

Original Research

## The effect of *Borago officinalis* on the signaling pathway of the NLRP3 inflammasome complex, TLR4 and some inflammatory cytokines in type II diabetic patients with acute respiratory distress syndrome

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**Abstract:** Acute respiratory distress syndrome (ARDS) is a life-threatening condition in which the lungs become severely inflamed, causing the alveoli to constrict or fill with fluid, which prevents the lungs from functioning properly. This disease becomes more dangerous when it occurs in patients with diabetes. Because of the clinical condition of these patients, it is not possible to treat them with usual medicines. One of the best options for treating these people is to use herbs. Borage (*Borago officinalis*) is a medicinal herb that, in addition to its anti-inflammatory properties, is also able to control blood sugar. Therefore, in the current study, the effect of borage oil was considered on the signaling pathway of the NLRP3 inflammasome complex, TLR4, and serum levels of inflammatory cytokines (IL-1 $\beta$  and IL-18) in type II diabetic patients with ARDS. For this purpose, 25 diabetic type II patients with ARDS were divided into three groups by ARDS Berlin Definition. Then, after providing the demographic and clinical characteristics of the patients, they were treated with 30 mg/day borage oil for seven days. The expression of NLRP3 and TLR4 genes (by Real-time PCR technique) and serum levels of IL-1 $\beta$  and IL-18 (by ELISA test) were evaluated before and after treatment with borage oil through blood samples taken from patients. The results showed that serum levels of inflammatory cytokines (IL-1 $\beta$  and IL-18), NLRP3 gene, and TLR4 gene were significantly decreased in diabetic type II patients with mild ARDS by treating with borage oil. IL-1 $\beta$  serum level and TLR4 were significantly decreased in diabetic type II patients with moderate ARDS. But there was not any significant decrease or increase in IL-1 $\beta$ , IL-18, NLRP3 gene, and TLR4 gene in diabetic type II patients with severe ARDS after 7 days of treatment with borage oil. According to the obtained results, borage oil can act as a double-edged blade. Thus, in the early and middle stages of ARDS, borage oil can be effective in reducing the inflammasome pathway of inflammation and also reduce blood sugar levels in these diabetic patients. But in the severe stage of ARDS, it not only does not help to treat the ARDS; it also increases systolic and diastolic blood pressure in diabetic patients.

**Key words:** ARDS; Borage oil; Diabetes type II; Interleukin-1 $\beta$ ; Interleukin-18; NLRP3; TLR4.

### Introduction

Diabetes is a metabolic disorder that results in impaired insulin secretion, function, or both, resulting in hyperglycemia with impaired metabolism of carbohydrates, fats, and proteins (1). Long-term consequences of diabetes include retinopathy, nephropathy, neuropathy, and an increased risk of cardiovascular disease (2). Disorders of metabolic regulation due to diabetes mellitus led to multiple cardiovascular complications that cause many problems for a person with diabetes and the community health system (3). The pulmonary complications of diabetes are very little known and the number of studies that have been done in this field is very small compared to other studies on the complications of diabetes (4). One of the most important pulmonary complications of diabetes is Acute Respiratory Distress Syndrome (ARDS), which is one of the most serious conditions with a high percentage of mortality (5).

Acute Respiratory Distress Syndrome (ARDS) oc-

curs when fluid collects in the small, flexible air sacs of the lungs (alveoli). This fluid prevents the lungs from filling with enough air, which means that the amount of oxygen received into the bloodstream is reduced (6). This condition prevents the body's organs from accessing the oxygen needed to function, completely. Many patients do not survive the symptoms of ARDS. The risk of death increases with age and the severity of the disease (7). Of the people who survive ARDS, some recover completely while others suffer from permanent lung damage. The disease also causes events such as thrombus, coagulation cascades, and inflammation (8).

During inflammation, various mediators, including proinflammatory cytokines, interleukin- $\beta$ 1 (IL-1 $\beta$ ), alpha tumor necrosis agents (TNF- $\alpha$ ), and interleukin-18 (IL-18) are released by immune cells and cause Intensity immune responses (9). The first step in detecting a pathogen in a living organ and initiating inflammatory responses is initiated by specific receptors, called pathogen-associated molecular patterns (PAMPs) that

are found in the cells of a living organism (10). These receptors are expressed intra-cytosolic and extra-cytosolic (11). One of the most effective messenger pathways in inflammation is the activation of the Toll-Like Receptor (TLR), which is an inflammatory response to the presence of saturated fatty acids (12). TLRs are a type of damage-associated molecular pattern (DAMPs) that triggers signals in response to PAMPs. Inflammation has been shown to be associated with increased recurrence of TLR, which causes post-event stages and increased expression of inflammatory cytokines such as IL-18, IL-1 $\beta$ , and TNF- $\alpha$  through independent MYD88 and non-independent MYD88, and all these serial factors lead to chronic systemic inflammation and increase the risk of infectious diseases (12, 13).

One of the most important pro-inflammatory cytokines derived from this pathway is IL-1 $\beta$ , which extensively affects inflammatory processes and requires precise control and production at transcriptional and post-translational levels (14). The main function of IL-1 $\beta$ , like TNF- $\alpha$ , is to act as a mediator of the host's inflammatory response to infections and other stimuli (15). IL-1 $\beta$  and TNF- $\alpha$  are involved in innate immunity and inflammation. IL-1 $\beta$  also regulates inflammatory responses and is involved in remodeling by increasing matrix metalloproteinase expression (16). Recent studies suggest that another set of DAMPs are NOD-like receptors (NLRs) that may play an important role in detecting associated signals and initiating inflammatory responses (17). Unlike TLRs, NLRs are cytoplasmic receptors whose main role is to detect microbial components or high-risk signals. After activation, some NLR proteins, including NLRP3, activate the inflammasome complex (18). This complex activates caspase-1; the process that leads to the secretion of IL-1 $\beta$  and IL-18. Another inflammatory cytokine affecting the signaling pathway of the inflammasome is IL-18 (19). Its activation and release are controlled by the cysteine protease caspase-1 (20). Clinical studies have shown that high plasma levels of IL-1 $\beta$  and IL-18 are significantly associated with gout, diabetes, Alzheimer's, and atherosclerosis (21).

Treatment of ARDS in diabetic patients is very complex and difficult. Because the drug used to treat these patients should not only treat ARDS but also not affect the blood sugar level of these patients (22, 23). In this regard, one of the effective ways as an adjunct medicine is the use of medicinal herbs. The use of herbal antioxidants has been shown to be an essential way to stimulate the response and counteract the effects of oxidative stress on body tissues, including the pancreas (24). Borage (*Borago officinalis*) is one of the most important medicinal herbs in the treatment and reduction of blood sugar (25, 26). Since several studies have shown that this herb also has anti-inflammatory properties (25), we decided to consider the effect of borage oil on the signaling pathway of the NLRP3 inflammasome complex, TLR4, and some inflammatory cytokines in type II diabetic patients with acute respiratory distress syndrome.

## Materials and Methods

### Patients

The present study was quasi-experimental. Research samples were selected from type II diabetic patients

with acute respiratory distress syndrome (ARDS). In addition to having type II diabetes, the inclusion criteria were ARDS Berlin Definition (27). These criteria include a sudden onset up to seven days after a specific tissue injury or respiratory symptoms and bilateral pulmonary infiltration seen as pulmonary edema on the radiograph. Based on ARDS Berlin Definition, 25 patients with type II diabetes were selected, of which 11 had mild ARDS, 8 had moderate ARDS, and 6 had severe ARDS. ARDS was graded based on PaO<sub>2</sub>/FIO<sub>2</sub> ratio. Mild ARDS has PaO<sub>2</sub>/FIO<sub>2</sub> ratio between 201-300 mmHg, moderate ARDS has PaO<sub>2</sub>/FIO<sub>2</sub> ratio between 101-200 mmHg, and severe ARDS had PaO<sub>2</sub>/FIO<sub>2</sub> ratio less than 100 mmHg. Among these 25 patients, 10 patients were women and 15 were men. These patients were treated with 30 mg/day borage oil. Demographic and clinical characteristics of these patients were recorded two times before and after borage oil (*Borago officinalis*) consumption. Then, fasting blood samples were taken to measure serum levels of cytokines and gene expressions.

### Oil-pressing of borage (*Borago officinalis*)

In order to prepare the borage oil, the seeds were halved and 10 ml of magnesium sulfate (10%) was added and oil-pressing was done by cold-pressed method (28). To provide oil from dried leaves and flowers, 100gr of dried leaves and flowers were first cleaned and soaked in 1000 ml double distilled water and kept at -4°C for 24 hours. The mixture was then brought to boiling point with gentle heat. After a quarter of the water remained, the mixture was pressed by hand and passed through a filter paper. Then 20 ml of base oil was added to the filtered solution through a filter paper and placed on a gentle flame. The ingredient that remains at the end is borage oil.

### Measurement of serum levels of inflammatory cytokines

After blood sampling was performed from the brachial vein, the samples were transferred to serum tubes. Anticoagulant-free samples were centrifuged to measure serum levels of IL-18 and IL-1 $\beta$  for later analysis. Serum levels of inflammatory cytokines were measured using the ELISA-Luminex method. The M500KCAF0Y BIO-RAD and HD42 BIO-RAD kits were used according to the catalog steps and then in the Elisa reader (Bio-Rad, USA) with a sensitivity of measuring 0.06 ng/ml, the accuracy of the test and the levels of IL-1 $\beta$  and IL-18 cytokines were measured.

### RNA extraction and cDNA synthesis

1000 $\mu$ l of EDTA-containing blood was poured into RNaseDNase Free microtubes and 1000 $\mu$ l of cell lubricating buffer solution was added to each microtube and, after mixing, centrifuged at 6000 rpm for two minutes. The top layer was then removed until a white pellet appeared inside the microtube. After this step, 1000 $\mu$ l of RNX-plus™ Reagent separator solution was added to the pellet and according to the catalog of this solution, the steps were performed in order. In this way, RNA was extracted and the Spectrophotometer NanoDrop ND-1000 (Bio-Rad, USA) was used to measure its concentration and purity. Then, for each sample, one microli-

**Table 1.** Primer Sequences of  $\beta$ -actin, TLR4, and NLRP3 genes.

Genes		Primer Sequence
$\beta$ -actin	Forward	5'-ATCAGCAAGCAGGAGTACGAT-3'
	Reverse	5'-AAAGGGTGTAAAACGCAGCTC-3'
TLR4	Forward	5'-AATCCCTGCATAGAGGTACTTCCTAAT-3'
	Reverse	5'-CTCAGATCTAGGTTCTTGGTTGAATAAG-3'
NLRP3	Forward	5'-ATGAAGATGGCAAGCA CCCG-3'
	Reverse	5'-CTACCAA GAAGGCTCAAAGACGAC-3

ter of RNA was added to the microtubes for the cDNA synthesis kit and the cDNAs were amplified using the PCR machine-based (Bio-Rad, USA) on the kit catalog in the appropriate temperature cycle.

### RT-PCR method

Reactions were performed based on SYBR®Green color. To evaluate the specific sequence, the  $\beta$ -actin gene was amplified as a reference gene with their temperature cycle. Specific primers for TLR4, NLRP3, and  $\beta$ -actin genes were designed using Genscript software and evaluated using OligoAnalyzer software. Then, to prepare the primers, their lyophilized powders were prepared from Bio-Rad (USA). The primer sequences of these three genes are shown in Table 1.

The temperature program used in Real-Time PCR included 95°C for 10 minutes, 95°C for 15 seconds, and 60°C for one minute (40 cycles repeated). The relative expression of required genes was also measured by the 2<sup>- $\Delta\Delta$ CT</sup> method. Finally, the mean CT numbers obtained from the heating system of the double kit samples were evaluated for changes in pre and post-test gene expression using the control group as a basis. When changes in gene expression were less than 1, then decrease in target gene expression and if changes in gene expression were greater than 1, an increase in target gene expression was considered. Finally, before analyzing the data, the obtained melting curve was examined to confirm the peak point of the desired genes and the absence of primer. To ensure the products of the AT-PCR, samples of  $\beta$ -actin, TLR4, and NLRP3 were screened for the presence of DNA on agarose gel by electrophoresis, and then by ultraviolet gel documentation.

### Statistical analysis

After confirming the normal distribution of data by Kolmogorov-Smirnov test and confirming the homogeneity of variance by Leven test, the ANOVA test was used to examine the mean difference between groups and the LSD test was used to compare the pairs with each other. All statistical operations of the study were performed by SPSS 16 software and a significance level was considered as  $P < 0.05$ .

## Results

### Clinical and demographic characteristics

Among 25 selected patients, 10 patients were women and 15 were men. Based on ARDS Berlin Definition, these patients with type II diabetes were selected, of which 11 had mild ARDS, 8 had moderate ARDS, and 6 had severe ARDS. ARDS was graded based on  $\text{PaO}_2/\text{FIO}_2$  ratio. Mild ARDS has  $\text{PaO}_2/\text{FIO}_2$  ratio between

201-300 mmHg, moderate ARDS has  $\text{PaO}_2/\text{FIO}_2$  ratio between 101-200 mmHg, and severe ARDS had  $\text{PaO}_2/\text{FIO}_2$  ratio less than 100 mmHg. These patients were treated with 30 mg/day borage oil (*Borago officinalis*) for one week. Clinical and demographic information of these patients were evaluated before and after treatment (Table 2). The results showed that the mean blood sugar in the mild ARDS group and moderate ARDS group decreased, significantly. However, in the severe ARDS group, although a decrease in blood sugar was observed, this decrease was not significant. Regarding systolic blood pressure, it increased in all three groups, but in the third group (Severe ARDS Group) this increase was significant. Regarding diastolic blood pressure, also, this amount increased significantly in the third group after treatment with borage oil.

### Serum levels of inflammatory cytokines results

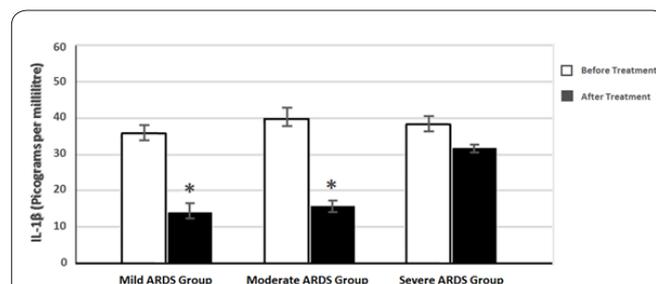
Serum levels of IL-1 $\beta$  in the mild ARDS group and moderate ARDS group decreased significantly after treatment with borage oil (*Borago officinalis*). In the case of the severe ARDS group, although the serum level decreased, this decrease was not significant (Figure 1).

Serum IL-18 levels in the mild ARDS group decreased significantly after treatment with borage oil (*Borago officinalis*). But in the other two groups, despite the decrease in serum levels, this decrease was not significant (Figure 2).

### Gene expression results

Regarding the expression of the NLRP3 gene, a significant decrease was observed only in the mild ARDS group after treatment with borage oil. In the other two groups, this medicinal herb did not affect the expression of the NLRP3 gene (Figure 3).

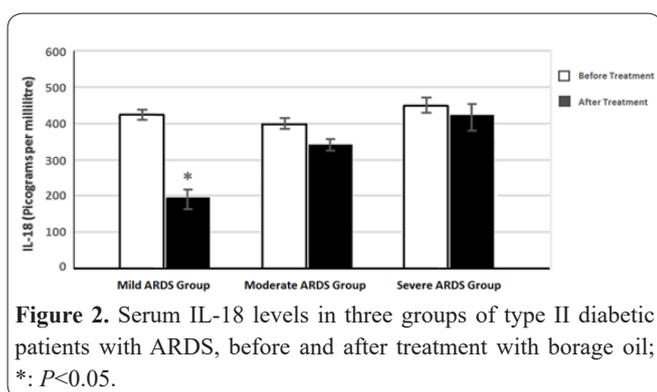
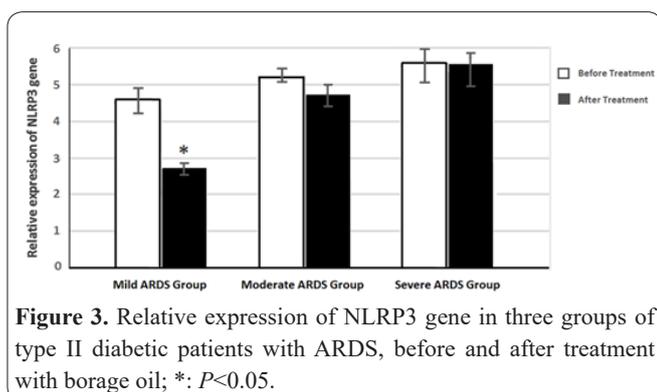
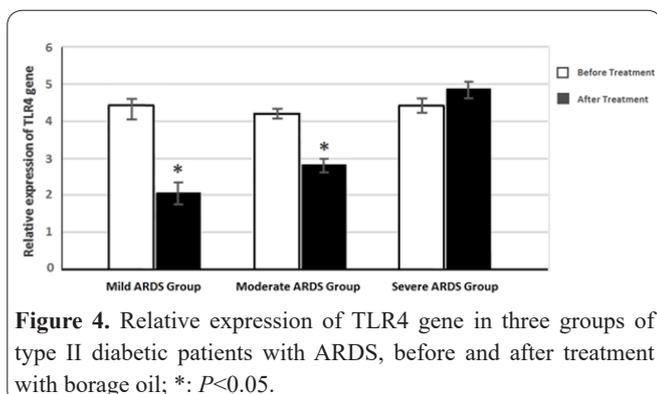
Regarding the expression of the TLR4 gene, a significant decrease was observed in the mild ARDS group after treatment with borage oil. In the moderate ARDS group, this reduction in gene expression was also signi-



**Figure 1.** Serum IL-1 $\beta$  levels in three groups of type II diabetic patients with ARDS, before and after treatment with borage oil; \*:  $P < 0.05$ .

**Table 2.** Clinical and demographic characteristics of 25 diabetic type II patients with ARDS before and after treated with *Borago officinalis*.

Variable	Mild ARDS Group (n=11)		Moderate ARDS Group (n=8)		Severe ARDS Group (n=6)	
	Before	After	Before	After	Before	After
Age (years)	59.61±1.31	59.61±1.31	57.28±2.05	57.28±2.05	62.03±4.35	62.03±4.35
Weight (Kg)	73.52±3.55	73.52±3.55	76.12±7.16	76.12±7.16	74.29±4.42	74.29±4.42
Height (cm)	175.32±30.21	175.32±30.21	171.41±25.44	171.41±25.44	174.11±21.67	174.11±21.67
Mean blood sugar (mg/dL)	181±12	130±9*	172±21	97±33**	176±26	166±19
Systolic blood pressure (mmHg)	127±3	129±5	126±8	129±2	127±5	135±6*
Diastolic blood pressure (mmHg)	85±3	84±7	82±9	85±4	83±5	91±2**

\*:  $P < 0.05$ ; \*\*:  $P < 0.01$ **Figure 2.** Serum IL-18 levels in three groups of type II diabetic patients with ARDS, before and after treatment with borage oil; \*:  $P < 0.05$ .**Figure 3.** Relative expression of NLRP3 gene in three groups of type II diabetic patients with ARDS, before and after treatment with borage oil; \*:  $P < 0.05$ .**Figure 4.** Relative expression of TLR4 gene in three groups of type II diabetic patients with ARDS, before and after treatment with borage oil; \*:  $P < 0.05$ .

ficant. In the severe ARDS group, gene expression increased, but this increase was not significant (Figure 4).

## Discussion

Acute Respiratory Distress Syndrome (ARDS) is not a primary disease but is caused by many infectious and non-infectious factors. Non-infectious causes include gastric aspiration, blood transfusions, trauma, inflam-

mation of the pancreas, and drug overdose (29). Infectious causes also include pneumonia, sepsis, severe sepsis, and septic shock (30). The most common causes are pneumonia and sepsis syndrome. A common feature of these agents is their ability to stimulate a systemic inflammatory response that activates neutrophils (29). Therefore, this disease affects the inflammatory pathways and increases the expression of inflammatory cytokine genes and inflammasome-related genes (31).

Many studies have shown that borage oil has anti-inflammatory properties (32). Since the role of this medicinal herb in lowering blood sugar has also been proven (33-34), in this study, its effect on type II diabetic patients with ARDS was evaluated. The results of clinical evaluations showed that patients in the mild ARDS group and moderate ARDS group significantly reduced blood sugar levels after treatment with borage oil. However, in the severe ARDS group, this reduction in blood sugar was not significant. This plant also increased systolic and diastolic blood pressure in all three groups. But this increase in blood pressure was significant in the severe ARDS group. This indicates that borage oil is not only clinically ineffective in patients with severe ARDS, but also dangerous for this group due to high blood pressure and inability to control blood sugar.

Different studies have shown that borage oil is very effective in treating ARDS. For example, Mancuso *et al.* (35) showed that borage oil may recuperate endotoxin-induced acute lung injury by suppressing the levels of some pro-inflammatory eicosanoids in bronchoalveolar lavage fluid and reducing pulmonary neutrophil accumulation. Another study by Hamilton *et al.* (36) showed that borage oil, due to its antioxidant properties, was beneficial in patients with ARDS by decreasing mortality and length of mechanical ventilation. The current results showed that serum levels of inflammatory cytokines (IL-1 $\beta$  and IL-18), NLRP3 gene, and TLR4 gene were significantly decreased in diabetic type II patients with mild ARDS by treating with borage oil. IL-1 $\beta$  serum level and TLR4 were significantly decreased in diabetic type II patients with moderate ARDS. But there was not any significant decrease or increase in IL-1 $\beta$ , IL-18, NLRP3 gene, and TLR4 gene in diabetic type II patients with severe ARDS after 7 days of treatment with borage oil.

These results showed that the exact mechanism in reducing the activity of inflammasome by borage oil is not known for the treatment of type II diabetic patients with

ARDS. Some inflammatory markers can be reduced after treatment with borage oil, especially in patients with mild ARDS. In fact, in ARDS, the inflammasome is up-regulated. In the early stages of the disease, when the disease has not yet intensified, borage oil can reduce the regulation of inflammation.

In general, borage oil in the early stages of ARDS in type II diabetic patients can significantly reduce the inflammatory effects of the disease. In other words, borage oil, in addition to helping to treat ARDS in type II diabetic patients with mild ARDS and even with moderate ARDS, causes a significant reduction in blood sugar in these patients. But when these diabetic patients are in the severe stage of ARDS, borage oil not only does not help to reduce inflammation and treat ARDS but also increases systolic and diastolic blood pressure in these patients.

In this study, the effect of the borage oil was investigated on the signaling pathway of the NLRP3 inflammasome complex, TLR4, and serum levels of inflammatory cytokines (IL-1 $\beta$  and IL-18) in type II diabetic patients with acute respiratory distress syndrome. According to the obtained results, in the mild to moderate stage of ARDS disease in patients with type II diabetes, borage oil in addition to reducing inflammatory markers and helping to treat ARDS, also reduced blood sugar levels in these patients. It should be noted that borage oil in the severe stage of ARDS in patients with type II diabetes not only did not help to reduce inflammatory markers but also increased systolic and diastolic blood pressure. Therefore, borage oil can be even dangerous for these patients at this stage.

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