ISSN 1859 - 4735

JOURNAL OF MEDICINAL MATERIALS

No. 6 - Vol. 30
12/2025

NATIONAL INSTITUTE OF MEDICINAL MATERIALS

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JOURNAL OF MEDICINAL MATERIALS (Print and Electronic Journals)

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Journal of Medicinal Materials, 2025, Vol. 30, No. 6 (440 - 445)

STUDY ON THE CHRONIC ANTI-INFLAMMATORY AND URIC ACID-LOWERING EFFECTS OF THE 45% ETHANOL EXTRACT FROM *HOMALOMENA OCCULTA* RHIZOME

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Received August 10th, 2025 Accepted December 4th, 2025

Summary

The rhizome of *Homalomena occulta* has been widely used in traditional medicine to strengthen tendons and bones, alleviating inflammation, and also relieving pain associated with rheumatoid arthritis and osteoarthritis in the aged individuals. This study aimed to investigate the xanthine oxidase inhibitory activity (*in vitro*) and to evaluate its anti-inflammatory effect on the Freund's Complete Adjuvant (FCA) - induced paw edema mouse model, as well as its uric acid-lowering effect in a potassium oxonate–induced chronic hyperuricemia model in male *Swiss albino* mice of the 45% ethanol extract from *H. occulta* rhizomes (HO). Although HO showed xanthine oxidase inhibitory activity (IC_{50} = 177.34 µg/mL), its effect was weaker than that of allopurinol. This study demonstrated that HO at doses of 0.412 g/kg and 0.824 g/kg (equivalent to 2.5 g/kg and 5 g/kg of raw material, respectively) significantly reduced paw edema in the chronic inflammation model and decreased plasma uric acid levels compared with the disease model group. The effects were comparable to those of standard therapeutic agents such as diclofenac and allopurinol, respectively. These findings support the potential development of *H. occulta* rhizome extract as a promising herbal preparation for the treatment of chronic inflammatory conditions and hyperuricemia.

Keywords: *Homalomena occulta*; *Anti-Inflammatory effect; Anti-Hyperuricemic effect; Xanthine oxidase; Chronic inflammation; Potassium oxonate.*

1. Introduction

Gout is a metabolic and inflammatory joint disorder that substantially reduces quality of life and functional capacity in affected individuals. It is a type of inflammatory arthritis, occurs due to elevated levels of uric acid in the blood, also known as anti-hyperuricemic effect. Hyperuricemia is the primary risk factor for gout development, characterized by elevated levels of uric acid in the body, with a subsequent increase in the risk of gout. Xanthine oxidase catalyzes the oxidation reactions of hypoxanthine to xanthine and finally to uric acid, which directly affects uric acid formation [1],[2].

The plant *H. occulta* (Lour.) Schott, belonging to the family Araceae, is distributed in Southeast Asia and parts of the South Pacific and has been traditionally used to treat rheumatoid arthritis and to strengthen tendons and bones. This traditional herb was also reported to exert hepatoprotective and renoprotective effects. *H. occulta* contains a variety of natural compounds, including sesquiterpenoids, triterpenoids, alkaloids, and phenolic acids [3]. Moreover, previous studies have reported that its sesquiterpenoids can stimulate the proliferation, differentiation, and mineralization of osteoblasts *in vitro* [4]. Despite being traditionally used for the treatment of rheumatoid arthritis, there are only a few reports on the anti-inflammatory research of natural compounds from the rhizomes of *H. occulta* [5]. The discovery of bioactive natural compounds has taken a long time [5]. Notwithstanding, there is no scientific investigation that has discussed the chronic anti-inflammatory and uric acid-lowering effects of *H. occulta* rhizome. This study was conducted to further evaluate the effects of 45% ethanolic extract from *H. occulta* rhizome as an alternative agent in treating gout by using mouse models.

2. Materials and methods

2.1. Plant materials

Homalomena occulta rhizomes were collected from Dong Nai province, Vietnam, in May 2023.

It was conserved in the Research Center of Ginseng and Medicinal Materials in Ho Chi Minh City (Code: ĐD-TNK 03/2023). The material was extracted with 45% ethanol at room temperature for 72 hours in a percolator apparatus (ratio 1:20, w:v). The 45% ethanol extract was collected at a rate of 2 mL/min and concentrated using a rotary evaporator at 60°C under reduced pressure to obtain crude ethanol extract (HO). The yield of HO was 16.48%. The moisture was 18.21%. HO extract at oral doses of 0.412 g/kg and 0.824 g/kg of mouse body weight (equivalent to 2.5 raw materials/kg and 5 g raw materials/kg) were selected for pharmacological study according to a previous study of *Homalomena* [6].

2.2. Animals

Male *Swiss albino* mice (aged 5-6 weeks) were used for the experiments. They were supplied by the Institute of Drug Quality Control Ho Chi Minh City. Prior to the experiments, all animals were kept for 1 week under the same laboratory conditions of temperature (22 ± 2 °C), relative humidity (70 ± 4%), and a 12-hour light/dark cycle and maintained on a standard rodent chow and tap water. All animal procedures were conducted according to the "Guidelines for Preclinical and Clinical Study of Traditional and Natural Medicines" approved by the Ministry of Health - Vietnam (attached with Decision No. 141/QĐ-K2ĐT dated 27/10/2015). The oral or injection volume was 10 mL/kg b.w..

2.3. Chemicals and reagents

Xanthine oxidase (XO), xanthine, allopurinol, potassium oxonate (Sigma-USA); uric acid quantification kit (Human Co., Germany); 96% ethanol (OPC-Vietnam). All other chemicals were of analytical grade.

2.4. Xanthine oxidase inhibition assay

The xanthine oxidase activity, using xanthine as the substrate, was measured spectrophotometrically by the method of Tadataka Noro *et al.* with the following modification [7]. The assay mixture consisted of 0.1 mL of HO solution (200, 175, 150, 125, and 100 µg/mL), 0.3 mL of 50 mM phosphate buffer (pH=7.5), and 0.1 mL of enzyme solution. After preincubation of the mixture at 37°C for 15 min, the reaction was initiated by adding 0.2 ml of 0.15 mM xanthine solution. This assay mixture was incubated at 37°C for 30 min. The reaction was stopped by adding 0.2 mL of 0.5 M HCl, and the absorbance of the assay mixture at 295 nm was measured spectrophotometrically. This experiment was assessed using allopurinol (Sigma, USA) as a positive control [7]. All analyses were run in triplicate.

Percentage inhibition (I%) was estimated using the following expression:

$$I\% = \frac{A_c - A_s}{A_c - A_0} \times 100$$

Where A_c, A_s, and A_0 are the absorbances of control, sample, and blank, respectively.

2.5. Evaluation of the chronic anti-inflammatory

Experimental mice were randomly divided into groups (8 mice per group) as follows:

- The untreated control group: they had access to distilled water and food freely for 3 weeks.

- The sample groups: they were orally treated with HO at a dose of 0.412 g extracts/kg or HO at a dose of 0.824 g extracts/kg and food for 3 weeks.

- The positive control group: they were orally treated with diclofenac at a dose of 5 mg/kg and food for 3 weeks.

The paw edema-model in mice was induced by a subcutaneous injection around the right hind paw joint using 50 µl Freund's complete adjuvant (FCA) for the first injection. One week after the initial injection, a second booster injection of FCA was administered at the same site on the right paw. The non-injected left paw served as the contralateral control.

Mice were administered the test samples daily after the first FCA injection. To assess the degree of inflammation in each group, the volume of both the right and left paws was measured using a plethysmometer (Ugo, Italy) on 7, 14, and 21 days of the experiment [8].

Measurements were taken twice, and the average was recorded. Paw edema in the experimental groups was calculated using the following formula:

$$\% \text{ Paw edema} = \frac{X - Y}{Y} \times 100$$

X: volume of the right paw (ml).

Y: volume of the left paw (ml).

2.6. Investigation of anti-hyperuricemic effect in a chronic hyperuricemia model

The mice were randomly divided into 5 groups as Table 1.

Table 1. Experimental design for the chronic hyperuricemia model

Group	Number of animals (n)	Treatment
Control	n=8	Vehicle
Hyperuricemia model	n=8	Potassium oxonate + Vehicle
Low-does treatment	n=8	Potassium oxonate + HO (0.412 g/kg)
High-dose treatment	n=8	Potassium oxonate + HO (0.824 g/kg)
Positive control	n=8	Potassium oxonate + Allopurinol (10 mg/kg)

Mice had an oral treatment with the samples after having been injected with potassium oxonate (300 mg/kg, i.p.) for an hour daily. After an hour of taking the samples of the 7thand 15th day, blood was collected from the tail vein of the mice to determine plasma uric acid levels using the uric acid Liquicolor kit from Human Diagnostic Ltd. Co. (Germany) [9],[10].

The hypouricemia effect in experimental mice was elevated by determining the percentage reduction in blood uric acid concentration in the test groups compared to the pathological control group, calculated using the following formula:

$$\% \text{ reduction in uric acid} = \frac{X_1 - Y_1}{X_1} \times 100$$

X_1: Uric acid level in the pathological condition group (The average uric acid level in the plasma of the untreated pathological condition).

Y_1: Uric acid level in treatment group (The average uric acid level in the plasma of the group treated with the extract or uric acid-lowering drug).

2.7. Data analysis

The data were expressed as mean values: Mean ± SEM (Standard error of the mean) and statistical treatment based on one-way ANOVA followed by theStudentNewman-Keuls test (SigmaStat 3.5). Test results were statistically significant at a 95% confidence level when $p < 0.05$ compared with respective controls.

3. Results

3.1. Xanthine oxidase inhibitory activity

Xanthine oxidase is an important enzyme in nucleic acid metabolism; it catalyzes the oxidation of xanthine and hypoxanthine to uric acid and generates free oxidative radicals. Therefore, inhibiting xanthine oxidase activity reduces uric acid formation, effectively halts or delays gout and its complications, and weakens tissue damage caused by free radicals, all of which are critical to human health. The extract can dose-dependently restrain xanthine oxidase from catalyzing the oxidation of xanthine into uric acid. The xanthine oxidase inhibitory activity of HO, with an IC_{50} value was 177.43 ± 1.83 (µg/ml), was weaker than allopurinol.

Table 2. Xanthine oxidase inhibition of the samples

Sample	Xanthine oxidase inhibitory activity (%)					IC_{50} (µg/mL)
Concentration (µg/mL)	***200***	***175***	***150***	***125***	***100***	
HO	58.24 ± 1.40	47.99 ± 0.34	40.03 ± 0.21	33.51 ± 2.81	26.15 ± 0.85	177.43 ± 1.83
Concentration (µg/mL)	***10.21***	***6.81***	***5.10***	***3.40***	***1.7***	
Allopurinol	79.65 ± 0.81	68.81 ± 0.59	57.52 ± 2.39	42.53 ± 1.39	28.74 ± 3.43	3.86 ± 0.25

Values represent mean/ Standard deviation (n=3).

3.2. Results of chronic anti-inflammatory activity

The results in Table 3 showed that the untreated control group, in which the right hind paw was injected with FCA, exhibited significant paw edema levels ranging from 106.33% to 146.43% during the 1st to 3rd week of the experiment, with the peak swelling observed at the 2nd week. A reduction in paw edema was noted by the 3rd week. At the same time, the untreated control group had a significant increase in paw edema level in comparison with the physiological ($p<0.001$). The FCA-induced group was orally treated by diclofenac at a dose of 5 mg/kg, having a significant reduction in paw edema levels (28.22% – 70.59%) compared to the untreated control group at the same time ($p=0.022$; $p<0.001$; $p<0.001$; respectively).

Table 3. Paw edema levels of the experimental groups (Mean ± SEM)

Groups (n = 8)	Paw edema level in mice (%)		
	After 1st week	After 2nd week	After 3rd week
Untreated control	106.33 ± 6.15	146.43 ± 9.79	110.66 ± 7.59
Diclofenac (5 mg/kg)	78.11 ± 7.27$^{\#}$	75.84 ± 5.45$^{\#\#\#}$	58.38 ± 5.69$^{\#\#\#}$
HO (0.412 g/kg)	82.35 ± 8.66$^{\#}$	117.50 ± 7.45$^{\#}$	74.28 ± 5.28$^{\#\#\#}$
HO (0.824 g/kg)	66.04 ± 5.95$^{\#\#}$	91.05 ± 6.99$^{\#\#\#}$	76.44 ± 4.59$^{\#\#\#}$

$^{\#}$: $p < 0.05$ compared to the untreated control group at the same time; $^{\#\#}$: $p < 0.01$ compared to the untreated control group at the same time; $^{\#\#\#}$: $p < 0.001$ compared to the untreated control group at the same time.

The groups of mice with paw edema treated with HO at doses of 0.412 g/kg and 0.824 g/kg showed a statistically significant reduction in paw edema levels compared to the untreated pathological control group at the same time. After the 1st and 3rd week of the experiment, HO at both tested doses exhibited chronic anti-inflammatory activity comparable to the reference drug diclofenac at a dose of 5 mg/kg (after a week: $p = 0.673$; $p = 0.387$, respectively; after 3 weeks: $p = 0.067$; $p = 0.095$, respectively). After the 2nd week of the experiment, HO at a dose of 0.412 g/kg showed a weaker anti-inflammatory effect compared to the reference drug diclofenac at 5 mg/kg ($p = 0.002$). In contrast, HO at a dose of 0.824 g/kg demonstrated a comparable reduction in paw edema to that of the reference drug diclofenac at 5 mg/kg ($p = 0.167$).

3.3. Results of uric acid–lowering effect

At all observed time points, the hyperuricemia modelgroup injected with potassium oxonate exhibited a significant increase in plasma uric acid levels (34.08%, 125.93%, and 105.38%, respectively), which were statistically significant compared to the control group at the same time ($p = 0.004$; $p < 0.001$; $p < 0.001$, respectively). The allopurinol (10 mg/kg)- orally treated group has a significant reduction in plasma uric acid levels (19.45%, 46.69%, and 49.60%, respectively) compared to the hyperuricemia model group at the same time ($p = 0.011$; $p < 0.001$; $p < 0.001$, respectively). Moreover, allopurinol (10 mg/kg) decreased plasma uric acid levels back to normal values in comparison with the control group at the same time ($p = 0.350$; $p = 0.136$; $p = 0.736$, respectively).

Table 4. Uric acid levels of the experimental groups (Mean ± SEM)

Groups (n = 8)	Uric acid levels (mg/dL)		
	At day 1	At day 7	At day 15
Control	0.63 ± 0.04	0.68 ± 0.05	0.73 ± 0.05
Hyperuricemia model	0.84 ± 0.05**	1.53 ± 0.08***	1.49 ± 0.04***
Allopurinol (10 mg/kg)	0.66 ± 0.03$^{\#}$	0.81 ± 0.05$^{\#\#\#}$	0.75 ± 0.05$^{\#\#\#}$

Groups (n = 8)	Uric acid levels (mg/dL)		
	At day 1	At day 7	At day 15
HO (0.412 g/kg)	0.79 ± 0.06	0.86 ± 0.06$^{\#\#\#}$	0.80 ± 0.04$^{\#\#\#}$
HO (0.824 g/kg)	0.75 ± 0.08	0.90 ± 0.08$^{\#\#\#}$	0.88 ± 0.07$^{\#\#\#}$

**: $p < 0.01$ compared to the control group at the same time; ***: $p < 0.001$ compared to the control group at the same time; $^{\#}$: $p < 0.05$ compared to the hyperuricemia model group at the same time; $^{\#\#\#}$: $p < 0.001$ compared to the hyperuricemia model group at the same time.

On the 1st day, HO at doses of 0.412 g/kg and 0.824 g/kg had not significantly reduced blood uric acid levels (6.08%–10.50%) compared to the hyperuricemia model group at the same time ($p = 0.511$; $p = 0.340$, respectively).

After 7 and 15 days of the experiment, the potassium oxonate-induced groups treated with HO at doses of 0.412 g/kg and 0.824 g/kg showed a statistically significant reduction in plasma uric acid levels compared to the *hyperuricemia model*group at the same time ($p < 0.001$); HO at both tested doses exhibited a uric acid-lowering effect comparable to the reference drug allopurinol at a dose of 10 mg/kg. It was also able to restore plasma uric acid levels to normal values when compared to the control group in the prolonged hyperuricemia mouse model.

4. Discussion

Hyperuricemia is associated with gout, an inflammatory arthritis caused by the deposition of uric acid in joints. The present study demonstrated that HO exhibits significant biological activities, including xanthine oxidase (XO) inhibition, chronic anti-inflammatory effects on the Freund's Complete Adjuvant (FCA)-induced paw edema mouse model, and hypouricemia effects in a mouse model of long-term hyperuricemia induced by potassium oxonate. In the past few years, screening studies of the rhizomes of *H. occulta* have yielded several new sesquiterpenoids with different frameworks, including six rarely reported naturally occurring oplopanane sesquiterpenoids. Sesquiterpenoids, including five new homalomenins A-E, have been isolated from the aqueous ethanol extract of this *H. occulta*. These sesquiterpenoids had various carbocyclic skeletons, including isodaucane, guaiane, eudesmane, oppositane, and aromadendrane types. The isolated sesquiterpenoids were evaluated for their inhibitory effects on COX-2 mRNA and COX-2 protein expression, as well as prostaglandin E2 (PGE2) production in Raw264.7 cells. Oppositane and aromadendrane compounds isolated from *H. occulta* showed potent anti-inflammatory activity by suppressing LPS-induced COX-2 expression and PGE2 production in a dose-dependent manner [11],[12].

In the hyperuricemia model induced by potassium oxonate injection, oral administration of HO resulted in a significant, time-dependent reduction in plasma uric acid levels, with efficacy comparable to that of allopurinol. Allopurinol works by inhibiting xanthine oxidase, an enzyme involved in the conversion of hypoxanthine and xanthine to uric acid. However, it may cause many side effects, such as hepatitis, nephropathy, and allergic reactions [13]. The uric acid levels in the *H. occulta* extract-treated groups showed a marked reduction when compared to the *hyperuricemia model*group. One of the bioactive contents of the *H. occulta* rhizome with xanthine oxidase inhibitory activity is apigenin, which may alleviate uric acid in purine bodies or potassium oxonate-induced hyperuricemia mice [14]. On the other hand, apigenin directly inhibited the uric acid transport mediated by transporters, including the URAT1 and GLUT9 dual-target inhibitory activity. Further kinetic and molecular docking experiments showed that apigenin may inhibit uric acid transport by URAT1 by competing for binding sites with uric acid. So, it inhibits the reabsorption of uric acid by URAT1 and GLUT9, promotes the excretion of uric acid through the kidney, and finally reduces the serum

level of urate [15]. With its anti-inflammatory and uric acid-lowering properties, *H. occulta* may become an effective adjunct therapy in the treatment of gout, helping to alleviate clinical symptoms and prevent recurrent acute gout attacks. This study not only clarifies the plant's potential in gout treatment but also opens up the opportunity to apply traditional medicinal plants in the development of modern therapeutic approaches. However, future research is necessary to identify the main chemical constituents in the *H. occulta* rhizome, which determine the pharmacological effects of this publication.

5. Conclusion

The 45% ethanolic extract from *Homalomena occulta* rhizome at both doses of 0.412 g/kg and 0.824 g/kg (equivalent to 2.5 g/kg and 5 g/kg of raw materials) exhibited the chronic anti-inflammatory and anti-hyperuricemic effects in mouse models.

Acknowledgments: *This work was supported by the National Institute of Medicinal Materials (NIMM)-Ministry of Health, project "Study on the anti-inflammatory and hypouricemia effects of the extract from Homalomena occulta (Lour.) Schott rhizome in the direction of supporting gout treatment".*

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