INTRODUCTION

Uric acid (UA) is the ultimate product of nucleic acids degradation in most mammals consequently to the action of xanthine oxidase (XO) enzyme [1]. The two-thirds of UA pool comes from the breakdown of endogenous purines while the remaining quantity resulted from dietary (exogenous) purines. Human is the only organism from the rest of the mammals cannot convert UA to a more soluble compound, allantoin due to lack of the uricase enzyme [2]. Most of UA released from the human body by the renal tract while the gastrointestinal tract secretes the residual. Approximately 90% of the UA that secreted by the kidneys is reabsorbed by renal tubules into the blood. The absence of uricase enzyme association with massive reabsorption of filtered UA results in the residual. Approximately 90% of the UA that secreted by the kidneys is reabsorbed by renal tubules into the blood. The absence of uricase enzyme association with massive reabsorption of filtered UA results in the reduction in the levels of UA in the blood to normal values in a long-term manner [5,11]. As a result, high serum UA may be one of the main serious factors for developing of the hyperuricemia, which may lead to the occurrence of gout [4,5]. Hyperuricemia can be expressed as the blood UA level larger than the normal values in both females (6 mg/dL) and males (7 mg/dL), and it arises from urate-underexcretion and/or overproduction of UA, where the main cause of hyperuricemia in the gouty patients is urate-underexcretion [6,7]. Gouty arthritis is an inflammatory, metabolic defect affecting elderly men and postmenopausal women that originates due to the formation and accumulation of monosodium urate (MSU) crystals in the kidneys and inflamed joints [7]. Clinical signs of such inflammatory disorder include gouty flares that represented by quite pain, edema, warmness, and redness [8]. Persisting of hyperuricemia leads to further MSU deposits crystals inducing chronic inflammatory responses that may lead to the tophi formation, chronic joint destruction, renal insufficiency, and cardiovascular problems [9,10]. Therapeutic management of gout involves two methods of treatment: The first one is rapid and aims to cure the nociception and inflammation caused by acute inflammatory attacks of gout, while the second method involves the reducing the levels of UA in the blood to normal values in a long-term manner [5,11]. The first approach to treatment comprises many types of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids; however, prolonged use of these drugs may produce critical side effects such as ulcersations and toxicity of gastrointestinal tract and renal toxicity [1]. The second approach of gout treatment, urate-lowering drugs (ULD) includes two categories of drugs: (a) XO inhibitors such as allopurinol and febuxastat and (b) uricurics agents such as probeneic and benzobromaron. In general, XO inhibitors are indicate to urate-overproduction patients, whereas uricosurics drugs are prescribe to urate-underexcretion patients. Although the use of ULD medication is effective in gout cure, but not without adverse effects such as severe hypersensitivity reactions, hepatotoxicity and renal defects [12]. Until now, although severity and serious complications of gout, there are still a few drugs that are used in the treatment, in addition to the serious side effects for many of these drugs. Therefore, it is necessary to search for new effective and safe urate-lowering agents with analgesic, antioxidant, and anti-inflammatory activities [13,14].

Alpha-lipoic acid (α-LA; also named as thioctic acid) is a dithiol substance existing in animals and plants that function as a coenzyme for the several enzymes of the energy-producing metabolism in the mitochondria [15,16]. α-LA acts as a potent antioxidant in the all parts of cellular environments due to its good solubility in both water and lipid [17]. In the different tissues of the human body, α-LA is rapidly changed into the reduced status, dihydrolipoic acid (DHLA) that works as more active than α-LA itself [18,19]. As well as the valuable antioxidant activity, α-LA and DHLA possess many different biological activities like the regeneration ability of other antioxidants (Vitamin E and C and glutathione) from oxidized forms into active reduced states.
also these acids are effective chelators of toxic metals and male fertility enhancers. Many studies revealed the ability of α-LA in the treatment and prevention of different oxidative-mediated pathological defects such as inflammation, diabetes neuropathy, cells aging, and cardiovascular diseases [28-22]. According to the potent antioxidant activity of α-LA, this study aimed to investigate the antiinociception, antiinflammatory and antihyperuricemic activity of α-LA in the gouty arthritis model in the rats.

MATERIALS AND METHODS

Animals

This study included the use of two types of animals and male in gender: Wistar rats (150–170 g) and albino Swiss mice. (25-30 g) which were supplied from the unit of animals’ house at College of Pharmacy, Basrah University. Both rats and mice were separated into different groups (n=6), then the animals were accommodated in isolated plastic cages and kept in the animal’s room under a regulated condition at temperature 25±2°C and humidity 30±15% with the 12-h dark/12-h light cycle for a week before being used for acclimatization. They were fed standard chow and water ad libitum, and all of dealing procedures with animals that described in this study were authorized by Animal Ethics Committee, University of Basrah, Iraq (No. 2013/32).

In vitro XO inhibitory activity

The XO inhibitory effect of α-LA was assessed spectrophotometrically at 290 nm according to Sunarni et al.[23] and Yumita et al.[24] with minor changes. The mixture assay consists of 0.9 mL of 0.05 M sodium phosphate buffer (pH 7.5 at 25°C), 1 mL of α-LA solution (100 µg/mL in DMSO), and 0.1 mL of XO enzyme solution (0.1 unit/mL in phosphate buffer, pH 7.5) was prepared in cold buffer directly before using. After a 15-min preincubation at 25°C, the reaction was started by addition of 2000 µL of a freshly prepared solution of substrate (0.15 mm xanthine solution). Next, a further incubation process was achieved for the reaction mixture at 25°C for 30 min. After addition of 1 mL of 1N HCl solution into assay mixture for stopping the reaction, the absorbance was recorded at wavelength 290 nm using UV/ViS spectrophotometer against the blank which is prepared in the same procedure but with the replacement of enzyme solution by phosphate buffer. The positive control solution was prepared using allopurinol (100 µg/mL) in DMSO. The inhibitory activity of XO was established as the inhibition percentage (%):

\[
\% \text{ XO inhibition} = \left(1 - \frac{\alpha}{\beta}\right) \times 100
\]

Where α is the activity of XO without tested substance (α-LA) and β is the activity of XO with the presence of α-LA.

Different concentrations of both α-LA and allopurinol (100, 50, 25, 10, 5, 4, 3, 2, and 1 µg/mL) were used for evaluation of XO inhibitory activities; then, the dose-response logarithmic curve was applied to determine the median maximum inhibitory concentration IC_{50}.

Drug administration

Allopurinol and α-LA were suspended in 0.5% sodium salt of carboxymethyl cellulose, Na (vehicle). Potassium oxonate (250 mg/kg), indomethacin (3 mg/kg), and MSU crystals (40 mg/mL) were suspended in 0.9% sterile saline. All solutions were prepared freshly before use for in vivo experiments.

Evaluation of antihyperuricemic activity

The antihyperuricemic activity of α-LA investigated using the potassium oxonate-induced hyperuricemia in the rat’s model according to Haidari et al.[25] and Nguyen et al.[26] with modifications. Animals were fasted by withdrawing of food and water 2 h before drugs administration. Experimental animals (rats) were divided randomly into six groups (n=6). The uricase inhibitor (potassium oxonate) at a dose of 250 mg/kg was injected intraperitoneally (i.p.) to rats of groups (2–6) in the 1st, 3rd, and 7th days of the experiment period. Rats groups were administered with oral treatments of the vehicle, allopurinol, and α-LA solutions by oral gavage 1 h after the administration of potassium oxonate, once a day for 7 consecutive days of the experiment. Animals of normal control (Group 1) and hyperuricemic control (Group 2) were received the only vehicle through oral administration. Standard drug group (Group 3) was treated orally with allopurinol (10 mg/kg). Sample Groups 4–6 were treated orally with α-LA at the doses 10, 25, and 50 mg/kg, respectively, once a day, throughout the days of the experiment. Whole blood samples were collected from each rat by cutting tail vein 2 h after last administration of tested drugs. The blood was permitted to clot for 0.5 h at room temperature and then centrifuged at 3500 rpm for 5 min to get the serum. The sera were stored at ~20°C until the UA is assayed.

UA assay

The enzymatic-colorimetric method employed to determine the serum UA levels using a standard diagnostic kit (Bioclin, Bioclin, France).

Anti-inflammatory effect of α-LA on gouty arthritis inflammation model in mice

An experimental model of gout as previously mentioned by Lima et al.[27] and Ferrari et al.[28] with some modifications carried out to investigate the anti-inflammatory effect of α-LA. The assay was performed within a period of 3 days. Animals (mice) were distributed into six groups (n=6). On the 1st day of the study, the inflammatory induction was achieved by intradermal injection of 100 µL (4 mg) of MSU crystals suspension into the right hind paws of mice. All groups of animals (2–6) were injected with MSU, except for normal control group (Group 1), which were injected with 100 µL of 0.9% sterile saline solution. All treatments were administered by oral gavage an hour before injection of MSU suspension on the 1st day of the experiment and repeated a once daily at the same time, for another 2 days. Mice of Group 1 and Group 2 were treated with the vehicle and served as normal control group and MSU-induced gouty (negative) control group, respectively. Group 3 animals were treated with a standard nonsteroidal anti-inflammatory agent, indomethacin (3 mg/kg) and served as a positive control group. Mice of groups (4–6) were treated with α-LA at the doses 10, 25, and 50 mg/kg. Thickness of mouse hind paw was measured with digital Vernier caliper (Numit, China) at 0, 4, 24, and 48 h after MSU injection and the inflammatory edema were expressed as a percentage of thickness variation (Δ).

Evaluation of analgesic activity of α-LA

Writhing test

This test performed as formerly explained by Spindola et al.[29] with modifications. Male albino mice were distributed into five groups each containing five mice. Animals were fasted for overnight and then were treated as following: Group 1 of mice were treated (10 mL/kg) of vehicle (0.9% saline solution) and served as normal control group and Group 2 of mice were treated 10 mg/kg of indomethacin and served as positive control group, while mice groups (3–5) were received 10, 25, and 50 mg/kg of α-LA, respectively. All treatments of vehicle, indomethacin, and α-linoleic acid were given orally by gastric gavage. After of 1 h, mice in all groups were treated with 10 mL/kg of 1% v/v acetic acid solution intraperitoneally (i.p.) to induce the nociception state (pain). 5 min after the giving of acetic acid, the number of observed writhings in the treated groups was counted for 15 min. The percentage inhibition (I%) of writhing (abdominal constrictions) was used to evaluate the analgesic potency and was calculated as the following formula:

\[
\% \text{ inhibition} = \left(\frac{N_s - N_t}{N_s}\right) \times 100
\]

Where N_s is the average of writhing numbers in the negative control group and N_t is the average of writhing numbers in the treated groups.

Hot plate test in mice

One of the evaluation methods of antinociception activity is the hot plate test in mice, which performed according to the previously described in the method of Schmidt et al.[30] with modifications. Five groups of Swiss albino mice of both sexes were used with six animals in each group in this experiment. Mice were fasted for overnight and then were treated as following: Group 1 of mice were treated (10 mL/kg, p.o)
of vehicle (0.9% saline solution) and served as negative control group and Group 2 of mice were intraperitoneally treated 10 mg/kg of tramadol and served as positive control group, while mice groups (3–5) were orally received 10, 25, and 50 mg/kg of α-LA, respectively. 1 h of all treatments, mice were put inside glass cylinder placed on the well-regulated hot plate maintained 55±1°C, and the difference time between placing of mice on the surface of hot plate and the occurrence of fore hind paws licking or jumping was recorded as reaction time. It has been taken into consideration that the cutoff period should not exceed 20 s maximum latency to avoid the injury of paws.

**Statistical analysis**

The results of all trials in this study stated as mean±structural equation modeling. Statistical analysis carried out by (ANOVA) pursued by the Dennett’s t-test. The values of probability (P) <0.05 are considered as statistically significant.

**RESULTS AND DISCUSSION**

**In vitro XO inhibitory activity**

The inhibitory effects of α-LA and allopurinol for bovine milk X0 at different concentrations represented in Table 1. Each has revealed >50% of XO inhibition at the concentration 4 µg/mL. At highest concentration 100 µg/mL, the α-LA resulted in 95% of XO inhibitory activity, whereas the standard XO inhibitor, allopurinol demonstrated 95% of XO inhibition activity at the same concentration. The XO inhibitory effects for both α-LA and allopurinol were also stated in the term of IC<sub>50</sub>, which is represent the concentration of standard drug or tested sample that is required for 50% inhibition of XO enzyme activity under the same experimental conditions. The IC<sub>50</sub> values were calculated according to the dose-response logarithmic curve using GraphPad Prism V 6.05 program (GraphPad Prism software, Inc., USA), where the value was equal to 1.734 µg/mL for allopurinol and 2.930 µg/mL for α-LA, respectively, as shown in Fig. 1.

**Antihyperuricemic activity**

To assess the existence of antihyperuricemic effect of the α-LA, the potassium oxonate-induced hyperuricemia model in rats used in this study. As shown in Table 2, the intraperitoneal injection of uricase inhibitor, potassium oxonate (250 mg/kg) obviously increased the serum UA levels in rats compared with healthy normal control group. The administration of standard XO inhibitor, allopurinol (10 mg/kg, p.o), was able to significantly reduce (p<0.001) the serum UA levels of hyperuricemic rats (positive control group) to values close of normal control. The consecutive 7-day treatment of rats with α-LA at the dose 10, 25, and 50 mg/kg significantly reduce (p<0.001) the serum UA levels as compared with hyperuricemic control group in all doses above.

**Effect of α-LA on MSU crystal-induced inflammation in mice**

As shown in Table 3, the injection of MSU crystals significantly increased (p<0.001) the thickness of the mice paws when compared to the normal animal group. The injection of both standard NSAIDs, indomethacin (3 mg/kg), and α-LA at all gradual doses (10, 25, and 50 mg/kg) was able to achieve a significant reduction (p<0.001) in the paw thickness at all periods of time assessment.

**Evaluation of analgesic activity of α-LA**

**Writhing test**

The results presented in Table 4 revealed that standard drug, indomethacin (10 mg/kg) significantly reduced the number of acetic acid-induced writhings in mice (75%) compared to the negative control group (p<0.001). Similar to indomethacin, α-LA at 10 and 25 mg/kg was able to produce a significant antinociception effect (p<0.001) by reducing the number of writhings in mice (52% and 67%, respectively), while at 50 mg/kg, the α-LA showed higher capacity than indomethacin (79%) in reduction of the writhings number in mice induced by injection of acetic acid.

![Xanthine oxidase inhibitory activity and IC<sub>50</sub> values of α-lipoic acid and allopurinol](image)

**Fig. 1: Xanthine oxidase inhibitory activity and IC<sub>50</sub> values of α-lipoic acid and allopurinol**

**Hotplate test**

The mean reaction time of pain responses to the thermal stimuli in the hot plate test is shown in Table 5. Three doses of α-LA (10, 25, and 50 mg/kg, p.o) significantly increased (p<0.001) the reaction times to the heat-induced pain in mice compared to the negative control group (vehicle). Positive drug, tramadol (10 m g/kg, s.c) markedly increased (p<0.001) the mean of reaction times from 3.14 s at negative control group to 11.65 s.

**DISCUSSION**

Gout is a chronic inflammatory condition associated with the deposition of sodium urate crystals, resulting in severe pain and swollen joints and soft tissue. Treatment methods for gout management include the first treatment of acute gout attacks involving the use of anti-inflammatory analgesic agents such as NSAIDs, colchicine, and corticosteroids. Subsequently, the lowering urate drugs such as allopurinol, febuxostat, and probenecid are used to treat hyperuricemia. Until now, the use of these drugs involves the emergence of many side effects, and none of the clinically available drugs can be used to treat the

<table>
<thead>
<tr>
<th>Concentration (µg/mL)</th>
<th>XO inhibitory activity (%) (mean±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>α-LA</td>
</tr>
<tr>
<td>100</td>
<td>95±1.5</td>
</tr>
<tr>
<td>50</td>
<td>89±0.6</td>
</tr>
<tr>
<td>25</td>
<td>80±1.1</td>
</tr>
<tr>
<td>10</td>
<td>73±2.1</td>
</tr>
<tr>
<td>5</td>
<td>67±2.0</td>
</tr>
<tr>
<td>4</td>
<td>61±0.4</td>
</tr>
<tr>
<td>3</td>
<td>55±0.6</td>
</tr>
<tr>
<td>2</td>
<td>53±1.6</td>
</tr>
<tr>
<td>1</td>
<td>44±1.2</td>
</tr>
</tbody>
</table>

SEM: Standard error of the mean, LA: Lipoic acid, XO: Xanthine oxidase

**Table 1: XO inhibitory activity of α-LA and allopurinol at different concentrations**

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>n</th>
<th>Serum UA (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>–</td>
<td>6</td>
<td>1.2±0.2</td>
</tr>
<tr>
<td>Hyperuricemic control</td>
<td>–</td>
<td>6</td>
<td>4.4±0.7</td>
</tr>
<tr>
<td>Standard drug (Allopurinol)</td>
<td>10</td>
<td>6</td>
<td>1.7±0.6***</td>
</tr>
<tr>
<td>Test (α-LA)</td>
<td>10</td>
<td>6</td>
<td>2.3±0.4***</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>6</td>
<td>2.1±0.5***</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>6</td>
<td>1.9±0.3***</td>
</tr>
</tbody>
</table>

Each value is the means±SEM, *p<0.05, **p<0.01, ***p<0.001 compared with hyperuricemic control. Data analyzed by using one-way ANOVA followed by Dennett’s t-test, SEM: Standard error of the mean, LA: Lipoic acid, UA: Uric acid

**Table 2: Effects of allopurinol and α-LA on the serum UA levels in the normal and potassium oxonate-induced hyperuricemic rats**

**GraphPad Prism software, Inc., USA**, where the value was equal to 1.734 µg/mL for allopurinol and 2.930 µg/mL for α-LA, respectively, as shown in Fig. 1.
Table 3: Effect of α-LA on MSU crystals-induced inflammation hind paw in mice

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Thickness variation Δ (mm) in paw edema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4h</td>
<td>24 h</td>
</tr>
<tr>
<td>Normal control</td>
<td>–</td>
<td>0.20±0.11</td>
</tr>
<tr>
<td>Negative control</td>
<td>–</td>
<td>1.81±0.25</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>3</td>
<td>0.32±0.12***</td>
</tr>
<tr>
<td>α-LA</td>
<td>10</td>
<td>0.66±0.10***</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>0.57±0.09***</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>0.41±0.17***</td>
</tr>
</tbody>
</table>

Each value is the mean±SEM for six mice, *p<0.05, **p<0.01, ***p<0.001 compared with normal control. Data analyzed by using one-way ANOVA followed by Dennett’s test, SEM: Standard error of the mean, LA: Lipoic acid, MSU: Monosodium urate

Table 4: Antinociceptive effect of α-LA on the acetic acid-induced writhings in mice

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Number of writhings</th>
<th>Inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative control (vehicle)</td>
<td>–</td>
<td>46.3±3.24</td>
<td>–</td>
</tr>
<tr>
<td>Positive control (indomethacin)</td>
<td>10</td>
<td>11.2±1.62***</td>
<td>75.77</td>
</tr>
<tr>
<td>α-LA</td>
<td>10</td>
<td>2.18±1.12***</td>
<td>52.88</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>15.01±2.71***</td>
<td>67.58</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>9.43±1.10***</td>
<td>79.63</td>
</tr>
</tbody>
</table>

Each value is the mean±SEM, *p<0.05, **p<0.01, ***p<0.001 compared with negative control. Data analyzed by using one-way ANOVA followed by Dennett’s test, SEM: Standard error of the mean, LA: Lipoic acid

Table 5: Antinociceptive effect of α-LA by hot plate method in mice

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Reaction time (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative control (vehicle)</td>
<td>–</td>
<td>3.14±0.57</td>
</tr>
<tr>
<td>Positive control (tramadol)</td>
<td>10</td>
<td>11.6±0.18***</td>
</tr>
<tr>
<td>α-LA</td>
<td>10</td>
<td>5.22±0.28***</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>6.86±0.36***</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>7.51±0.62***</td>
</tr>
</tbody>
</table>

Each value is the mean±SEM, *p<0.05, **p<0.01, ***p<0.001 compared with negative control. Data analyzed by using one-way ANOVA followed by Dennett’s test, SEM: Standard error of the mean, LA: Lipoic acid

In the present study, MSU crystal-induced inflammation model used to trigger the occurrence of gout acute attacks through the accumulation of the urate crystals in the joints, promoting the initiation of a series of inflammatory reactions, which, in turn, result in acute inflammation and tissue damage [32]. Injection of the MSU crystals produced an important increase in the thickness of mice hind paws as matched to the negative control. Treatment with both indomethacin at a dose (3 mg/kg) and α-LA at doses (10, 25, and 50 mg/kg) resulted in significant reduction in the thickness of mice paws at 4, 24, and 48 h of injection of MSU crystals. These results confirm the ability of α-LA to block the synthesis and releasing of inflammatory mediators because the α-LA can work efficiently in the initial and last stages of the inflammatory process.

The antinociception activity of new drugs can verify by assessing their effects centrally or peripherally, where the hot plate test used to evaluate the central acting analgesic effect and the acetic acid-induced writhings test used to evaluate the peripheral acting analgesic effect [33]. In the present study, we employed both techniques to not only verify antinociceptive influence but also to determine the mechanism action of the antinociceptive effect of α-LA. The inhibition of the acetic acid-induced writhings is an indication of potential analgesic of α-LA. The pain induction by acetic acid is due to liberating endogenous substances such as histamine, serotonin, prostaglandin, and bradykinin and those which stimulate nerve endings [29]. Thus, the antinociceptive effect of α-LA may be peripherally mediated by the inhibition of synthesis and releasing of prostaglandins through inhibition of cyclooxygenase enzymes. Since acetic acid-induced contractions test involves several different types of nociceptive mechanisms, we have tested the hot plate to assess the possibility of α-LA from showing any central analgesic effect. The ability of α-LA to lengthen the reaction latency to the thermal-induced pain of mice by the hot plate strongly supports its most central analgesic activity. Consequently, α-LA may exhibit its antinociceptive effect by involving peripheral and central mechanisms.

CONCLUSIONS

The results of the current study demonstrated that the α-LA has remarkable effects in the treatment of gout and associated diseases. It was noted that it was able to potentially reduce the urate levels in the gout arthritis symptoms together such as pain, hyperuricemia, and inflammation [18]. The present study aimed to investigate the XO inhibitory, antihyperuricemic, anti-inflammatory, and antinociceptive activity of α-LA.

UA produced as a main final product of purine metabolism by the action of XO enzyme that accelerates the hypoxanthine conversion to xanthine and then xanthine into UA. Therefore, the inhibition of XO activity can be considered as a useful therapeutic method in the treatment of gout and other XO-related complications [25]. Different concentrations of α-LA and allopurinol were assessed for in vitro bovine milk XO inhibitory activity. The XO inhibition percentage results are revealed in Table 1 indicated that at the final concentration 100 µg/mL, the α-LA potentially inhibited the XO activity with 88% as compared to 95% for the standard drug, allopurinol at the same concentration. Further, the IC₅₀ value for the α-LA (2.93 µg/mL) clearly denotes that it is a potent XO inhibitor as compared with the value of well-known XO inhibitor, allopurinol (IC₅₀=1.73 µg/mL).

Potassium oxonate is a well-known xanthine oxidase inhibitor in animal models of hyperuricemia due to low-cost and rapid-acting substance. The potassium oxonate-induced hyperuricemic rats are the most suitable animal model to assess new drugs that affect levels of UA in the blood [31]. In this study, treatment of rats with potassium oxonate resulted in a significant elevation in the serum urate levels as compared to normal group, revealing that the rat model has been successfully established. A 7-day oral treatment of the α-LA at doses (10, 25, and 50 mg/kg) significantly decreased (p<0.001) in a dose-dependent mode the serum UA levels when associated with the hyperuricemic control group. In contrast, the same treatment with the standard hypouricemic drug, allopurinol (10 mg/kg) also led to a significant reduction (p<0.001) in serum urate levels. The reduction in the serum UA levels and preceded by a significant efficacy of inhibition of XO, these results designate that the overall activity of the α-LA as antihyperuricemic is markedly associated with inhibition of XO activity, and this maybe the mechanism of action.

In this study, MSU crystal-induced inflammation model used to trigger the occurrence of gout acute attacks through the accumulation of the urate crystals in the joints, promoting the initiation of a series of inflammatory reactions, which, in turn, result in acute inflammation and tissue damage [32]. Injection of the MSU crystals produced an important increase in the thickness of mice hind paws as matched to the negative control. Treatment with both indomethacin at a dose (3 mg/kg) and α-LA at doses (10, 25, and 50 mg/kg) resulted in significant reduction in the thickness of mice paws at 4, 24, and 48 h of injection of MSU crystals. These results confirm the ability of α-LA to block the synthesis and releasing of inflammatory mediators because the α-LA can work efficiently in the initial and last stages of the inflammatory process.
in gouty arthritis: Anti-hyperuricemic. Anti-hyperuricemic, anti-inflammatory and analgesic effects of leaves extracts exert hypouricemic effects.


REFERENCES

There are no conflicts of interest.

AUTHOR'S CONTRIBUTIONS
Both authors have the same contribution to this research by implementing search, data collection, data analysis, and format manuscript.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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serum of potassium oxonate-induced hyperuricemic rats through the potent inhibitory activity for XO in vitro. Furthermore, α-LA was able to reduce MSU crystal-induced edema hind paw in mice significantly. Furthermore, α-LA possesses significant efficient as peripheral and central analgesic agent through acetic acid-induced writhing and hot plate tests.


