2021)** observed that *A.offcinarum* extract (AOE) and its primary bioactive components were found to have anti-inflammatory effects on LPS-induced inflammation. As a result, inhibiting these pro inflammatory chemokines may reduce the inflammatory response, as evidenced by histological investigation. **Ni *et al*., (2022)** showed that AOHP significantly improved IL-6. Likewise, **Song *et al*., (2021)** observed that oral administration of AOWex dramatically lowered these serum proinflammatory such as TNF-α, because AOWex contains galangin, protocatechuic acid, and epicatechin were discovered to be promising anti-inflammatory compounds. Furthermore, **Lin *et al*., (2020)** demonstrated that treatment with total flavonoids derived from the rhizomes of *A. officinarum* reduced high levels of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) in gastric tissue. Similarly, **Zhao *et al*., (2019)** observed that IL-6 and TNF-α were down-regulated obviously by *A. officinarum* extracts could potentially be attributable to its antioxidant action, which was validated in our study.

Regarding the level of IgE, **Jantan *et al*., (2023)** demonstrated that the effects of *A. officinarum* on the immune system, particularly through inflammation-related signalling pathways. Similarly, **Ni *et al*., (2022)** found that the mice innate immune state was improved by therapy with a water-soluble polysaccharide derived from *A. officinarum*, and no evident harm was seen. **Song *et al*., (2021)** observed that the oral of AOWex considerably

lowered serum IgE levels, which was validated in our study. Likewise, **Meng *et al.*, (2018)** found that *A.officinarum* administration reversed lgE levels significantly. Likewise, **Lee *et al.*, (2018)** observed that the combination of quercetin and galangin as a main ingredient of AO were more effective in lowering IgE levels.

Table (8): Effect of *A. officinarum* aqueous extract (AOAex) on the proinflammatory cytokines and IgE in lung tissues for LPS induced acute lung injury.

Parameters / Groups	IL- 1β	IL-6	IL-10	TNF-α	IgE
	pg/Ml				(ng/ml)
Control (-ve)	13.34± 0.70^{e}	20.24± 0.94^{e}	11.73 ± 0.12^{d}	70.42±0.80^{e}	170.73± 1.6^{e}
LPS	70.42± 1.07^{a}	75.44± 1.60^{a}	22.31 ± 1.72^{a}	200.23± 2.25^{a}	350.02 ±2.3^{a}
AOAex 100 mg/kg	38.50± 0.10^{b}	45.91± 0.50^{b}	18.80 ± 1.70^{b}	145.10± 0.81^{b}	258.03 ±3.1^{b}
AOAex 150 mg/kg	28.22± 0.07^{c}	35.02± 0.40^{c}	16.92 ± 0.11^{c}	115.51± 0.99^{c}	205.01 ±2.4^{c}
AOAex 200 mg/kg	18.33± 0.73^{d}	25.13± 0.80^{d}	14.64 ± 3.09^{d}	75.21± 0.88^{d}	185.04 ±1.3^{d}

Interleukin-1 (IL-1β), Interleukin-6 (IL-6), Interleukin-10 (IL-10), Tumor necrotic factor-α (TNF-α) and Immunoglobulin E (IgE). Results are expressed as mean ± SE. Values in each column which have different letters are significantly different at ($P \leq 0.05$).

Results of a lung histopathology examination

To establish the preventive efficacy of AO, the lung tissues of rats exposed to LPS-induced ALI were investigated histopathologically. Macroscopic examination of control (ve-) lungs indicated normal histological structure (normal bronchioles and alveoli) (Photo A). On the other hand, the lungs of rats (LPS) group displayed thickening of interstitial septa with inflammatory cells interstitial pneumonia (Photo B). Meanwhile, rats from group 3 had localised interstitial pneumonia (Photo C). However, no histopathological alterations were found in the lungs of rats from group 4 evaluated in other sections (Photos D and D1). On the other hand, group 5 investigated sections revealed no histopathological changes (Photo E).

These results are consistent with **Shokry *et al.*, (2022) and Su *et al.*, (2023)** observed that histopathological examinations in LPS-induced ALI

revealed an inflammatory response marked by alveolar epithelial cell desquamation, thickening of the interalveolar septum due to haemorrhage and inflammation, fibroblast development, and excessive leukocyte infiltration.

The current study, on the other hand, found that *A.*officinarum protected against ALI produced by LPS injection by exerting antioxidant activity and preventing tissue degradation via suppression of inflammatory cytokines and lipid peroxidation. These findings are in line with **Zhao *et al.*, (2019)** observed that pathological sections of lung tissue showed that *A. officinarum* could reduce the infiltration of inflammatory cells, pulmonary edema and pulmonary fibrosis. Similarly, **Dikmen *et al.*, (2021)** showed that plant-derived substances reduced lung tissue damage and demonstrated therapeutic properties.

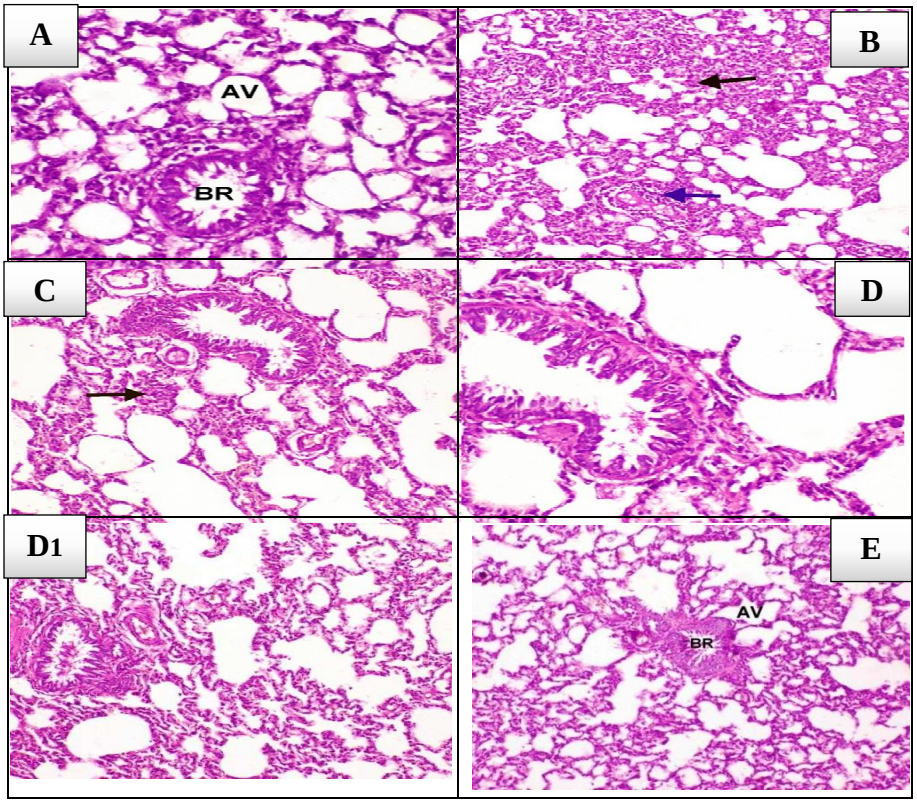

Photo (1): Photomicrograph of rats lung of H&E X 100 and X 200. A= Groups (1)

(ve-) showing the normal histological structure (normal bronchiole (BR) and normal

alveoli (AV). B= group (2) LPS; C= group (3) AOAex 100 mg/kg; D and D1= group

(4) AOAex 150 mg/kg and E= group (5) group AOAex 200 mg/kg.

Conclusion

LPS-induced ALI is protected from by A. *officinarum* aqueous extract (AOAex) through lowering lung inflammatory response suppress the levels of proinflammatory cytokines, reduced neutrophil infiltration and IgE levels, lightened the oxidative stresses, and reduced histopathological changes and tissue damage, due to its anti-inflammatory and anti-oxidant properties. AOAex is a possible option for functional foods to prevent chronic inflammatory illnesses and it may be a promising therapeutic agent in future.

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تأثير مستخلص الخولنجان المائى على اصابة الرئة الحادة الناتجة عن عديد السكاريد الدهنى فى الفئران

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الملخص العربي:

كان الهدف من هذه الدراسة هو تقييم تأثير مستخلص الخولنجان المائي على اصابة الرئة الحادة الناتجة عن الحقن بمادة عديد السكاريد الدهنى. تم تقسيم خمسين من ذكورالفئران البالغة من سلالة الألبينو وزنها (١٨٠±١٠جم) بشكل عشوائى إلى مجموعتين رئيسيتين:المجموعة الرئيسية الأولى وعددها ٩ فئران تلقت النظام الغذائى الأساسى كمجموعة ضابطة سالبة. والمجموعة الرئيسية الثانية وعددها ٤١ فأر وتم حقن فئران هذه المجموعة بعديد السكاريد الدهنى بجرعة ٥٠ ملجم / كجم من وزن الجسم لاحداث اصابة الرئة ، وبعد ذلك تم تشريح ٥ فئران للتأكد من اصابة الرئة. ثم تم إعادة تقسيم الفئران المصابة إلى ٤ مجموعات متساوية (٩ فئران لكل منها) على النحو التالي: حيث اعتبرت مجموعة واحدة منهم كمجموعة ضابطة موجبة و٣مجموعات تم تغذيتهم على نظام غذائي اساسى مع جرعات فموية من مستخلص الخولنجان المائى بجرعات (١٠٠، ١٥٠، ٢٠٠) ملجم / كجم على التوالى لمدة ٢٨ يوم . اشارت النتائج الى أن المجموعات التي تلقت مستخلص الخولنجان المائى انخفضت فيهم مستويات السيتوكينات المؤيدة للالتهابات (IL-1β,) (IL-6, IL-10, TNF-α والإجهاد التأكسدي. وايضا انخفض تسلل الخلايا neutrophil lymphocytes, monocytes ومستوى IgE. في المقابل تم تحسين القياسات الدموية (Hb, HCT, RBCs, WBCs) والإنزيمات المضادة للأكسدة (SOD, CAT, GSH and GPX) بشكل كبير في الدم ، انسجة الرئة وسائل غسيل القصبات الهوائية. بالإضافة إلى ذلك كانت هناك تحسينات كبيرة في الفحص الهستوباثولوجي لانسجة الرئة المصابة بعديد السكاريد الدهنى. يمكن التوصية بأن استهلاك المستخلص المائي للخولنجان له تأثيرات مضادة للأكسدة ومضادة للالتهابات والتي تلعب دورًا أكثر أمانًا في علاج إصابة الرئة الحادة وتمنع الالتهابات والمضاعفات في الفئران.

الكلمات المفتاحية : الخولنجان ، متلازمة الضائقة التنفسية الحادة ، التليف الرئوى ، السيتوكينات المسببة للالتهابات ، عديد السكاريد الدهنى ، الاجهاد التأكسدى ، فئران.

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