STUDY THE ANTIHYPERURICEMIC EFFECT OF *Boswellia carterii* EXTRACT ON OXONATE-INDUCED HYPERURICEMIA IN RATS

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ABSTRACT

The present study aims to evaluate the anti-hyperuricemic activity and mechanism action of Boswellia carterii in potassium oxonate-induced hyperuricemia in rats. Also, this study assessed the safety of using this plant by examining liver and kidney function. Rats used in the research were randomized into five groups (n=6). The rats in the negative, allopurinol, olibanum 50 mg/kg, and olibanum 100 mg/kg groups received intraperitoneal injections of potassium oxonate (PO) twice a week at a dose of 250 mg/kg. The normal control group was supplied food and drink without any intervention. Treatment groups received daily oral administration of 50 and 100 mg/kg of olibanum powder dissolved in 0.5 mL of distilled water, respectively. Allopurinol (5 mg/kg) was administered orally to rats in the allopurinol group daily. Each group's animals were slaughtered, blood was taken, and serum was isolated for uric acid (UA) laboratory analysis and other biochemical parameters. Uric acid (UUA) and creatinine (UCr) in urine were also measured. The investigation results demonstrated a significantly substantial reduction in blood UA and modest inhibition of xanthine oxide (XOD) in rats with hyperuricemia that were given olibanum solution. Compared to the hyperuricemic control group, all groups showed non-significant variations in the kidney (Urea and CreaC) and liver (ALT, AlkP, and AST) functioning. Based on the present study's findings, olibanum

powder significantly reduced uric acid via uricosuric activities and minor xanthine oxidase inhibition.

Keywords: *Boswellia carterii*, Olibanum, Uric acid, Renal function, potassium oxonate, Liver function, Hyperuricemia, Xanthine oxidase.

INTRODUCTION

Hyperuricemia (HU) is well-defined as a persistent elevate of uric acid (UA) in circulating blood and is predictable as the crucial cause of the development of gout (1). In which serum uric acid concentration is more significant than 6.8 mg/dL in the body of a human (2). High serum urate is accompanied by higher body mass index, hypercholesterolemia (4), hypertriglyceridemia (5), increased fasting plasma glucose (6), 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). Hyperuricemia is the most critical risk factor for cardiovascular disease (CVD), chronic kidney disease (CKD), gout, and metabolicc syndrome (7). Due to its rapidly increasing significant impact on many clinical implications, hyperuricemia is quickly emerging as one of the international population's most severe public health concerns (8). Hyperuricemia 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 hyperuricemia, CKD, hypothyroidism, cachexia, myelo- and lymphoproliferative diseases, tumor lysis syndrome in oncologic patients, and relatively rare genetically determined hyperuricemia (9).

With a prevalence rate that has increased over the past 30 years, arthritis affects more than nine million Americans, or 4% of adults (10). The incidence in men is 2-6 times higher than in

women. Gout prevalence is gradually increasing worldwide due to poor dietary behaviors such as junk foods, lack of exercise, increasing prevalence of obesity, and metabolic syndrome (11). Gout is caused by the sedimentation of monosodium urate crystals onto different joints, followed by a very painful immune response (12). Three consecutive stages were identified years ago in the historical relationship between hyperuricemia and gout: asymptomatic hyperuricemia, intermittent gout, and chronic gout (13).

Many drugs are taken for the treatment and management of gout, and HU, such as xanthine oxidase inhibitors (XOI), reduces uric acid generation; These medications serve as the first line of gout treatment to reducing urate levels, as they are efficacious in the majority of hyperuricemic patients and have an acceptable tolerability profile (14). XOI drugs, like allopurinol, inhibit xanthine oxidase and reduce uric acid production (15). Treatment-related adverse effects include Allopurinol Hypersensitivity (AHS), which is rare but fatal, severe skin reactions, hepatitis, interstitial nephritis, and eosinophilia (16). Uricosuric medicines reduce uric acid reabsorption in the proximal renal tubule, increasing UA clearance in the kidneys (17). Benzbromarone has been a uricosuric drug for decades, used to treat gout by decreasing urate reabsorption and increasing urate excretion through the urine; however, because of hepatotoxicity, it was withdrawn from several markets in 2003 (18). Urate-lowering therapy (ULT) generally leads to an amplified flare rate and accompanying pain as a direct consequence of urate crystal dissolution (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, which yields frankincense or Olibanum (21, 22). 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 (23), and complementary therapies for arthritis (24, 25). Oleo gum resin "Olibanum" also has cardioprotective and antioxidant properties (26, 20). Terpenoids, such as pentacyclic triterpenes, tetracyclic triterpenes, diterpenes, and monoterpenes, are the major chemical components of B. carterii gum resin. There are also essential oils, organic acids, and polysaccharides (27-29). The current study aimed to assess the anti-hyperuricemic effect of the *Boswellia arterii* plant and to analyze its urate-lowering impact by increasing UA excretion and lowering UA synthesis by suppressing the XOD enzyme.

EXPERIMENTAL

Chemicals and reagents

Sigma Aldrich Co., USA, supplied Potassium Oxonate (PO) and Zyloric® drug. The reagents and chemicals utilized in this investigation with analytical quality.

Plant and olibanum powder preparation

In May 2021, Olibanum was obtained at a local market in Basrah City. The dried 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. 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 g from the animal house of the College of Pharmacy, University of Basrah. Mice (n = 6) were separated into five groups with distinct traits. Mice were housed in insulated plastic cages for a month, and animal areas were maintained at 22 ± 2 °C, 30 ± 12% RH, and a 12 h/12 h day-dark cycle. The animals had free access to regular feed and tap 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 with 500ml of distilled water (D.W). PO 250 mg/ kg in the warm normal saline (N.S) was dissolved (30)**.** Olibanum powder 100 mg and 50 mg/kg was dissolved with 0.5 mL of Distilled Water (DW). Each solution was prepared freshly before the experiments (31).

Induction of Hyperuricemia (HU)

The HU in the experiment was stimulated by intraperitoneal (*i.p.*) injection of Potassium Oxonate into experimental rats at a dose of 250 mg/kg twice a week for one month (30)**.**

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 fasted for 2 hours before receiving medications and a vehicle by withdrawing water and food. The rats were randomly sorted into five groups (n=6). PO was injected intraperitoneally (*i.p.*) into the animal groups twice weekly throughout the study duration, which lasted one month. 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). Hyperurecimic rats were injected intraperitoneally (*i.p.*) 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 (Bio laboratory, France). XOD concentrations were measured using BT-LAB enzyme-linked immunosorbent assay kits (Bioassay -Laboratory, China). Uric acid (UUA) and creatinine (UCr) 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

In vivo XO inhibitory activity

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

As can be seen from the results 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 XOD in the negative control group, which led to increased production of uric acid (4.95 ± 1.1 mg/dL) compared with the normal control group uric acid (2.35 ± 0.7mg/dL) in each blood sample, because of PO which causes the level of XO to rise (35).

While in the allopurinol group, when compared with negative control, there was a highly considerable (p < 0.001) decrease in XOD, 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 activity (p <0.05). In contrast, the Olibanum at the (50 mg/Kg) dose inhibited the XO enzyme activity significantly (p <0.01) compared with the negative group.

Any substance may diminish xanthine oxide enzyme activity, inhibiting uric acid formation. Olibanum powder in both doses (50 and 100 mg/kg) was revealed to have a significant inhibitory effect on xanthine oxidase *in vivo*. Many bioactive substances, such as polyphenols, have been found in Olibanum. The low amounts of polyphenols in olibanum powder may be responsible for its xanthine oxidase inhibitory action (37, 38); increasing the dose or sample size may improve the outcomes.

Serum Uric Acid (SUA)

Table 1 and Figure 2 shown SUA 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 (15). 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.

Liver and kidney function

Such as mentioned in Table 1 and Figure 3, All treated groups had no significant alterations in liver function in terms of AST, ALT, and ALP, and kidney function (blood urea and serum creatinine (S. Cr) as compared with the normal control group. However, there is a high elevation ($p<0.001$) in AST, ALP, and Urea in the negative control group and also 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 potassium oxonate (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, 42).

Urinary Uric Acid and Creatinine

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 seven 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 hyperuricemia (39, 40).

The consecutive treatment of rats with Olibanum at the amount of 50 mg/kg significantly (p<0.05) increased the excretion of uric acid after seven days and highly significant (p<0.01) after 14 days and more significant 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 seven 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 HCG. In the standard drug (allopurinol) group, which 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, 21and 28 days in the allopurinol group when compared with the negative control group(15).

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 (Figure 4) (43).

Olibanum powder increased uric acid 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, 42).

Concerning urinary creatinine, as shown in Table 3 and Figure 5, 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 buildup, urine volume decrease, and reduced urea and creatinine clearance, which are signs of kidney impairment (44).

While as seen in Table 3 and Figure 5, there was a significant (p<0.01) increment in the level of urinary creatinine after seven and highly influential (p<0.001) after14 21and 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 seven days and it persisted a highly significant (p<0.001) after14, 21 and 28 days, respectively in comparison with the negative control group.

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 ROS formation may help avoid renal ischemia (9). All of this contributes to an increase in creatinine excretion.

Despite the prevalence of gout and hyperuricemia, only a few medications may reduce uric acid levels in the blood. Their usage is often restricted owing to undesirable side effects. Anti-hyperuricemic medicines might be developed naturally (45)(42). 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(42)(46). This experiment is the earliest to examine the olibanum as anti hyperuricemic impact in PO-generated 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 (23). 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(24).

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.

CONCLUSION

Based on the results of the current study, *Boswellia carterii* (Olibanum) significantly reduced UA levels in the blood of potassium oxonate-induced hyperuricemia in rats via uricosuric and minor xanthine oxidase inhibitory activities. Using Olibanum greatly protects the liver and kidneys against hyperuricemia caused by potassium oxonate.

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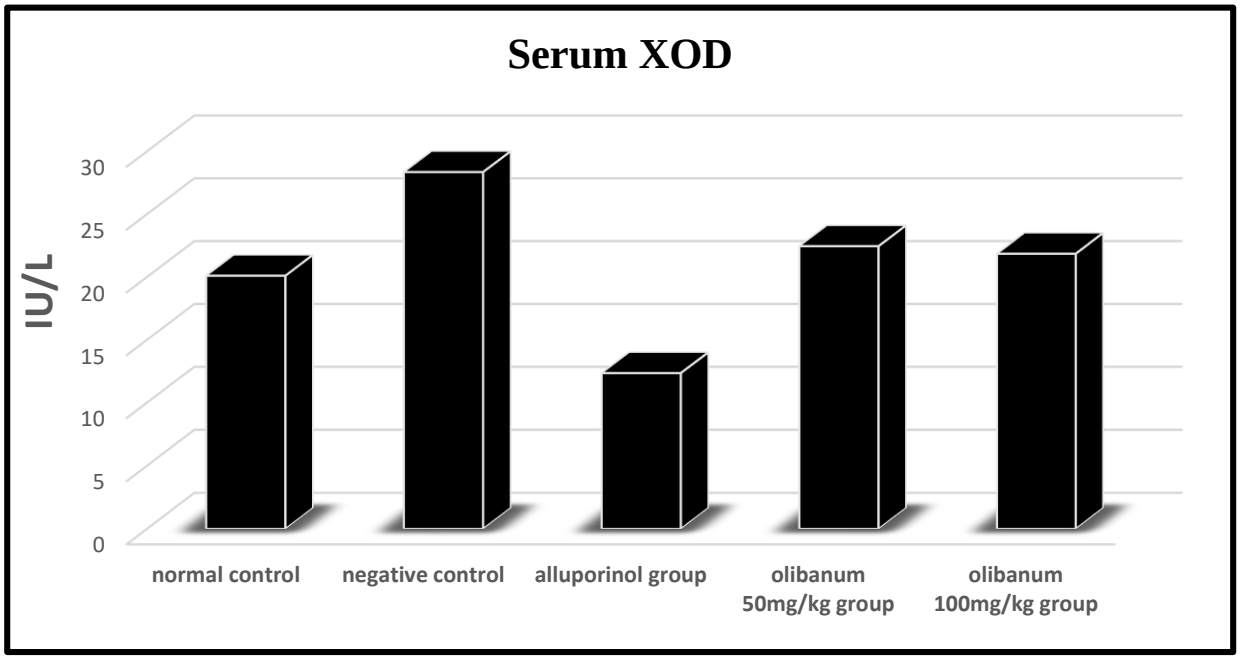
Table 1. Biochemical petameters of all groups of rats.

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

Group	Xanthine (IU/L)	UA (mg / dL)	ALT (IU/ L)	AST (IU/ L)	AlkP (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 50mg/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 100mg/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 5mg/kg	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 **

Figure 1. XOD levels (IU/L) in the serum of all groups of rats.



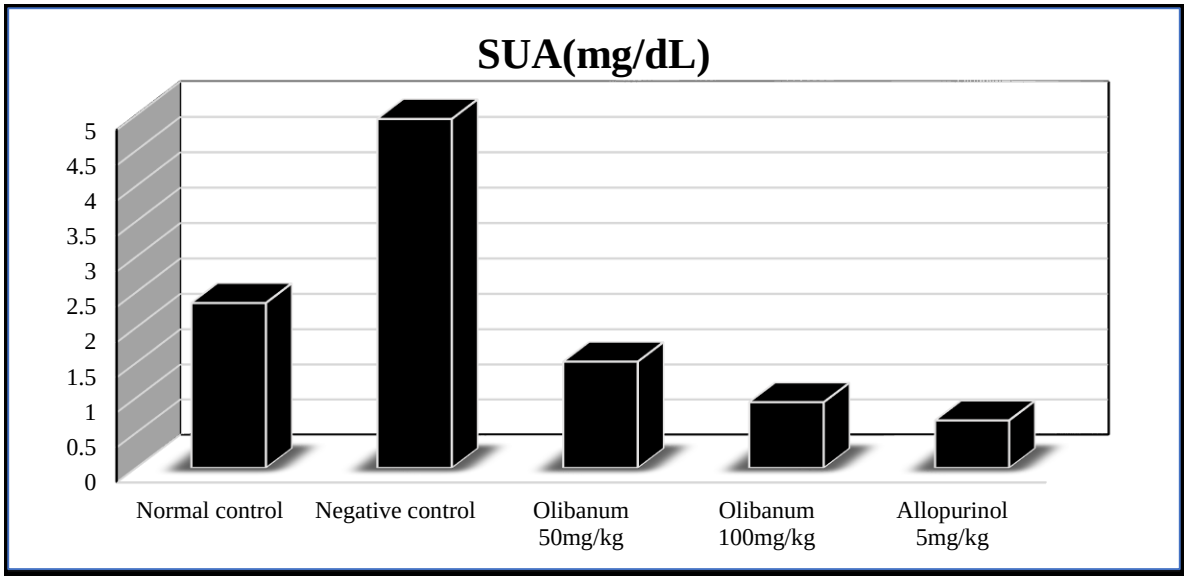


Figure 2. UA levels (mg /dl) in the serum of all groups of rats.

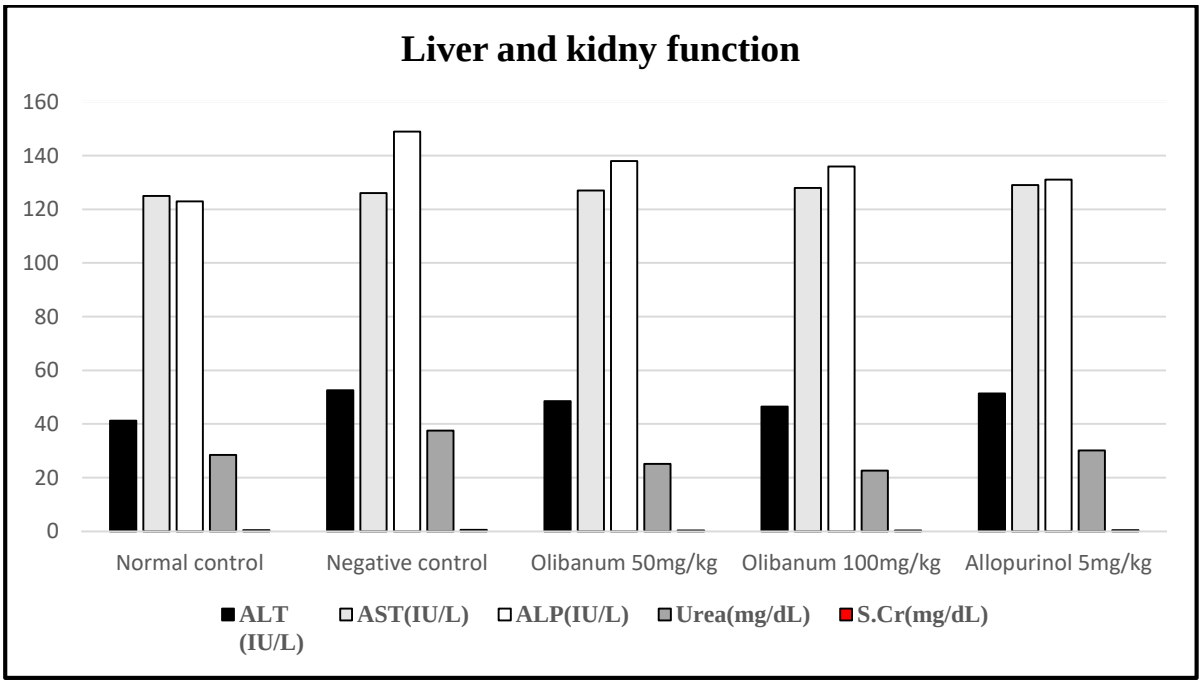


Figure 3. ALT, AST, ALP levels (UI/L), Urea, and S. Cr (mg/d) in the serum of rats for groups.

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

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

Group	Urinary Uric Acid (mg/dl) at different times (weekly)				
	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 5 mg/kg	14.65 ± 1.7	12.02 ± 1.3 *	11.59 ± 1.4 *	10.62 ± 1.4 *	10.83 ± 1.6 *

Figure 4. Urinary uric acid (mg/dL) at different times.

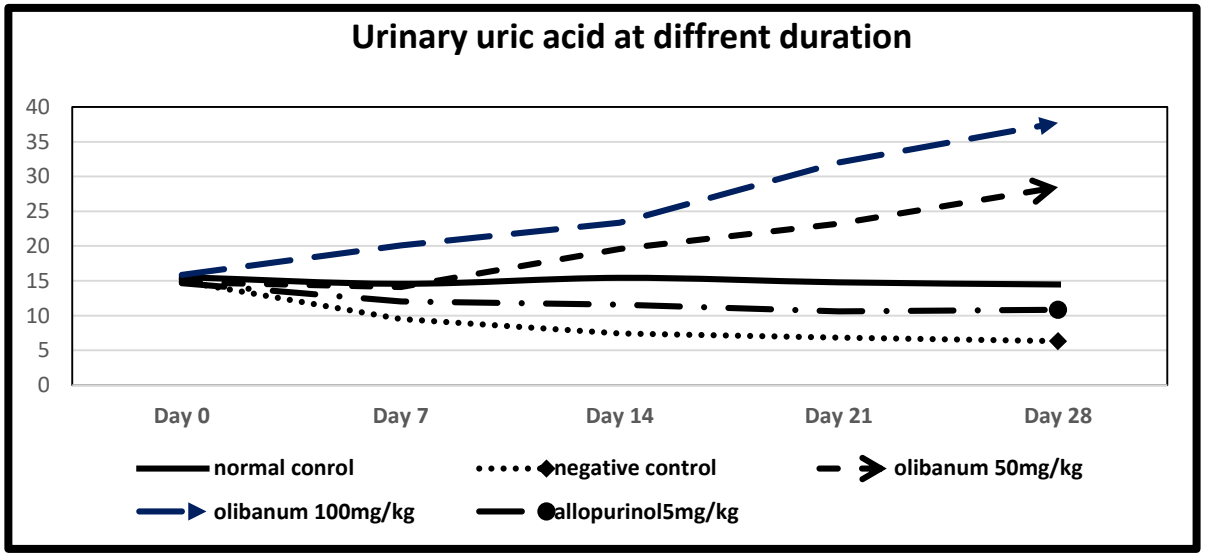


Table 3. Urinary creatinine (mg/dl) at different times (weekly).

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

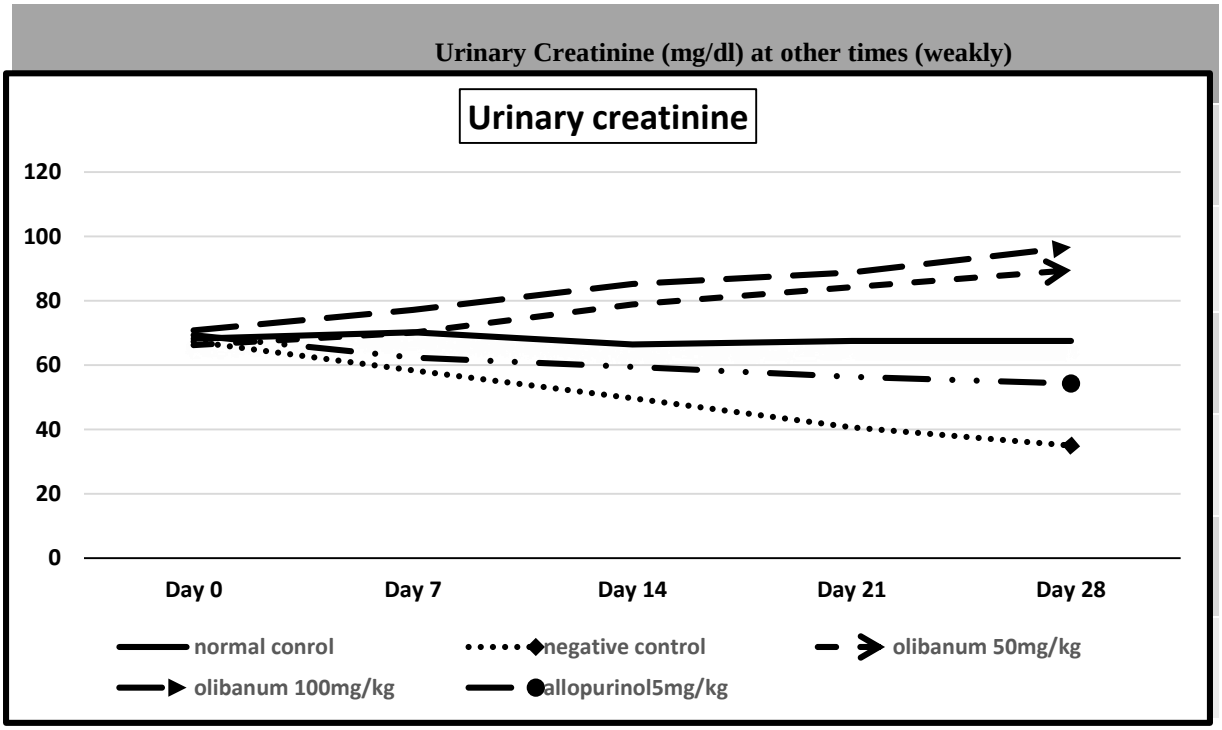


Figure 5. Urinary Creatinine (mg/dl) at different times (weakly).