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Study the Effect of Olibanum (Boswellia Carterii) on Hyperuricemia in Rat's Module

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Abstract

The current study aims to assess the antihyperuricemic activity of the olibanum resin and study the urate-lowering effect in a rat model of hyperuricemia generated by potassium oxonate (PO). Rats used in the research were randomized into 5 groups (n = 6). All rat groups received intraperitoneal injections of PO twice a week at a dose of 250 mg/kg for one month, except the normal control group, which was supplied with food and drink without any intervention. Simultaneously, as a treated control group, the olibanum 50 mg/kg group received daily oral administration of 50 mg/kg of olibanum powder dissolved in 0.5 ml of distilled water. The olibanum 100mg/kg group was treated with 100 mg/kg of olibanum powder dissolved in 0.5 ml of distal water orally each day. Allopurinol (5mg/kg) was administered daily to rats in the allopurinol group as a standard control. The negative control group received intraperitoneal injections of PO without treatment. Each group's animals were sacrificed, blood was taken, and serum was isolated for uric acid laboratory analysis and other biochemical parameters. Uric acid and creatinine in urine were also measured. The investigation results demonstrated a significantly substantial reduction in blood uric acid and modest inhibition of xanthine oxidase in rats with hyperuricemia that were given olibanum solution compared to the hyperuricemic control group; all groups showed non-significant variations in kidney and liver functioning. Based on the present study's findings, olibanum powder significantly reduced uric acid via uricosuric activity and xanthine oxidase enzyme inhibition.
Keywords: Olibanum; Uric acid; Renal function; Liver function; Hyperuricemia; Xanthine oxidase.

دراسة تأثير مستخلص اللبان (*Boswellia carterii*) على فرط حمض يوريك المستحدث في دم الجرذان.

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الخلاصة

الهدف من الدراسة الحالية هو تقييم النشاط المضاد لفرط حمض اليوريك في الدم لنبات Boswellia Carterii (اللبان أو راتنج اللبان) والتحقيق في تأثير خفض اليورات في نموذج الجرذان المصابة بزيادة حمض اليوريك في الدم الناتج عن أكسونات البوتاسيوم. تم تقسيم الجرذان المستخدمة في البحث بصورة عشوائية إلى خمس مجموعات كل مجموعة تتكون من ٦ جرذان. تلقت جميع مجموعات الجرذان حقنًا داخل الصفاق من اكسونات البوتاسيوم مرتين في الأسبوع بجرعة ٢٥٠ مجم / كجم لمدة شهر واحد باستثناء مجموعة المراقبه العادية ، والتي تم تزويدها بالعلم والشراب فقط دون علاج. في نفس الوقت ، كمجموعة ضابطة معالجة ، تلقت مجموعة اللبان ٥٠ مجم / كجم جرعة يومية عن طريق الفم قدرها ٥٠ مجم / كجم من مسحوق اللبان المذاب في ٠,٥ مل من الماء المقطر ، وتم معالجة مجموعة اللبانوم ١٠٠ مجم / كجم بـ ١٠٠ مجم / كجم من اللبانوم مسحوق يذاب في ٠,٥ مل من الماء المقطر عن طريق الفم كل يوم. تم إعطاء الوبيورينول (٥ مجم / كجم) عن طريق الفم للجرذان في مجموعة الوبيورينول يوميًا كمعيار. تلقت المجموعة الضابطة السلبية الحقن داخل الصفاق من اكسونات البوتاسيوم دون علاج. تم التضحية بحيوانات كل مجموعة ، وأخذ الدم ، وعزل المصل لتحليل معمل حمض البوليك وغيرها من المعايير البيوكيميائية. تم أيضًا قياس حمض اليوريك والكرياتينين في البول. أظهرت نتائج الفحص انخفاضًا كبيرًا في حامض اليوريك في الدم وتثبيطًا معتدلًا لأكسيداز الزانثين في الجرذان المصابة بفرط حمض يوريك الدم التي تم إعطاؤها محلول اللبان مقارنة بمجموعة الضابطة السلبية في فرط حمض يوريك الدم. أظهرت جميع المجموعات اختلافات غير مهمة في وظائف الكلى والكبد. بناءً على نتائج الدراسة الحالية ، قلل مسحوق اللبان بشكل كبير من حمض اليوريك عن طريق نشاط حمض اليوريك وتثبيط إنزيم أوكسيديز الزانثين.
الكلمات المفتاحية : اللبان، حمض اليوريك وظيفة الكلى، وظائف الكبد، فرط حمض يوريك الدم، أوكسيديز زانثين.

Introduction

Hyperuricemia (HU) is a persistent elevation of uric acid (UA) >6.8 mg/dL in the peripheral blood. It is predictable in the human body as the crucial cause of the development of gout [1,2]High serum urate is usually accompanied by high body mass index, hypercholesterolemia [3], hypertriglyceridemia [4], increased fasting plasma glucose [5], and insulin resistance. The high production of UA and elimination insufficiency are the major significant causes of HU. Over 90% of HU is produced due to inadequate UA elimination [2]. HU is the most critical risk factor for gout, cardiovascular disease, chronic kidney disease (CKD), and metabolicc syndrome [6]. Due to its rapidly increasing significant impact on many clinical implications, HU is quickly emerging as one of the international population's most severe public health concerns [7]. HU has developed rapidly due to changes in dietary patterns (excess consumption of fructose, seafood, red meat, poultry, sweet drink, and purine-rich vegetables), particularly among teenagers and adults [1]. Additionally, heavy alcohol consumption is one of the primary causes of HU, also CKD, hypothyroidism, cachexia, myelo- and lymphoproliferative diseases, tumour lysis syndrome in oncologic patients, and relatively rare genetically determined HU [8].

HU incidence in men is 2–6 times higher than in women, with a prevalence rate that has increased over the past 30 years [9,10]. Gout is caused by the sedimentation of monosodium urate crystals onto different joints, followed by a very painful immune response [10,11]. Three consecutive stages were identified years ago in the historical relationship between HU and gout: asymptomatic hyperuricemia, intermittent gout, and chronic gout [12]. Many drugs are taken to treat and manage gout and HU, such as xanthine oxidase inhibitors (XOI), which reduce UA generation. These medications serve as the

first line of gout treatment to reduce urate levels, as they are efficacious in most hyperuricemic patients and have an acceptable tolerability profile as allopurinol [13,14]. Treatment-related adverse effects include Allopurinol Hypersensitivity (AHS), which is rare but fatal; severe skin reactions; hepatitis; interstitial nephritis; and eosinophilia [15]. Uricosuric medicines reduce uric acid reabsorption in the proximal renal tubule and increase UA clearance in the kidneys as benzbromarone; however, because of hepatotoxicity, it was withdrawn from several markets in 2003 [16,17]. Urate-lowering therapy generally leads to an amplified flare rate and accompanying pain as a direct consequence of urate crystal dissolution [18].

Olibanum is a natural oleo-gum substance derived by making incisions in the trunks of *Boswellia* trees [19]. The *Boswellia* tree, known as frankincense or olibanum, is a deciduous tree belonging to the *Burseraceae* family [20]. Saudi Arabia, Somalia, Yemen, eastern Mediterranean nations, and Sudan are home to the *Boswellia carterii* plant [21]. *Boswellia carterii* primarily comprises volatile oils and terpenes, such as pentacyclic triterpenes, tetracyclic triterpenes, diterpenes, and monoterpenes, which are the major chemical components of olibanum. It also contains essential oils, organic acids, and polysaccharides [22,23]. The active chemicals in *Boswellia carterii* gum and resin, namely mono-, sesqui-, di-, and tri-terpenoids, have been shown to have anti-inflammatory, cytotoxic, hepatoprotective, antibacterial, and antifungal functions [24], and complementary therapies for arthritis [25,26]. Oleo gum resin "Olibanum" also has cardioprotective and antioxidant properties [20,27]. The current study aimed to assess the anti-hyperuricemic effect of the *Boswellia carterii* plant and to analyze its urate-lowering impact by increasing UA excretion and lowering UA synthesis by suppressing the xanthine oxidase (XO) enzyme.

Experimental

Chemicals and reagents

Sigma Aldrich Co., USA, supplied Potassium Oxonate (PO) and Zyloric® drugs. Nanjing KeyGEN Biotech. Co., Ltd. (Nanjing, China) provided the uric acid, xanthine oxidase, and all experimental kits. The reagents and chemicals utilized in this investigation are of analytical quality.

Olibanum powder preparation

In May 2021, dried olibanum was obtained at a local market in Basrah City. The olibanum was then milled into a fine powder using an electrical miller (Silver Crest, Germany) and stored in an airtight glassware container at room temperature to be dissolved in 0.5 ml of distilled water according to the specified dose and given to rats. This research was done in November and December 2021 at the College of Pharmacy, University of Basrah, in Basrah, Iraq.

Animals

This study used 30 mature male Swiss rats weighing about 150-180 grams from the animal house of the College of Pharmacy, University of Basra, Iraq. Rats were separated into 5 groups (n = 6) with distinct traits. Rats were housed in insulated plastic cages for a week, and animal areas were maintained at 22 ± 4 °C, 30 ± 15 percent humidity, and a 12-hour dark/12-hour light cycle. The animals had free access to regular feed and water throughout the study. Animal Ethics Board No. 2013/32 of the University of Basrah, Iraq, approved all animal handling techniques described in this paper.

Drug Administration

Allopurinol (5 mg/kg) was suspended in 0.5 ml of distilled water (D.W) and given orally. PO 250 mg/kg in warm normal saline was dissolved and given by Intraperitoneal injection [28]. Olibanum

powder, 100 and 50 mg/kg, was dissolved in 0.5 ml of DW and given orally. Each solution was prepared freshly before the experiments [29].

Induction of hyperuricemia

Intraperitoneal (*i.p.*) PO injections into experimental rats at a dose of 250 mg/kg twice a week for one month stimulated the HU in the experiment [28]. The mechanism of HU was studied in this work by environmentally created animal models involving pharmacologic inhibition of uricase, which transforms the UA into a more water-soluble allantoin. When a specific competitive uricase inhibitor (Potassium Oxonate) is used to block hepatic uricase and reduce renal urate excretion, urate nephropathy results in a rise up in blood UA levels [30,31].

Experimental study design

The olibanum impact on urinary UA, urinary creatinine, serum uric acid (SUA) level, xanthine oxidase, and levels of antioxidant enzymes was demonstrated using the PO-induced HU rat model with slight modifications [32]. The rats were randomly sorted into 5 groups (n=6). The rats fasted for 2 hours before receiving medications and a vehicle by withdrawing water and food. PO was injected intraperitoneally into the animal groups twice weekly throughout the study duration, which lasted one month. At the same time, once daily, the vehicle, allopurinol, and olibanum solution were given orally to the rat groups via oral gavage. Normal control group animals received only vehicles (distilled water). Negative control group rats were injected intraperitoneally at a dose of 250 mg/kg of a PO with no treatment. The standard-drug group was treated with allopurinol at 5 mg/kg. The treated groups were administered orally once daily with olibanum solutions at 50 mg/kg and 100 mg/kg.

Collection of urine and blood samples

The rats were moved to the metabolic cages on days 0, 7, 14, and 28 of the trial to collect urine for 24 hours. To get the supernatant, urine samples were spun in a centrifuge at 2000 rpm and then used to measure urinary creatinine and uric acid. At the end of the one-month examination interval, the rats were euthanized, and a heart puncture was performed to obtain from each rat total blood samples. The samples were allowed for 30 minutes at room temperature, intended for coagulation, along with 10 minutes for centrifuging at 4000 rotations per minute to get a hold of blood serum. Serum and urinary samples maintained at - 20 ^{O}C up to biochemical characteristics could be determined.

Biochemical parameter assays

The serum levels of SUA, creatinine (SCr), alanine transaminase (ALT), alkaline phosphatase (ALP), and aspartate transaminase (AST), and blood urea were evaluated using conventional diagnostic kits using enzymatic colorimetric techniques. XO concentrations were measured using BT-LAB enzyme-linked immunosorbent assay kits. UA and creatinine in urine were also measured.

Statistical analysis

Results for each experiment are shown as mean ± SD. Statistical analysis was performed via one-way ANOVA after Dunnett's t-test. A probability (*P*) less than 0.05 is considered statistically significant.

Results and Discussion

Xanthine oxidase (XO) is an important enzyme that converts the xanthine to hypoxanthine and then into UA, so a high XO level leads to excessive production of UA [33].

As can be seen from the results illustrated in Table 1 and Figure 1, it has been observed that the serum level of XO in the normal control group is (20.1 ± 2.5) IU/L, and this is the normal value depending on other studies [34]. There was a considerable (P<0.01) rise in XO in the negative control group, which led to increased production of UA compared with the normal control group UA in each blood sample, because of PO, which causes the level of XO to rise [35].

While in the allopurinol group, when compared with the negative control, there was a highly considerable (p < 0.001) decrease in XO, allopurinol considered the essential XO inhibitor, which exhibited 95% of XO inhibition action at a similar concentration [36]. The olibanum at a (100 mg/Kg) dose significantly decreased the XO enzyme level (p <0.05). In contrast, the olibanum at the (50 mg/Kg) dose inhibited the XO enzyme level significantly (p <0.01) compared with the negative group.

Any substance may diminish XO enzyme activity, inhibiting UA formation. Olibanum powder in both doses (50 and 100 mg/kg) was revealed to have a significant inhibitory effect on XO *in vivo*. The phytochemical analysis by chromatographic techniques for olibanum revealed that their resin content contains phenylpropanoids, terpenoids, phenolic compounds, and flavonoids, among others [37]. Several *in-vivo* and *in-vitro* investigations have shown that antioxidants contained in several plants, such as flavonoids and phenolic compounds, have a real effect on UA issues by inhibiting the XO enzyme, increasing renal UA production, and decreasing UA reabsorption.

Polyphenols and flavonoids, which have a similar chemical structure to xanthine, can block the XO enzyme activity. XO enzymes use polyphenols and flavonoids as substrates. Polyphenols and flavonoids will bind electrons from the XO enzyme responsible for oxidizing xanthine to UA. XO

enzymes prefer to oxidize polyphenols and flavonoids rather than xanthine due to the high affinity toward these compounds compared to hypoxanthine and xanthine. Therefore, this competition will reduce UA generation. The combination of XO enzymes, polyphenols, and flavonoids results in a rise in the concentration of non-oxidized xanthine in the blood, followed by the excretion of xanthine readily soluble in urine, and a reduction in serum UA levels [38,34].

Table 1.Biochemical parameters of all groups of rats

Group	XO (IU/L)	UA (mg/dL)	ALT (IU/ L)	AST (IU/L)	ALP (IU/ L)	Urea (mg/dL)	S. Cr (mg/dL)
Normal control	20.1± 2.5	2.35 ± 0.7	41.24 ± 4.2	125 ± 9.5	123 ± 9.7	28.5 ± 3.4	0.42 ± 0.1
Negative control	28.35 ± 3.2 **	4.95 ± 1.1 **	52.55 ± 5.3 **	144 ± 10.5***	149 ± 10.6***	37.6 ± 4.7 ***	0.54 ± 0.2 **
Olibanum 50 mg/kg	22.45 ± 2.4 *	1.52 ± 0.4 ***	48.58 ± 4.6 *	123 ± 8.4 ***	138 ± 8.5 **	25.2 ± 4.1 ***	0.39 ± 0.1 **
Olibanum 100 mg/kg	21.85 ± 3.1 **	0.94 ± 0.2 ***	46.45 ± 5.2 *	136 ± 7.5 **	136 ± 7.3 **	22.6 ± 2.8 ***	0.33 ± 0.2 ***
Allopurinol group	12.35± 2.3 ***	0.68 ± 0.3 ***	51.35 ± 5.5**	137 ± 11.3 **	131 ± 8.8 **	30.2 ± 3.7 ***	0.46 ± 0.1 **

Values are expressed as mean ± standard deviation, * Significant at $p < 0.05$; ** significant at $p < 0.01$; *** significant at $p < 0.001$.

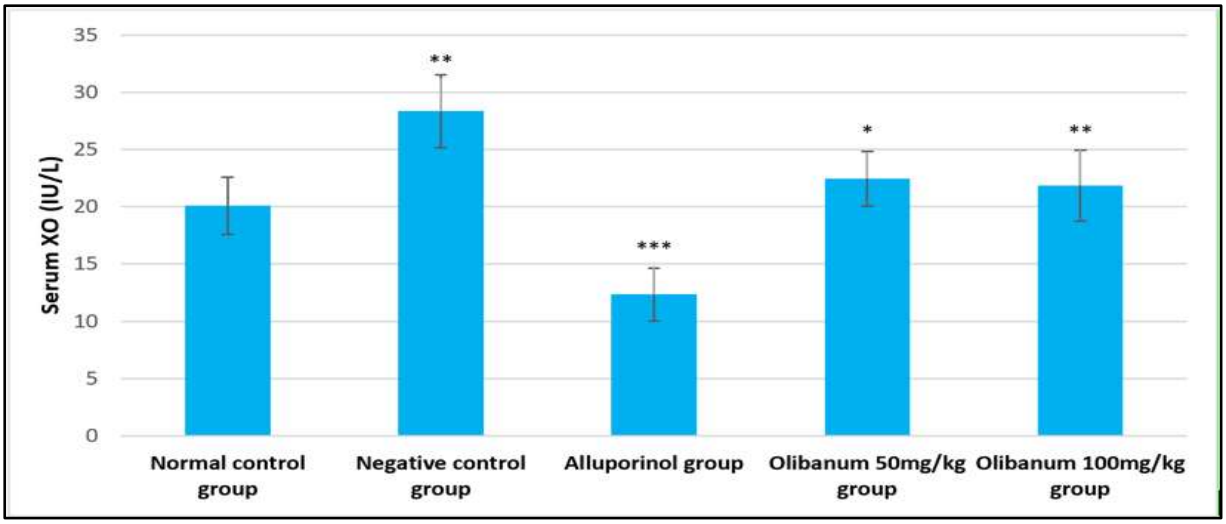

Figure 1. **Xanthine oxidase levels (IU/L) in serum of all groups. Values are expressed as mean ± standard deviation, * Significant at p < 0.05; ** significant at p < 0.01; *** significant at p < 0.001.**

In Table 1 and Figure 2 show SUA (4.95 ± 1.1 **) increased significantly ($p < 0.01$) in negative control as compared to normal control due to the increase in XO activity by PO induction, which led to a rise in uric acid synthesis and decreased the excretion of uric acid by inhibiting hepatic uricase and decreasing renal urine excretion, leading to the accumulation and subsequent increase of SUA levels [39,40].

SUA decreased significantly ($p< 0.001$) in the allopurinol group compared to the negative control. Allopurinol is considered a standard xanthine oxidase inhibitor, leading to decreased UA production [14]. Also, the daily oral dosing of olibanum of 50 m/kg and 100 mg/kg treatment led to a significant decrease ($p<0.001$) in serum UA compared to the negative group due to partial XO enzyme inhibition and mainly to an increase in UA secretion. Table 1 and Figure 3 mentioned that all treated groups had no significant alterations in liver function regarding AST, ALT, and ALP, and kidney function (blood urea and serum creatinine (S. Cr)) compared to the normal control group. However, there is a high elevation ($p<0.001$) in AST, ALP, and Urea in the negative control group and a significant ($p <0.01$) elevation in serum ALT and creatinine in comparison with other treated groups. These effects may be caused by the impact of PO, which causes an increase in uric acid production and, consequently, an increase in the production of free radicals and oxidative status, resulting in hepatotoxicity and nephropathy in rats [41] .

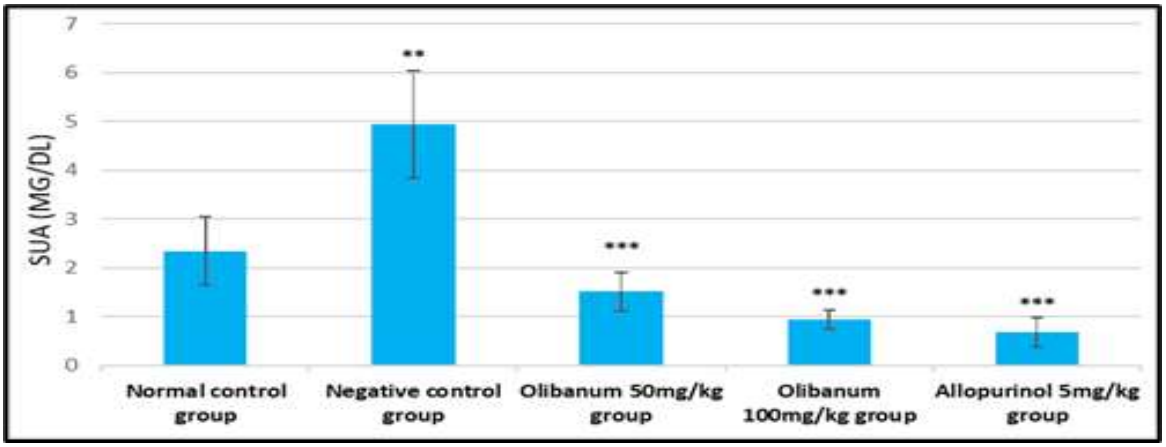

Figure 2. uric acid levels (mg /dl) in the serum of all groups of rats. Values are expressed as mean ± standard deviation, * Significant at p < 0.05; ** significant at p < 0.01; * significant at p < 0.001.**

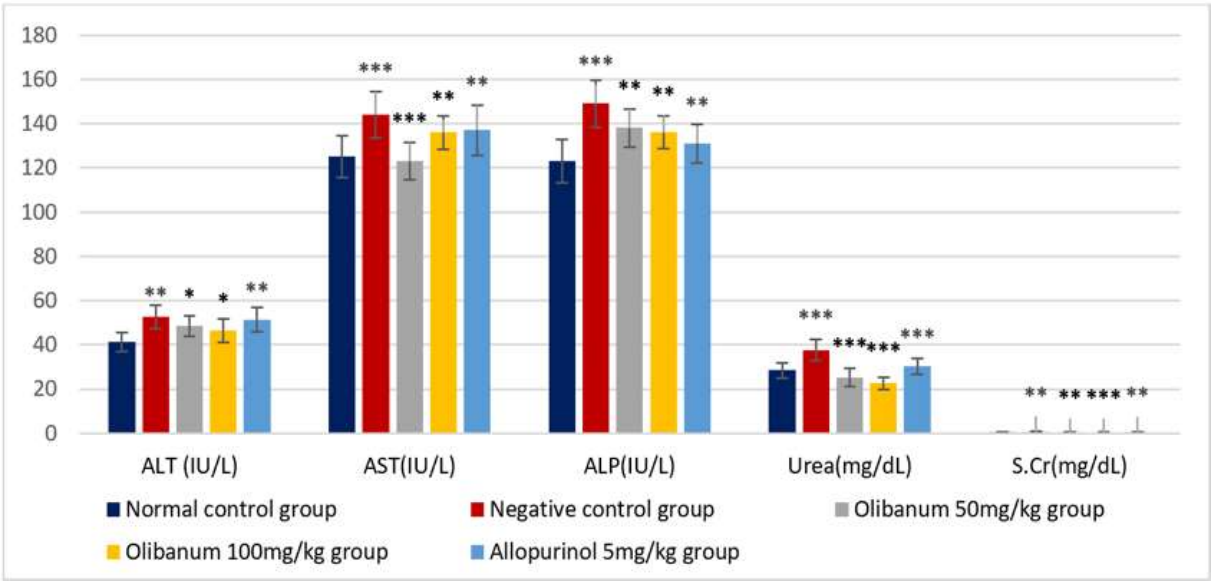

Figure 3. ALT, AST, ALP levels (UI/L), Urea, and S. Cr (mg/d) in the serum of rats for groups. Values are expressed as mean ± standard deviation, * Significant at p < 0.05; ** significant at p < 0.01; * significant at p < 0.001.**

As shown in Table 2 and Figure 4, when comparing the negative control group with the normal control group, the level of urinary uric acid was significantly (p <0.05) reduced after 7 days. The reduction continued significantly (p <0.01) after 14, 21, and 28 days. The generation of HU in rats produced a considerable decrease in urine excretion and an increase in blood UA concentration by a significant amount. These results demonstrate that the employed model induced HU.

The consecutive treatment of rats with olibanum at the amount of 50 mg/kg significantly (p<0.05) increased the excretion of UA after 7 days. It was highly significant (p<0.01) after 14 days and the highest considerable increasing (p<0.001) after 21 and 28 days. In contrast, the dosing of olibanum at 100 mg led to a significant (p<0.01) increase in the excretion of uric acid after 7 days and a highly significant (p<0.001) rise in the excretion of UA after 14, 21, 28 days in the urine as compared with the animals of the negative control group. The standard drug (allopurinol) group is represented in Table 2 and Figure 4. There was a significant (p<0.05) reduction in the level of urinary UA after 7,14, 21 and 28 days in the allopurinol group when compared with the negative control group [14]. Allopurinol inhibits the transformation of xanthine to hypoxanthine and hypoxanthine to UA, reducing serum uric acid. The 5 mg/kg allopurinol dose decreased urate excretion by 35% relative to the normal control group [42].

Olibanum powder increased UA clearance and blood UA reduction in a dosage-related manner. olibanum at 100 mg dose is more effective in exerting the uric acid in urine than at 50 mg. Both doses of olibanum have a potent uricosuric agent compared to the negative control and allopurinol group [41].

Table 2. Urinary uric acid (mg/dl) at different times (weekly).

Urinary uric acid (mg/dl) at different times					
Group	**Day 0**	**Day 7**	**Day 14**	**Day21**	**Day 28**
Normal control	15.52 ± 2.1	14.55 ± 1.5	15.42 ± 2.0	14.76 ± 0.8	14.45 ± 1.1
Negative control	14.91 ± 1.5	9.52 ± 1.2 *	7.41 ± 0.6 **	6.85 ± 0.7 **	6.31 ± 0.8 **
Olibanum 50 mg/Kg	14.81 ± 0.9	14.12 ± 2.3 *	19.59 ± 3.2 **	23.24 ± 3.1***	28.46 ± 3.8***
Olibanum 100 mg/kg	15.83 ± 2.3	20.1 ± 3.2 **	23.37 ± 2.9***	32.02 ± 2.6***	37.72 ± 4.1***
Allopurinol 5mg/kg	14.65 ± 1.7	12.02 ± 1.3 *	11.59 ± 1.4 *	10.62 ± 1.4 *	10.83 ± 1.6 *

Values are expressed as mean ± standard deviation, * Significant at $p < 0.05$; ** significant at $p < 0.01$; *** significant at $p < 0.001$.

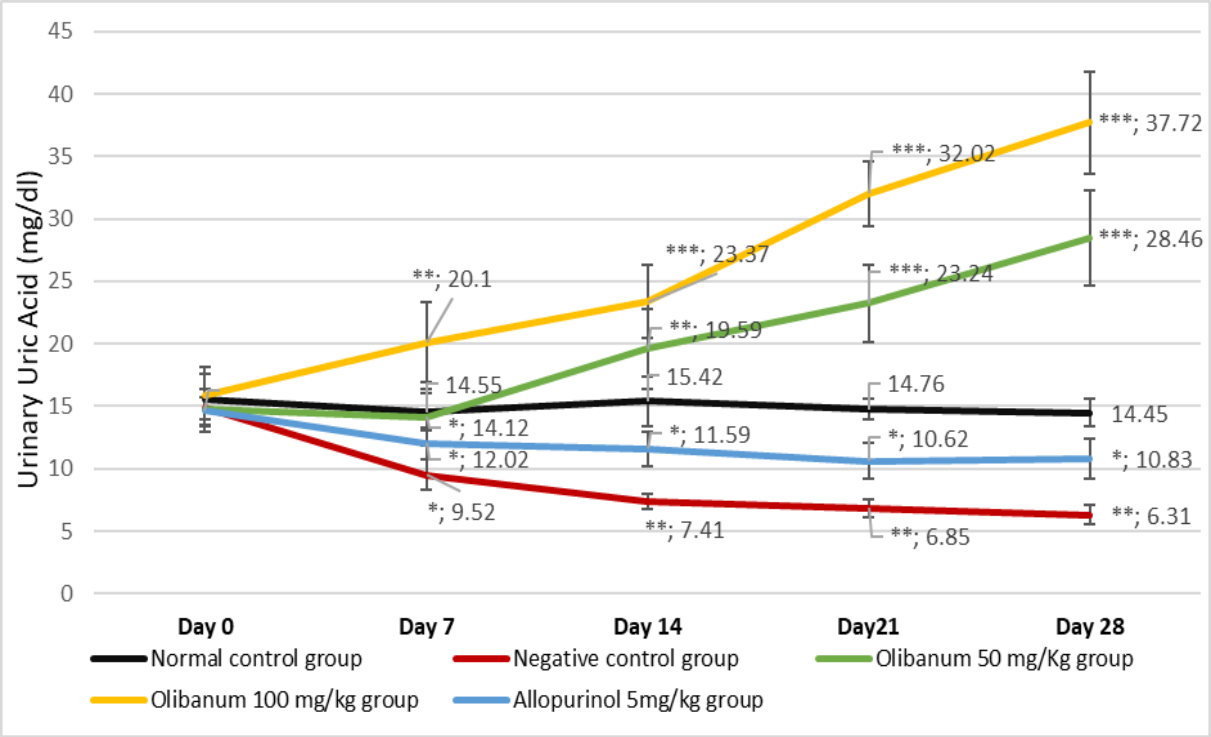

Figure 4. Urinary uric acid (mg/dL) at different times. Values are expressed as mean ± standard deviation, * Significant at $p < 0.05$; ** significant at $p < 0.01$; * significant at $p < 0.001$.**

Concerning urinary creatinine, as shown in Table 3, when comparing the negative control with the normal control group, the level of urinary creatinine reduced significantly ($p<0.01$) after 14 days, it continued to decrease highly significantly ($p<0.001$) after 21 and 28 days, respectively. PO causes SUA build-up, urine volume decrease, and reduced urea and creatinine clearance, which are signs of kidney impairment [43]. While as seen in Table 3, there was a significant ($p<0.01$) increment in the level of urinary creatinine after 7 days and highly influential ($p<0.001$) after 14, 21 and 28 days in olibanum 50 mg/kg group when compared with the negative control group while the administration of olibanum at dose 100 mg/kg led to highly significant ($p<0.001$) increment after 7 days. A highly significant ($p<0.001$) persisted after 14, 21, and 28 days, respectively, compared with the negative control group.

Table 3. Urinary creatinine (mg/dl) at different times.

Urinary Creatinine (mg/dl) at other times					
Group	**Day 0**	**Day 7**	**Day 14**	**Day21**	**Day 28**
Normal control	68.24 ± 5.1	70.21 ± 4.3	66.47 ± 3.8	67.52 ± 4.5	73.39
Negative control	67.35 ± 5.1	58.36 ± 3.4 **	49.72 ± 3.3***	40.65 ± 2.7***	34.93 ± 2.2***
Olibanum 50 mg/Kg	66.28 ± 3.6	70.07 ± 4.2 **	78.91 ± 5.6***	84.22 ± 5.6***	89.57 ± 6.2***
Olibanum 100 mg/kg	70.85 ± 4.7	77.23 ± 6.1***	85.25 ± 5.4***	88.84 ± 5.1***	96.71 ± 5.5***
Allopurinol group	69.35 ± 4.8	62.35 ± 4.4 *	59.46 ± 5.4 **	56.35 ± 4.6***	54.24 ± 5.1***

Values are expressed as mean ± standard deviation, * Significant at $p < 0.05$; ** significant at $p < 0.01$; *** significant at $p < 0.001$.

Even though PO causes renal toxicity, olibanum powder treatment has been demonstrated to minimize glomerular damage. According to another study, an increase in renal antioxidant enzymes and a decrease in renal reactive oxygen species formation may help avoid renal ischemia [8]. All of this contributes to an increase in creatinine excretion.

Despite the prevalence of gout and hyperuricemia, only a few medications may reduce UA levels in the blood. Their usage is often restricted owing to undesirable side effects. Anti-hyperuricemic medicines might be developed naturally [44,45]. More than 90% of gouty individuals have low uric acid excretion; thus, the uricosuric action of olibanum powder might be very useful in treating gout and associated disorders [45,46]. This experiment is the earliest to examine the olibanum as an anti-hyperuricemic impact in PO-induced HU in rats. Moreover, the principal mechanism of olibanum might be via uricosuric action, increasing UA elimination in the urine.

The administration of olibanum significantly reduced UA levels in hyperuricemic animals. Furthermore, similar dosing significantly increased the secretion and clearance of UA. Unlike ordinary uricosuric medicines, it was informed that olibanum has anti-inflammatory, hepatoprotective, antibacterial, and antifungal properties [24]. Alternative and complementary therapies for arthritis have grown in popularity since they are said to have clinical effectiveness with fewer side effects than conventional treatments [25].

Olibanum powder has already been proven to have antioxidant and anti-inflammatory activities, and it has also been demonstrated to regulate plasma levels of urea and creatinine. Additionally, it protects against the advancement of renal failure [47]. This characteristic makes olibanum displays an additional advantage across the uricosuric drug.

Conclusions

Based on the results of the current study, olibanum (*Boswellia carterii)* significantly reduced UA levels in the blood of rats (PO-induced HU) in100 mg/kg doses more than ٥٠ mg/kg doses via uricosuric and minor xanthine oxidase inhibitory level. Using olibanum greatly protects the liver and kidneys against hyperuricemia caused by PO.

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Ethical Considerations

All experiments were conducted at the Basrah University Animal House Department, Faculty of Pharmacy, by the guidelines (No. 2013/32) of the Animal Care and Use Committee.

Conflict of Interest

The conflict of interest does not exist

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