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Evaluation of the Activity of Olibanum Oil as an Immune Booster in Rats

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Abstract

The applications of herbal medicine have recently acquired growing interest in range of the prophylaxis and treatment of diseases. Olibanum has been used since ancient eras and several reports studied the pharmacological characteristics of boswellic acid, particularly their effect on the inflammatory response, analgesic properties, and anti-arthritic activity mostly in cell lines, but new approaches include animal models to assess these natural derivatives effects taking into consideration of being safer than synthetic preparations. The impact of olibanum oil on several parameters was studied in rats during this study. These included white blood cell (WBC) count, lactate dehydrogenase (LDH), and C reactive protein (CRP), as well as other pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), and the cytokine interleukin -10 (IL-10) that is anti-inflammatory. Total WBCs in addition to IL-10 levels significantly increased in the oil-treated group in comparison with the control one, while the rats treated with olibanum oil revealed a significant reduced level of LDH, CRP, IL-6 and TNF- α compared with the controls ($p < 0.05$). These outcomes indicate that olibanum oil treatment are manifested by cytokine changes, it can improve the anti-inflammatory response and down-regulate the pro-inflammatory cytokines. So, the promising impact of olibanum oils as an immunomodulator could be used in alternative therapies.

Keywords: Olibanum oil, inflammatory cytokines, CRP, LDH, Rats

تقييم فعالية زيت لبان الذكر كمعزز مناعي في الجرذان

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الخلاصة

اكتسب طب الأعشاب وتطبيقاته في السنوات الاخيرة اهتمامًا متزايدًا في مجال الوقاية من الأمراض وعلاجها. حيث استخدم اللبان الذكر منذ العصور القديمة وتركزت معظم البحوث المنشورة على الفاعلية الدوائية لحمض البوزويلك ، وتحديداً على خصائصه المضادة للالتهابات ، المسكنة للألم والمضادة لالتهاب المفاصل ،ركزت تلك الدراسات على دراسة فاعلية هذه المواد في الخطوط الخلوية ولكن الأبحاث الحديثة اهتمت بدراسة تلك التأثيرات على الحيوانات المختبرية بالاخذ بنظر الاعتبار ان المنتجات الطبيعية أكثر أمانًا من الأدوية المصنعة. تم دراسة تأثير زيت اللبان الذكر في تعداد كريات الدم البيضاء و إنزيم نازع لهيدروجين اللاكتات LDH ، والبروتين المتفاعل سي ، وكذلك في بعض الحركيات الخلوية المحفزة للالتهابات إنترلوكين 6- ، وعامل نخر الورم -ألفا والحركي الخلوي المضاد للالتهابات إنترلوكين 10- في الفئران. بالمقارنة مع

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مجموعة السيطرة ، أظهرت الفئران المعالجة بزيت اللبان انخفاضًا ملحوظًا في مستويات LDH ، CRP ، TNF- α و IL-6 (p <0.05) ؛ بينما زاد IL-10 ومجموع خلايا الدم البيضاء بشكل معنوي في المجموعة المعالجة بالزيت مقارنة مع مجموعة السيطرة. تشير هذه النتائج إلى أن تأثيرعلاج زيت اللبان الذكر يظهر من خلال التغييرات في الحركيات الخلوية ، فهو يحسن الاستجابة المضادة للالتهابات ويقلل من الحركيات الخلوية المحفزة للالتهابات ، وبالتالي ، يمكن استخدام التأثيرات المناعية الواعدة لزيوت اللبان الذكر في العلاجات البديلة.

1. Introduction

Some plants have immunomodulatory criteria that are implicated in multiple components of the immune system on molecular and cellular basis and in both humoral and cellular immune responses [1]. It has been proved that essential oils have certain effects in several medical fields like cancer, pain, otolaryngology, dermatology, nephrology neuropsychiatry, urology as well as circulatory, digestive, endocrine, respiratory and immune systems [2, 3]. Antiviral properties of essential oils are being speculated to have effect on SARC-CoV-2 [4] and could be used for application in pharmaceutical industries [5]. The Burseraceae family is considered the source of the aromatic resin "Frankincense"[6], while the essential oil which is also known as olibanum is obtained from *Boswellia* trees. These trees are available in abundance in in Middle Eastern countries (Oman and Yemen), in Africa (Ethiopia and Somalia), and in South Asia (India). The French word *franc encens*, which means a nobility and pure incense of high quality, is the origin of frankincense name [7]. Whereas the Latin term, *Oleum libani* is the origin of olibanum nomenclature, from which the other name of frankincense was derived. Some reports have illustrated that *Boswellia* gum resins possess the ability to lower blood sugar and lipid levels [8]. The hepato-protective potential of essential oil make it an important oil in the management of liver diseases by using it in the formulation of phytomedicine [9]. Its potential is related to antimicrobial, antioxidant, anti-inflammatory, and antitumor activities [3, 8] that help in treating arthritis, chronic bowel diseases, asthma, cerebral odema, chronic pain syndrome, and cancer [10]. For instance, it has been proved that olibanum oils in cosmetic and other applications may enhance learning and improve memory [8]. The increased acute phase proteins, defective cytokine production, and enhancement of inflammatory signals are the main characteristics of inflammatory response [11]. Lactate dehydrogenase (LDH) is a nonspecific biomarker which is shown to be elevated in multiple diseases; but few reports have evaluated the role of LDH in the prognosis of diseases [12]. Similarly, several studies utilized C-reactive protein (CRP) to predict sudden cardiac death, peripheral vascular disease, myocardial infarction, and stroke [11]. Immunomodulation reflects the action that directs the immune response towards improving (immunostimulation) or inhibiting (immunesuppression) its function [13]. The oil obtained from *Boswellia* spp. had an immunostimulant activity [14]. It is regulated via a cascade of various inflammatory mediators, for example prostaglandin (PG) nitric-oxide (NO), proinflammatory cytokines; interleukins (IL- 2, IL-1β and IL-6) as well as tumor necrosis factor-α (TNF-α)[15]. Adipose tissue is considered as a main director for chronic inflammatory response. Cytokines secretion of the pro inflammatory type like TNF-α and ILs is mediated by adipose tissue , making it a main source of interleukin-6, a proinflammatory cytokine which enhances B, T helper cell proliferation and survival and the main stimulator of CRP production in the liver [11]. IL-10 acts as a damper of inflammation by suppressing the defective release of cytokines that promotes inflammation like TNF which controls IL-10 synthesis. Thus, the expression chronology of cytokines is essential over the inflammatory events [16]. The tree of *Boswellia* and its extracted derivatives are consumed in ayurvedic medicine as analgesic, anti-leukotriene, immunomodulatory, and anti-inflammatory[17]. The cons of using non-steroidal anti-inflammatory drugs (NSAID) are the possible aftereffect on the gut or circulation. However, much work has been done to develop medicines that overcome such side effects

though this target still needs more to be achieved, which makes it of great importance to find other products [18]. *Boswellia* species have been considered the top as an active inflammation antagonist herbal product [19]. The current study sought to ascertain whether olibanum oil affects the production of inflammatory cytokines in rats in both a pro- and anti-inflammatory manner.

2. Methods

2.1 Animal management

Healthy mature male rats were gained from Biotechnology Research center/ Al Nahrain University. The ethical approval of the study was obtained from the Ethics Committee (University of Baghdad, College of science, Department of Biology, Ref. no. CSEC/ 0322/0028 on 25th March, 2022).

Thirty male rats were employed. They were (8–10) weeks old, and their weight was around 200 ± 10g during the research. They were split into two groups at random, each group included 15 animals. The rats were kept in a suitable setting at 20–25°C with unrestricted access to food and water.

2.2 Essential Oil Extraction

Boswellia papyrifera (Olibanum) resin was used for the extraction of volatile or aromatic oil. Ethiopian olibanum resin was bought from local market, and then oil extractions were made by Clevenger apparatus applying the hydro-distillation technique. Discreetly crushed resin weighing 100 grams was combined with 300 ml of purified water. Then transferred to Clevenger apparatus and the distillation was carried out for 2hr. Volatile oil layer was collected, and stored in sealed containers at 4°C for further investigations [20].

2.3 Experimental design

Two groups of rats were enrolled in this study, as shown below:

Group A (N=15): Given tap water and served as a control.

Group B (N=15): Given olibanum volatile oil 200 mg/ kg body weight and administered orally [9] for 20 days.

Following the completion of the experiment, blood samples from both groups were taken after the rats got anesthetized with chloroform. About five ml of blood was directly collected from the heart via cardiac puncture through using 5 ml syringe and a 22 gauge needle. Two milliliters were placed in a vial where an anticoagulant was present in order to carry out a test for complete blood count for the rats. The other three milliliters were placed in sterile gel test tubes at room temperature, and thereafter centrifuged for 15 min at 3000 rpm, then kept in deep freeze at - 18°C for determining LDH, TNF, IL-6, and IL-10.

2.4 Laboratory tests

Hematologic tests were performed by using automated analyzer to count white blood cells (WBCs). Total and differential count of WBC was calculated by automated digital counter machine from Bengaluru, India. LDH were estimated by using kit provided from (Randox/British), The Randox lactate dehydrogenase (LDH) P-L assay utilizes the UV method using liquid ready-to-use and lyophilized reagents. The enzyme-linked immunosorbent assay (ELISA) was performed to detect CRP as well as the levels of IL-6 and 10 (BioSystem S,A.Costa Brava Barcelona/Spain). ELISA technique was also used to determine TNF-α concentration (Elabscience, China).

2.5 Statistical Analysis

Version 9.1 of the Statistical Analysis System (SAS) was employed in this study to analyze the impact of different factors on the study variables. Comparing means of the two groups under investigation was done using the t-test[21].

3. Results

The hematological examination of total differential count of WBCs revealed a notable elevation in total count of WBCs in rats that treated with olibanum oil than the controls (6.06 ±1.67 Cell x103 and 4.63±1.2 Cell x103 respectively) with significant differences between the two groups ($p < 0.05$) as illustrated in Table 1.

Moreover, Table 1 illustrates the differential count of WBCs; it reveals a significantly higher neutrophil percentage in the group treated with olibanum oil than in the control group ($p < 0.05$). Whereas the percentage of these lymphocytes dropped significantly in the treated animals as compared with the control ones; ($p < 0.05$). Yet, insignificant differences in monocyte, basophil and eosinophil percentage were detected between the two groups ($p \geq 0.05$).

Table 1: The effect of olibanum oil 200 mg/kg on total and differential count of W.B.C.

Groups	Mean ± SE					
	WBC Cellx10^3	Neutrophil%	Lymphocyte %	Monocyte %	Basophil%	Eosinophil %
Control (N= 15)	4.63±1.2	48.42 ±4.60	44.26 ±3.31	2.39 ±0.37	1.93 ±0.35	2.43 ±1.43
Olibanum oil 200 mg/kg (N=15)	6.06 ±1.67*	60.50 ±5.32*	33.11 ±3.65*	2.86 ±0.73 NS	1. ±0.07 NS	2.15 ±0.14 NS
*= significant differences; ($p < 0.05$)						

On the other hand, the mean level of LDH in the olibanum oil- treated group decreased significantly, also a similar tendency of decrease was observed according to CRP , these decreases were statistically significant ($p < 0.05$) as shown in Table 2.

Table 2 : The effect of olibanum oil 200 mg/kg on LDH and CRP in rats.

Group	Mean ± SE	
	LDH (U/L)	CRP (pg/ml)
Control (N=15)	164.32±8.42	7.50 ±1.73
Olibanum oil 200 mg/kg (N=15)	144.05 ±3.67*	4.26 ±0.53*
*= significant differences, ($p < 0.05$)		

In regard with cytokines, this study outcome revealed that there is a sharp decrease in both of the cytokines that promote inflammation (TNF- α and IL-6) versus obvious increase in anti-inflammatory cytokine (IL-10) in the group that was treated with olibanum oil compared with the control one, with significant differences ($p < 0.05$) as shown in Table 3.

Table 3: The impact of olibanum oil 200 mg/kg on some cytokines

Group	Mean ± SE		
	IL-6 (pg/ml)	IL-10 (pg/ml)	TNF-α (pg/ml)
Control (N=15)	8.42 ± 0.75	74.14 ± 4.57	68.15±0.54
Olibanum oil 200 mg/kg (N=15)	5.12 ± 1.64*	85.1 6 ± 3.98*	43.32±9.10*
*= significant differences, (p <0.05)			

4. Discussion

Due to the high expense of medications, drug resistance, and the difficulties many people have accessing them, particularly in countries that are less developed, the demand for conventional remedies improvement has increased [1, 2]. Olibanum is one of the most important alternatives for traditional medicine [13, 22]. The present study evaluated the impact of olibanum oil on the inflammatory response in rats. It revealed a noticeable increase in total white blood cells and neutrophils suggesting the enhancement of innate immune system. Similar studies revealed that eucalyptus oil, clove essential oils, and ginseng extracts increased the phagocytic efficacy of macrophages and circulating monocytes. This enhanced phagocytosis and upregulated CD44 receptor expression led to enhanced bacterial clearance and extravasation [23]. Additionally, they were demonstrated to restore the total WBC count and to activate immunity through both humoral and cell-mediated mechanisms in immune-compromised mice [24].

A recent study signalized a pivotal role of LDH in type I diabetes mellitus progression in rats [25]. Animal- model researches have reported that *Boswellia* parts which are soluble in water potentially worked on lowering the levels of cholesterol [8]. Similarly, reduced levels of cholesterol and elevated levels of heavy-density lipoproteins (HDL) were reported when extracts of *Boswellia* gum resins were used in rats , while remarkable decreased levels of blood low-density lipoprotein (LDL), and liver enzymes SGPT and SGOT were noted [26]. In agreement with previous observations, a notable decreased level of LDH was noted in the current study. In a part study, a breast malignant cell death induced by olibanum oil was quantified by LDH release to detect whether the restricted cell activity comes from cell death augmentation and how cells reacted in a preliminary stage of therapy. Cell death acceleration was recorded in all cell lines of breast cancer after treating with essential oil of *Boswellia* [27]. In the same trend, CRP is considered as a critical biomarker that increased in acute infections [28, 29]. Correspondingly, the lower serum level of pro-inflammatory cytokines represented with TNF-α and IL-6 and the high level of anti-inflammatory cytokine (IL-10) were recorded in olibanum oil–treated animals. It has been reported that hypertriglyceridemia and lipid metabolism were affected by TNF-α via damping of lipoprotein lipase activity in adipocytes. Moreover, it was linked to increased levels of triglycerides and promoted fatty acid synthesis in liver [30]. However, in the present study, obvious decrease in TNF-α was recorded, suggesting that olibanum oil showed a positive anti-inflammatory activity which is harmonious with some articles regarding the ability to inhibit the inflammation mediated by LPS, nitric oxide responses and NF-κB production, resulting in the down-regulation of the expression of TNF-α in human monocytes [31, 32]. Interestingly, decreased phosphorylation of NF_κB also associated with decreased levels of IL-6, TNF-α, IL-1β, and nitric oxide. Additionally, LPS-stimulated synthesis of IL-6, and TNF-α was significantly reduced in cells pretreated with eucalyptus and clove essential oils [13]. Evidently, essential oils generally demonstrated fair anti-inflammatory efficacy, which is superior to the commercial product (Ibuprofen); this was accomplished by notably lowering the synthesis of inflammatory

cytokines, such as NF-κB, cyclooxygenase 2 (COX-2), IL-6TNF-α *in vivo*. Therefore, it is reasonable to suggest that alternative medicine products such as these essential oils can be used as anti-inflammatory drugs with minimal adverse effects [33]. It is generally recognized that IL-10, an anti-inflammatory cytokine, is mostly produced by antigen-presenting cells, the anti-inflammatory potential of *Boswellia* is mainly attributed to boswellic acid, this component inhibits pro-inflammatory responses by damping of 5-lipooxygenase and cyclo-oxygenase and acting on the complement cascade, Additionally, boswellic acid inhibits 5-lipoxygenase, which reduces leukotriene formation, and many chronic inflammatory illnesses are linked to elevated leukotriene action[8]. Conversely, *Boswellia* components may boosts the humoral immune response by turning the cytokine modality across T helper 2 side as it observed with eugenol, a component of clove oil [34]. It's known that the dominant white blood cells in mammals are neutrophils, which are considered the premier barrier of innate immunity against pervading pathogens or other exotic bodies. In addition, they play pivotal roles in modulating acquired immunity and work as regulators of the whole immune response and inflammatory reactions [35].

Regarding lymphocyte proliferation as an adaptive immune response, enhancement of T-lymphocyte production reflects immunostimulation, whereas reduction the activity of T-lymphocyte reflects immunosuppression [31]. Treatment with boswellic acid suggests that the significant decrease in migration of leukocytes from the blood stream into the site of inflammation was linked with its anti-inflammatory effectiveness [36]. The present elevated levels of IL-10 are related to the multiplication of neutrophils, and antigen presenting cells (APCs) with the elevation in these parameters suggesting an anti-inflammatory effect. Interestingly, our study outcomes agreed with previously mentioned reports [32].

5. Conclusions

Our study revealed that the effectiveness of olibanum oil treatment are represented by cytokine alterations; olibanum oil improves the anti-inflammatory response and downregulates the pro-inflammatory cytokines which could add a value to previously recorded immunomodulatory, anti-inflammatory effects of this oil. This can encourage the use of olibanum oil as natural innate immune booster and inexpensive anti- inflammatory alternative. More study is needed, though, to comprehend the anti-inflammatory and antibacterial characteristics of olibanum extracts and products.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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