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Evaluation Levels of Interleukins in Rheumatoid Arthritis and treatment with *Senegalia senegal* (gum Arabic) and *Boswellia*

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ABSTRACT

This study aimed to explain the effect of *Senegalia Senegal* (Gum Arabic) and *Boswellia* on some Interleukin. Thirty adult male rats were used after induction of arthritis. They were divided into six groups, with five rats for each group. The first group was the negative control group (rats without arthritis induction and treatment), the second group was the positive control group (rats with arthritis induction), the third group was (the group arthritis induction and intubated orally with 250 mg kg B.W Boswellia), the fourth group was (the group arthritis induction and intubated orally 400 mg/kg B.W. gum arabic), and the fifth group was (the group arthritis induction and intubated orally with Boswellia and gum arabic). The sixth group was arthritis induction and intubated 0.75 mg/kg of methotrexate. Blood samples were obtained after two and six weeks. to tests were Interleukins IL-6, IL-1,IL-10, IL-2 and TNF-α in comparison to two weeks and six weeks for one group . The study indicated a significant increase in IL-6, IL-1, and TNF-α after two weeks and after six weeks, while IL-10 showed a significant decrease after two weeks and an increase after six weeks in as comparing with group G0.

Keywords: *Arthritis, Boswellia, Gum Arabic, Interleukins, TNF-α.*

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune condition that causes joint damage and synovial hyperplasia. It can cause joint deformity and impairment due to its gradual and invasive onset. The illness can present with a broad range of symptoms, clinical manifestations (Mohammed and Moosavi, 2022). cytokines Important mediators used intricate networks to control immunological and inflammatory responses and act as biomarkers for a variety of disorders (Liu et al., 2021), can be divided into a variety of groups, including interleukins (ILs), tumor necrosis factors (TNFs), colony stimulating factors monokines, lymphokines, interferons (IFNs), and transforming growth factors (TGFs). Rheumatoid factor (RF), originally defined as pathological antibodies is a member of the immunoglobulin (Ig) family, which comprises several isotypes and affinities that are specific to the Fc region of IgG. as the first form of autoantibodies to be found in patients with the disease, possibility that this component contributes to the pathophysiology of RA made it significant not only for differential diagnosis but also for etiology (Newkirk, 2002; Delft Myrth and Huizinga, 2020; Beduleva et al., 2020). Interleukin 1 (IL-1) active B and T cells as well as macrophages release this cytokine. This cytokine promotes fibroblast assembly in RA. IL-6 is considerable amount of released by macrophages during RA, Since appears at higher levels in synovial fluid during the acute phase of the illness, it is believed to be an indicator of the severity of the condition (Dayer et al., 2017). Interleukin 2 (IL-2) is primarily produced by T helper (CD4+) lymphocytes. It increases the activity and proliferation of all cytotoxic cell clones, regulates the growth and differentiation of B lymphocytes, and activates cell-mediated immune responses (Olejniczak and Kasprzak, 2008). Interleukin 10 (IL-10) this cytokine is secreted by T and B cells , natural killer, and mononuclear cells all release this cytokine. Because it stimulates the synthesis of IL-1Ra and TNF-α receptors and suppresses the release of multiple inflammatory cytokines, including IL-8, IL-6, IL-1β, and TNF-α, IL-10 improves a number of inflammatory immunological illnesses by suppressing several components of the immune response (Mielle et al., 2018). Interleukin 6 (IL-6) this cytokine is released by fibroblasts, T cells, and macrophages. A considerable amount of IL-6 is released by macrophages during RA. By causing the release of TNF-α and IL-1, this cytokine can cause inflammation. Furthermore, it encourages B cells to secrete immunoglobulins. Furthermore, osteoporosis results from this cytokine's activation of osteogenic cells and disruption of endothelial cell function (Brennan and McInnes, 2008). Since IL-6 appears at higher levels in synovial fluid during the acute phase of the illness, it is believed to be an indicator of the severity of the condition.

In this study we used a natural substance that can function as a biologically active substance against chronic inflammatory disease. These natural substances include Senegalia senegal (gum Arabic) and Boswellia carterii. Boswellia carterii is aromatic oleo- gum –resin secreted from Boswellia carterii, reputed as Frankincense. It is widely used in traditional medicine. Boswellia carterii is belonging to the family of Burseraceae (Al-Yahya et al., 2020). It exudes the resin of the Boswellia carterii species, which is cut to allow a white, milky resin to flow (Nwachukwu, 2020). Frankincense, or olibanum resin, comes from the tree of the genus Boswellia carterii, species Boswellia (family Burseraceae) (Maksimović, 2021). It has anti-arthritic and anti-inflammatory properties (Ammon, 2002; Sharma et al., 2004). Senegalia Senegal or Acacia senegal (Gum Arabic or Gum acacia) (GA), is a dietary fiber that is heteropolysaccharide and soluble in water is a glutinous or gummy exudation from the trunks of Acacia species (Yasseen et al., 2014; Lopez-Torrez et al., 2015; Jaafar, 2019).

GA is a natural compound that was shipped from Arabian ports (BeMiller, James, 2018). It is the other natural substance that was used in this study, which has anti-inflammatory properties by decreasing inflammatory markers and disease severity scores among rheumatoid arthritis and antioxidant activity via the increasing biosynthesis of antioxidant biomolecules (Ali et al., 2009; Kamal et al., 2018). Methotrexate is a drug that was used in the treatment of rheumatoid arthritis that treats inflammatory arthritis (Kong et al., 2014). That drug has side effects that cause congenital anomalies with impaired renal function and cause bone marrow suppression and hepatotoxicity (AL-Chalabi et al., 2014; Wang and Peng, 2020). It acts through inhibition of purine and pyrimidine synthesis and reduction in T-cell dependent proliferation and suppression of inflammation (Cronstein, 2005).

2- Materials and Methods

2-1- Experimental Animals:

Thirty adult male Sprague–Dawley albino rats weighing 20-300g at the age of 10-12 weeks were purchased from the animal house. They were kept for two weeks in special plastic cages with wood shavings to raise rats with metal caps so as to allow for adaptation before treatment under the controlled temperature condition of 25°C. Animals were provided with rat pellets and tap water for feeding and drinking.

2-2- Experimental design:

Thirty adult male rats were used in this experiment and divided randomly into six groups. The animal's weight was 200-250g each group consisted of five rats as follows: Group 0: negative control. Group 1: positive control (arthritis induced, untreated). Group 2: *Senegalia senegal* (gum Arabic), 400 mg / kg B.W[25]. Group3: *Boswellia carterii*, 250 mg/kg B.W (Al-Yahya et al., 2020). Group4: *Senegalia sengal* (gum arabic) and *Boswellia carterii* Group (5): intraperitoneal (i.p.) 0.75mg /kg B.W. drug methotrexate (El-Tanbouly and Abdelrahman, 2022).

2-3- Induction of Arthritis:

Rheumatoid arthritis was induced in rats by using a complete Freund adjuvant according to (Tian and Cronstein, 2007). Arthritis was induced by injecting 0.1 ml of complete Freund adjuvant (CFA) in the right foot of the rat and measuring foot thickness by machine Caplier vernier before the arthritis induction and after 24 hours of injection. Symptoms such as redness, severe swelling, stiffness, and increased thickness of the foot arthritis develop within 10-45 days after injection (Alwachi and Alsaadi, 2013). Then at the end of the experiment, a knee joint for the right and left sides was taken for the histological study for all groups.

2-4- Preparation of aqueous extract:

Boswellia carterii and *Senegalia senegal* were obtained from a herbal shop in Baghdad Governorate. They were cleaned of impurities and ground with a grinder to obtain a very fine powder. We prepared a watery decoction of *Boswellia carterii* and *Senegalia senegal*. *Senegalia senegal* (gum Arabic) 400 mg/kg B.W (Ali et al., 2020), and *Boswellia carterii* 250 mg/kg B.W (Al-Yahya et al., 2020). Then, the extracts were stored in a clean glass container in the refrigerator and extracts were stored at 4°C in a glass container until use.

2-5- blood collection:

Rats of all groups were observed on day 30 from the induction of arthritis (day 51 of the experiment). Blood was collected from rats at two weeks, and at the end of the experiment by cardiac puncture technique, the blood sample was kept in gel clot activator tubes. Then, serum was separated from coagulant blood by centrifugation at 5000 rpm for 10 min and stored at $^{-}$20 C to study the TNF-α according to (Yin et al., 2008). The concentration of serum Interleukin 1 (IL-1), Interleukin 2 (IL-2), Interleukin 6 (IL-6) was measured by using ELISA technique, Interleukin 10 (IL-10) according to (Zhang et al., 2010).

2-6- Statistical Analysis:

The Statistical Analysis System- SAS (2018) program was used to detect the effect of difference factors (Groups and Time) in study parameters. Least significant difference –LSD test (Analysis of Variation-ANOVA) was used to significant compare between means in this study (OS, 2023).

Result:

Serum TNF-α (PG/ml)

A- After 2 weeks

Results of Serum TNF-α value in the present study in table (1) showed after 2 weeks, a significant increase ($P \leq 0.01$) in the concentration of Serum TNF-α in G1(443.71 ±30.47A), G2(144.49 ±6.59), G3 (146.76 ±12.41), G4 (146.76 ±12.41) was reported compared with control group (62.93 ±8.16).

B- After 6 weeks

showed that there was significant increase after 6 weeks in Serum TNF-α at G1 (151.47 ±23.78) and G5 (97.27 ±8.21) compared with control group (66.09 ±5.02) .

Comparing between 2 weeks and 6 weeks

The current results showed non-Significant differences in Table (1) are in G0(66.09 ±5.02) in 6 weeks period compared to the same groups in 2 weeks period, while there was a significant decrease G1, G2, G3, G4, G5 compared to the G0.

Table (1): Effect of *Sengalia senegal* (Gum arabic) 400 mg / kg B.W *Boswellia carterii* 250mg / kg B.W on TNF concentration (PG/ml) on induced arthritic male rats after 2 weeks and 6 weeks

Mean ± SE of TNF-α			LSD value
Group	2 Week after	After 6 week	
G0	62.93 ±8.16D	66.09 ±5.02BC	18.469 NS
G1	443.71 ±30.47A	151.47 ±23.78A	70.048 **
G2	144.49 ±6.59BC	94.27 ±11.17BC	30.059 **
G3	146.76 ±12.41B	62.59 ±3.76C	25.456 **
G4	146.76 ±12.40B	62.59 ±3.76C	25.456 **
G5	102.79 ±2.34DC	97.27 ±8.21B	15.622 **
LSD value	43.820 **	33.943 **	---

Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01), NS: Non-Significant. G0: negative control (nonarthritis induction). G1: positive control (arthritic animal without treatment). G2: Arthritic animals treated with Senegalia sengal (Gum Arabic) 400 mg/kg B.W. G3: Arthritic animals treated with Boswellia 250 mg/kg B.W. G4: Arthritic animals treated with Boswellia and Senegalia (Gum Arabic). G5: Arthritic animals treated with drug methotrexate 0.75mg /kg B.W..

Serum Interleukin 1 (IL-1) (PG/ml)

A- After 2 weeks

Table (2) showed a significant increase (P≤0.01) in Serum Interleukin 1 (IL-1) in G1,G3 (377.59 ±44.59 , 487.18 ±102.78) groups respectively as compared with G0 (75.61 ±6.37.(

B- After 6weeks

There was a significant increase (P≤0.01) in Serum Interleukin 1 (IL-1) in G1,G3 (252.81 ±33.57, 192.29 ±41.51) as compared with G0 (73.91 ±3.65).

C- Comparing between 2 weeks and 6 weeks

Non-significant differences were noticed in G0 (73.91 ±3.65) after 2 weeks period as compared with the same groups after 6 weeks period, while highly significant decrease (P≤0.01) in G1,G2,G3,G4,G5 in Interleukin 1 (IL-1) (252.81 ±33.57, 129.26 ±5.64, 192.29 ±41.51, 88.52 ±4.32 , 127.44 ±1.17)

Table (2): Effect of *Sengalia senegal* (Gum Arabic) 400 mg / kg B.W *Boswellia carterii* 250mg / kg B.W on IL-1 concentration (PG/ml) on induced arthritic male rats after 2 weeks and 6 weeks .

Mean ± SE of IL-1			LSD value
Group	2 Week	After 6 week	
(G0)	75.61 ±6.37B	73.91 ±3.65C	16.40 NS
(G1)	377.59 ±44.59A	252.81 ±33.57A	100.67 **
(G2)	166.94 ±23.54B	129.26 ±5.64BC	44.24 **
(G3)	487.18 ±102.78A	192.29 ±41.51AB	270.55 **
(G4)	138.24 ±4.68B	88.52 ±4.32C	13.59 **
(G5)	191.55 ±14.38B	127.44 ±1.17C	34.382 **
LSD value	137.80 **	64.35 **	---
Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01), NS: Non-Significant. G0: negative control (nonarthritis induction). G1: positive control (arthritic animal without treatment). G2: Arthritic animals treated with Senegalia sengal (Gum Arabic) 400 mg/kg B.W. G3: Arthritic animals treated with Boswellia 250 mg/kg B.W. G4: Arthritic animals treated with Boswellia and Senegalia (Gum Arabic). G5: Arthritic animals treated with drug methotrexate 0.75mg /kg B.W.			

Serum Interleukin 2 (IL-2) (PG/ml)

A- After 2 weeks

Results of Interleukin 2 (IL-2) in the present study in table (3) showed after 2 weeks, a significant increase (P≤0.01) in the concentration of IL-2 in G1,G2,G3, G5 groups(404.49 ±48.11 , 210.89 ±9.51 , 512.03 ±93.09, 202.86 ±20.87) was reported compared with a control group (60.77 ±10.37) .

B- After 6weeks

showed that there was significant increase after 6 weeks in Interleukin 2 (IL-2) at G1, G3, G5 groups (298.71 ±40.62, 221.87 ±37.99, 141.19 ±12.33) compared to control group (71.68 ±0.84) .

C- Comparing between 2 weeks and 6 weeks

Comparing Interleukin 2 (IL-2) between periods of 2 weeks and 6 weeks, there was no significant difference in G0 (60.77 ±10.37) in 2 weeks and

(71.68 ±0.84) in 6 weeks, higher significant reduce (P≤0.01) in G1,G2,G3,G4, and significant reduce (P≤0.05) in G5(202.86 ±20.87) in 2 weeks and (141.19 ±12.33) in 6 weeks .

Table (3): Effect of Sengalia senegal (Gum arabic) 400 mg / kg B.W Boswellia carterii 250mg / kg B.W on IL-2 concentration (PG/ml) on induced arthritic male rats after 2 weeks and 6 weeks

Mean ± SE of IL-2			LSD value
Group	2 Week	After 6 week	
G0	60.77 ±10.37C	71.68 ±0.84D	157.23 NS
G1	404.49 ±48.11A	298.71 ±40.62A	112.09 **
G2	210.89 ±9.51B	127.96 ±9.23DC	23.614 **

G3	512.03 ±93.09A	221.87 ±37.99B	245.23 **
G4	161.80 ±7.72BC	109.75 ±7.61DC	20.475 **
G5	202.86 ±20.87B	141.19 ±12.33C	53.118 *
LSD value	128.75 **	69.378 **	---

Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01), NS: Non-Significant. G0: negative control (nonarthritis induction). G1: positive control (arthritic animal without treatment). G2: Arthritic animals treated with Senegalia sengal (Gum Arabic) 400 mg/kg B.W. G3: Arthritic animals treated with Boswellia 250 mg/kg B.W. G4: Arthritic animals treated with Boswellia and Senegalia (Gum Arabic). G5: Arthritic animals treated with drug methotrexate 0.75mg /kg B.W..

Serum Interleukin 6 (IL-6)(PG/ml)

A- After 2 weeks

Results of Interleukin 6 (IL-6)in the present study in table (4) showed after 2 weeks, a significant increase (P≤0.01) in the concentration of IL-6 in G1,G2,G3, G5 groups (785.18 ±87.18 , 491.09 ±73.55 , 1004.20 ±183.41 , 401.30 ±39.21) compared with a control group(122.29 ±18.39).

B- After 6weeks

Showed that there was significant increase after 6 weeks in Interleukin 6 (IL-6) in G1,G3 (590.67 ±80.58 , 446.46 ±75.81) compared with a control group(133.09 ±2.11).

C- Comparing between 2 weeks and 6 weeks

Comparing Interleukin 6 (IL-6) between periods of 2 weeks and 6 weeks, there was highly significant reduce (P≤0.01) was recorded in G1,G2 ,G3 ,G4 ,G5 in 6 weeks period as compared with the same groups after 2 weeks period.

Table 4: Effect of Sengalia senegal (Gum arabic) 400 mg / kg B.W Boswellia carterii 250mg / kg B.W on IL-6 concentration (PG/ml) on induced arthritic male rats after 2 weeks and 6 weeks

Mean ± SE of IL-6			LSD value
Group	2 Week	After 6 week	
G0	122.29 ±18.39C	133.09 ±2.11C	40.969 *
G1	785.18 ±87.18A	590.67 ±80.58A	211.29 **
G2	491.09 ±73.55B	248.26 ±17.59C	134.58 **
G3	1004.20 ±183.41A	446.46 ±75.81B	478.34 **
G4	326.22 ±15.90BC	218.52 ±17.02C	42.553 **
G5	301.30 ±39.21B	195.80 ±26.49C	103.16 **
LSD value	263.18 **	138.69 **	---

Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01), NS: Non-Significant. G0: negative control (nonarthritis induction). G1: positive control (arthritic animal without treatment). G2: Arthritic animals treated with Senegalia sengal (Gum Arabic) 400 mg/kg B.W. G3: Arthritic animals treated with Boswellia 250 mg/kg B.W. G4: Arthritic animals treated with Boswellia and Senegalia (Gum Arabic). G5: Arthritic animals treated with drug methotrexate 0.75mg /kg B.W.

Interleukin 10 (IL-10) (PG/ml)

A- After 2 weeks

Results in table (5) showed significant decrease (P≤0.01) in G1(155.53 ±25.12) ,G3 (268.65 ±55.67) , G4(279.44 ±31.20) compared with a control group (392.03 ±43.91).

B- After 6weeks

showed significant increase (P≤0.01) in IL-10 in G2,G3, G4,G5 groups(531.06 ±1.46 , 333.36 ±31.51, 664.82± 6.24 , 512.75 ±35.56) compared with a control groupG0(403.46 ±8.55) .

C- Comparing between 2 weeks and 6 weeks

Comparing Interleukin 10 (IL-10) between periods of 2 weeks and 6 weeks, there was no significant difference in G0(392.03 ±43.91)) in 2 weeks and (403.46 ±8.55) in 6 weeks , higher significant increase (P≤0.01) was recorded in G1,G2,G3,G4,G5 in 6 weeks period as compared with the same groups after 2 weeks period.

Table 5: Effect of Sengalia senegal (Gum arabic) 400 mg / kg B.W Boswellia carterii 250mg / kg B.W on IL-10 concentration (PG/ml) on induced arthritic male rats after 2 weeks and 6 weeks

Mean ± SE of IL-10			LSD value
Group	2 Week	After 6 week	
G0	392.03 ±43.91A	403.46 ±8.55C	146.86 NS
G1	155.53 ±25.12C	421.31 ±27.57C	66.357 **
G2	329.51 ±38.44AB	531.06 ±1.46B	68.459 **
G3	268.65 ±55.67B	333.36 ±31.51D	130.16 **
G4	279.44 ±31.20B	664.82 ±6.24A	56.689 **
G5	396.66 ±17.58A	512.75 ±35.56B	72.746 **
LSD value	109.34 **	66.70 **	---

Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01), NS: Non-Significant. G0: negative control (nonarthritis induction). G1: positive control (arthritic animal without treatment). G2: Arthritic animals treated with Senegalia sengal (Gum Arabic) 400 mg/kg B.W. G3: Arthritic animals treated with Boswellia 250 mg/kg B.W. G4: Arthritic animals treated with Boswellia and Senegalia (Gum Arabic). G5: Arthritic animals treated with drug methotrexate 0.75mg /kg B.W.

The present study was designed to explore the possible anti-inflammatory effect of each *Boswellia carterii* and *Senegalia sengal* in animal induced arthritis. Traditional herbal formulas used to treat inflammatory arthritis include Boswellia carterii contain boswellic acids (BAs) which have been shown to exhibit anti-inflammatory and anti-arthritic properties (Chevrier et al., 2005).

The Boswellia resin's chemical structure is similar to that of other pentacyclic triterpenes, which closely resembles that of anti-inflammatory steroids (Trivedi et al., 2023), that has exhibited efficacy against various chronic diseases like arthritis, diabetes, asthma, cancer, inflammatory bowel disease, Parkinson's disease, Alzheimer's [34]. The active constituents are contained in the extracted Boswellia terpenoid portion and are composed of boswellic acids (BAs) (Safayhi et al., 1992). Human rheumatoid arthritis has a strong immune-mediated component and is marked by increased activated levels of TH1 cells and their cytokines, interleukin-2 (IL-2) and gamma interferon (IFN-γ), with fewer immunomodulatory TH2 cells and their cytokines, IL-4, IL-5, IL-10 and IL-13 (Luo et al., 2022). It is possible, then, that the beneficial effect of boswellins in inflammatory arthritis may derive in part from immune modulatory activity in addition to anti-inflammatory properties . Through treatment with gum arabic, a decrease in the level of TNF occurred, and this is consistent with what Mastomoto

stated, who noted that consuming 25 grams of gum arabic doubles the serum butyrate, which works to reduce the level of TNF by inhibiting NF-kB (Kamal et al., 2018). MTX anti-inflammatory effects, can significantly reduce the level of pro-inflammatory cytokines (IL-1,IL6) through modulating the infiltration of a great deal of immune and inflammatory cells, including neutrophils, monocytes, mast cells, helper T (Th) cells and B lymphocytes in RA synovium (Zhao et al., 2022).

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