ANTI-INFLAMMATORY ACTIVITIES OF HUYET GIAC TO MOC CHI GIAP HOA THANG EXTRACT IN MICE

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ABSTRACT

Objective: *To determine anti-inflammatory activities of Huyet giac to moc chi giap hoa thang (HG) liquid extract in mice.*

Subjects and methods: *Carrageenan-induced paw edema and cotton pellet-induced granulomatous formation models were applied in mice.*

Results: *At two tested doses of 24.96 and 74.88 g of dried herbal material/kg/day for 7 consecutive days, HG liquid extract significantly reduced mice's paw volumes compared to those of the control group and was not notably different from those of diclofenac sodium at a dose of 24 mg/kg/day for 7 days. Furthermore, it remarkably reduced the weights of wet and dry granulomas of the tested groups compared to those of the control group and showed high effects akin to those of oral prednisolone at a dose of 7.2 mg/kg/day for 7 days.*

Conclusion: *The HG liquid extract possesses anti-inflammatory activities against acute and chronic inflammations at two tested doses.*

Keywords: *Huyet giac to moc chi giap hoa thang, HG extract, anti-inflammatory activity.*

INTRODUCTION

Inflammation is a natural protective reaction of the body, involving the activation of immune and non-immune cells in response to harmful agents such as infections, toxic compounds, damaged cells, or radiation, to restore tissue homeostasis. Acute inflammation is considered helpful in removing unwanted debris (pathogens or damaged tissue), facilitating repair and regeneration. Ideally, the inflammation ceases and the body returns to its original state within a few days to a few weeks after the inflammatory agents has been removed. Conversely, an inflammation becomes harmful when it (i) becomes chronic, lasting for days or years, leading to fibrosis and/or dysfunction; or (ii) accelerates and spreads, causing serious damage to other tissues and organs [1]. Thus, anti-inflammatory drugs are necessary in these cases. Besides chemical drugs, research and development of herbal medicines is receiving increasing attention and is a popular trend not only in Vietnam but also in other countries around the world in recent years. Several herbal medicines have demonstrated their powerful pharmacological effects, safety, and effectiveness, contributing significantly to the prevention and treatment of inflammation.

Huyet giac to moc chi giap hoa thang (HG) is an herbal remedy cited in the book Nam Y nghiem phuong by Nguyen Duc Doan [2]. It has five medicinal herbs consisting of *Lignum Dracaenae, Lignum Sappan, Folium Lawsoniae, Herba Artemisiae vulgaris* and *Rhizoma Curcumae longae*, which have long been used in Vietnamese traditional medicine to treat injuries, sprains, hematomas, inflammation and swelling, and protecting joint cartilage. Although it has been used in traditional treatment, there has been no scientific publication on its safety and effects when combining the five above medicinal ingredients.

Some studies have evaluated the biological activities of the medicinal ingredients when used separately. In particular, typical studies have shown that *Lignum Dracaenae* has its analgesic, blood stasis removal, anti-inflammatory and good antibacterial effects [3]. *Lignum Sappan* exhibits anti-inflammatory, antibacterial effects and liver protection [4]. *Folium Lawsoniae* reveals antibacterial, antioxidant, anticancer, and immunomodulatory results [5]. *Herba Artemisiae vulgaris* manifests antipyretic, antimalarial, antibacterial, antifungal effects, menstrual cycle regulation, and pregnancy-stabilizing effects [6],[7]. Meanwhile, turmeric demonstrates anti-inflammatory, analgesic, antibacterial, blood cholesterol-lowering and immune-boosting outcomes [8],[9].

The question is how the pharmacological effects of the drug combination are expressed when using five above medicinal herbs in one compound formula. Therefore, to have further scientific evidence to this medicine's development from available and potential

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medicinal herbs, we evaluate one aspect of its biological effects, namely the anti-inflammatory effects of HG liquid extract on mice.

MATERIALS AND METHODS

Test sample

The HG liquid extract was prepared by extracting a mixture of five medicinal herbs with water to obtain a stock sample with a dry herb-to-water ratio of 2:1. Each 52 ml of this stock sample already contained five medicinal herbs that met the standards of the manufacturer or the Vietnamese Pharmacopoeia V [10], including *Lignum Dracaenae* 24.0g, *Lignum Sappan* 20.0g, *Folium Lawsoniae* 20.0g, *Herba Artemisiae vulgaris* 24.0g, *Rhizoma Curcumae longae* 16.0g and 0.35 ml of a mixture of mugwort and turmeric essential oils that had been previously distilled. The specific extraction process was as follows. In the beginning, mugwort and turmeric were pulled out for essential oils by steam distillations. These two herbs were thinly sliced (4-5 mm) and placed separately into differentiated distillation flasks. Water was then added to these flasks to achieve herb/water ratios of (1:3) and distilled for 5 and 6 hours, respectively. The extracted essential oils were placed in a tightly sealed container, while the remaining herbal residues were retained for further decoction. Next, the residues of mugwort and turmeric after essential oil extraction, along with the remaining three herbs, were combined and pulled out three times with water, each time for 2.5 hours. After that, the extracts were combined and concentrated at a temperature not exceeding 60°C until a 2:1 liquid extract was obtained. Finally, the above mixture of mugwort and turmeric essential oils was dissolved in tween 80 at a ratio of 1:2 and mixed into the extract, then stirred well. This stock sample was diluted with distilled water to form extracts of different concentrations used in the experiments.

HG liquid extract is intended for the treatment of injuries, hematomas, inflammation, and swelling in humans at a dose of 104 g of dried herb/day/person. For an average person weighing 50kg, the expected dose would be 2.08g of dried herbal material/kg/day, equivalent to 24.96 g of dried herbal material/kg/day in mice. The following dosages are calculated based on dried medicinal herbs and are abbreviated as g/kg/day.

Experimental animals

Swiss albino mice, provided by the National Institute of Hygiene and Epidemiology, met criteria consisting of 4-5 weeks old, weighing 20 ± 2g, mature, healthy, and indistinguishable by sex. Female mice were not pregnant and had never reproduced. The mice were kept in stable conditions for 3 days before the study under experimental conditions like temperature 22-25°C, humidity 50-60%, and a 12/12-hour light-dark cycle, with the light cycle from 6:30 AM to 6:30 PM.

The research was conducted at the Vietnam University of Traditional Medicine.

Drugs and chemicals

Diclofenac sodium 75 mg tablets (Uphace), batch 250915, expiry date 06/09/2028, VD-23083-15. Prednisolone 5mg tablets (Khanh Hoa Pharmaceutical Company), batch number 5740723, expiry date August 2026. Carrageenan (Macklin), batch C16470862, CAS 11114-20-8. Trichloromethane (Merck KGaA), batch K56335145447, CAS No. 67-66-3. Diethyl ether (Merck KGaA), batch K55849321416, CAS No. 60-29-7.

Time and location: This study was conducted between November 2025 and January 2026 at Vietnam University of Traditional Medicine.

Methods

Carrageenan-induced paw edema:

The acute anti-inflammatory activity of HG liquid extract was measured by the modified carrageenan-induced paw edema method described in the literature [11],[12],[13]. Mice were randomly divided into 4 groups of 10 mice each. In group 1 (the control group), mice were given saline in a volume equivalent to the treatment group's volume, which was 0.1 ml/10 g of body weight. Mice in group 2 were given diclofenac sodium 24 mg/kg/day, while those in groups 3 and 4 were given HG extracts at doses of 24.96 and 74.88 g/kg/day, respectively. The mice were given the reference drug or test samples daily for 7 consecutive days at the above doses by delivering the drugs directly into their stomachs via blunt needles. On day 7, one hour after administration, all mice were induced with foot inflammation and edema by injecting 0.05 ml of 1% carrageenan (diluted in physiological saline) into their right hind paws. Next, all right hind paws were marked at their ankle joints to ensure consistent immersion in the measurement chamber. Paw volumes were measured using a Plethysmometer No. 7250, immediately before sub plantar injection (V0), and 1, 2, 4, 6, 24, and 48 hours thereafter (V1, V2, V4, V6, V24 and V48, respectively).

Subsequently, the increase in paw volumes was calculated using the following formula: $X\% = (Vt - V0) / V0 \times 100$, where X% is the percentage of increase in paw volume, and V0 and Vt are the paw volumes before and after inflammation induction. Finally, the anti-inflammatory effect of the drug was evaluated by its ability to inhibit edema (Y%) with $Y\% = (Mc - Mt) / Mc \times 100$, where Y% is the percentage of reduction in paw edema, while Mt and Mc are the percentages of increase in paw volumes in the treated and the control groups, respectively.

Cotton pellet granuloma method:

The anti-inflammatory effects of HG liquid extract on chronic inflammation were evaluated by the modified cotton pellet granuloma induction method in mice described in the literature [14],[15]. All 40 mice were anesthetized with diethyl ether and then granulated by subcutaneous implantation between the two scapulae of each mouse with a sterile cotton pellet weighing 30 ± 1 mg. Next, they were randomly divided into 4 groups of 10 mice each. In which, mice in group 1 (the control) were given distilled water at a volume of 0.1 ml/10 g body weight. Mice in group 2 were taken prednisolone 7.2 mg/kg/day, while others in groups 3 and 4 were drunk HG at doses of 24.96 and 74.88 g/kg/day, respectively. All mice were administered samples continuously for 7 days through blunt-tipped needles so the samples went directly into their stomachs. On the eighth day, they were euthanized using trichloromethane. Then, their granulomas surrounding the cotton pellets were surgically removed, and granulomas' actual weight was determined after subtracting the weight of the cotton pellets. After that, these granulomas were dried to constant weight at 56°C for 24 hours and weighed a second time. The average weight of the granulomas (both wet and dried) was then compared among groups to assess inhibitory effects on chronic inflammation.

The study parameters included the weight of wet and dried granulomas and percentages of granuloma weight reduction compared to that of the control one, which were calculated using the formula X% = (Mc-Mt)/Mc × 100, where Mc and Mt are the granular weights of the control and test groups, respectively.

Data processing

Data are expressed as means ± standard deviations (Mean ± SD). They were processed using SPSS 22.0 software according to medical statistics methods, employing Student's t-test, Paired-Samples T-Test, and One-way ANOVA. Post-hoc analyses were performed using Tukey's HSD. p values < 0.05 was considered statistically significant for differences.

Ethics

The study protocol was approved by Decision No. 4881/QD-HVYDCT dated November 21, 2025, of the Director of Vietnam University of Traditional Medicine. Animals were disposed of according to regulations after the study. We commit to ensuring there are no conflicts of interest in this research.

RESULTS

Carrageenan-induced paw edema

Both HG liquid extract and diclofenac sodium exhibited high paw edema reduction effects at all study time points and displayed impressive reductions in edema at 1, 6, 24, and 48 hours (Tables 1-3).

Table 1. Paw edema in mice after carrageenan-induced inflammation

Group (n = 10)	Mice's paw volumes (mean ± SD, ml)							p(V0-Vi)
	Before inflammation (V0)	After inflammation						
		1 hr (V1)	2 hrs (V2)	4 hrs (V4)	6 hrs (V6)	24 hrs (V24)	48 hrs (V48)	
1: control, saline	0.144 ± 0.015	0.208± 0.04	0.235 ± 0.025	0.262 ± 0.029	0.228 ± 0.023	0.194 ± 0.018	0.157 ± 0.014	< 0.001 except for p (V0-V48) > 0.05
2: diclofenac sodium 24 mg/kg/day	0.145 ± 0.014	0.177± 0.021	0.207 ± 0.008	0.219 ± 0.015	0.181 ± 0.012	0.165 ± 0.017	0.151 ± 0.013	
3: HG 24.96 g/kg/day	0.142 ± 0.018	0.175± 0.023	0.208 ± 0.018	0.225 ± 0.023	0.194 ± 0.016	0.169 ± 0.011	0.151 ± 0.014	
4: HG 74.88 g/kg/day	0.146 ± 0.01	0.177± 0.014	0.206 ± 0.018	0.227 ± 0.019	0.201 ± 0.016	0.178 ± 0.015	0.151 ± 0.011	
p(1-2), (1-3), (1-4)	> 0.05	< 0.05	< 0.05	< 0.01	< 0.01	< 0.05	> 0.05	

(Vi is the mouse's paw volume at each study time point; p (2-3), (2-4), (3-4) > 0.05)

Before and 48 hours after inflammation induction, mice's paw volumes in four different groups did not differ notably (p>0.05). However, after 1, 2, and 4 hours of inflammation induction, the paw volumes of all four groups increased significantly compared to those before administration (p < 0.001), increasing linearly with time and reaching their peaks at 4 hours. Subsequently, these volumes gradually decreased at 6 and 24 hours but remained remarkably higher than before inflammation induction (p<0.001). Furthermore, the paw volumes of mice in the diclofenac reference group and the two HG extract groups were statistically significantly lower than those of the control one at 1, 2, 4, 6, and 24 hours (p values < 0.05 and < 0.01). However, the paw volumes of mice in groups 2, 3, and 4 did not differ remarkably (p>0.05).

Table 2. Percentages of increase in mice's paw volumes compared to that before inflammation

Group (n = 10)	Percentages of increase in mice's paw volumes at different study time points (%)					
	1 hr (V1-V0)	2 hrs (V2-V0)	4 hrs (V4-V0)	6 hrs (V6-V0)	24 hrs (V24-V0)	48 hrs (V48-V0)
1: control, saline	44.52 ± 22.58	64.36 ± 20.17	83.66 ± 26.81	60.61 ± 29.35	36.61 ± 24.16	9.28 ± 5.20
2: diclofenac sodium 24 mg/kg/day	22.57 ± 15.01	43.89 ± 14.84	52.4 ± 19.25	26.1 ± 17.12	14.35 ± 12.38	4.4 ± 7.08
3: HG 24.96 g/kg/day	22.77 ± 12.30	48.72 ± 23.59	60.66 ± 25.38	38.69 ± 21.36	20.43 ± 14.41	7.44 ± 13.86*
4: HG 74.88 g/kg/day	21.3 ± 6.72	41.12 ± 9.00	55.58 ± 9.62	37.95 ± 11.26	22.23 ± 11.69	3.48 ± 4.98

*(p (1-2), (1-3), (1-4) < 0.05 except for *, p (2-3), (2-4), (3-4) > 0.05)*

The percentages of increase in mouse paw volume in groups 2, 3, and 4 differed insignificantly (p>0.05) but were statistically significantly lower than the control group at each study time point (p<0.05), except for the value of the group receiving HG at a dose of 24.96 g/kg/day at 48 hours. Nevertheless, the differences between the HG groups and the diclofenac group were not significant (p>0.05).

Table 3. Percentages of reduction in mice's paw edema compared to that of the control group

Group (n = 10)	Percentages of reduction in mice's paw edema at differentiated study time points (%)					
	1 hr	2 hrs	4 hrs	6 hrs	24 hrs	48 hrs
2: Diclofenac sodium 24 mg/kg/day	49.30	31.82	37.37	56.94	60.80	52.65
3: HG 24.96 g/kg/day	46.61	24.31	27.50	36.16	44.20	19.9
4: HG 74.88 g/kg/day	52.16	36.11	33.57	37.39	39.28	62.55

Overall, mice in all three groups (2, 3, and 4) indicated impactful rates of reduction in paw edema. In which, the group treated with HG 24.96 g/kg/day had lower rates of reduction in paw edema compared to those of the ones treated with HG 74.88 g/kg/day and diclofenac sodium 24 mg/kg/day.

Figure 1. Paws of mouse #7 (the control group) before inducing inflammation

Figure 2. Paws of mouse #14 (group 2) after 2 hours of inflammation induction

Figure 3. Paws of mouse #26 (group 3) after 4 hours of inflammation induction

Figure 4. Paws of mouse #34 (group 4) after 6 hours of inflammation induction

Figure 5. Paws of mouse #24 (group 3) after 24 hours of inflammation induction

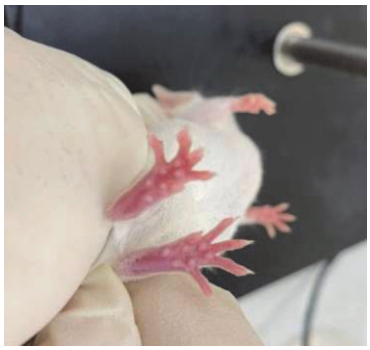

Figure 6. Paws of mouse #39 (group 4) after 48 hours of inflammation induction

After the inflammation was induced, the mice's right hind paws became swollen, red, and larger than their other paws. Nevertheless, at 48 hours after the inflammation, the mice's paws had shrunk back to near their normal sizes.

Cotton pellet granuloma method

The anti-chronic inflammatory activities of HG liquid extract on a mouse model of granulomatous disease induced by cotton pellets are shown in Table 4.

Table 4. Weight of granulomas in mice

Group (n = 10)	Weight of granulomas (mean ± SD, mg)			Percentages of granuloma weight loss compared to the control group (%)	
	Before implantation	Wet	Dried	Wet	Dried
1: control, distilled water	30.15 ± 0.95	526.95 ± 65.19	71.2 ± 16.82	-	-
2: prednisolone 7.2 mg/kg/day	30.45 ± 0.41	329.83 ± 45.26	51.01 ± 7.36	37.41	28.36
3: HG 24.96 g/kg/day	30.07 ± 0.73	314.57 ± 46.65	54.50 ± 9.97	40.30	23.46
4: HG 74.88 g/kg/day	30.1 ± 0.61	346.38 ± 33.66	54.82 ± 9.63	34.27	23.01
p(1-2),(1-3),(1-4)	> 0.05	< 0.001	< 0.01		

Both prednisolone and HG liquid extract at the tested doses reduced the weight of wet and dried granulomas compared to those of the control group, with p values < 0.001 and < 0.01, respectively. HG liquid extract at regimen doses of 24.96 and 74.88 g/kg/day × 7 days showed similar anti-inflammatory effects to prednisolone 7.2 mg/kg/day × 7 days, as evidenced by study indices that differed only slightly from that of the reference group (p > 0.05).

DISCUSSION

Carrageenin is the name given to a mucopolysaccharide, an extract from the red algae *Chondrus crispus* found along the rocky areas of the Atlantic coast of the British Isles, Europe, and North America. It was discovered by the British pharmacist Stanford in 1862. Later, it was named carrageenan to match the suffix "-an" for polysaccharides. Carrageenan causes acute, non-immune inflammation, with the main symptoms comprising edema, increased pain sensitivity, and skin redness. These symptoms appear immediately after subcutaneous injection, due to the action of inflammatory substances such as bradykinin, histamine, tachykinin, complement, and reactive oxygen species. These inflammatory substances can be produced at the site of injury or by invading cells. Neutrophils readily migrate to inflamed sites and can produce inflammatory reactive oxygen species and others [16].

In this study, the chosen reference drug was diclofenac sodium, an NSAID that exerts its acute anti-inflammatory effect primarily by inhibiting

cyclooxygenase enzymes (COX-1 and COX-2). This mechanism prevents the synthesis of prostaglandins - chemical mediators that cause swelling, heat, redness, and pain at the site of inflammation. Therefore, it helps reduce acute inflammatory responses and relieve pain. The dose of diclofenac sodium administered to mice (24 mg/kg/day) was extrapolated from the typically effective dose in humans (100 mg/day or 2 mg/kg/day for a 50 kg person) [17]. The results revealed that mice in all groups exhibited swelling, redness, and warmth in their right hind paws, with the strongest inflammation and edema occurring 4 hours after injection and then gradually decreasing. The control group showed the strongest signs of inflammation and swelling due to the lack of intervention, while others in the HG and diclofenac groups indicated lower levels of inflammation and edema. These symptoms are consistent with the results of determining mouse paw volumes, in which the paw volume values of the control group reached the highest and statistically significantly higher than the other ones, except for the paw volumes at 48 hours because the levels of inflammation in all four groups decreased sharply and were close to normal values. Similarly, the rates of increase in mice's paw volumes at the study points compared to those before inflammation in two HG groups were significantly lower than those of the control group, except for the value of group 3 at 48 hours, and not remarkably different from the diclofenac sodium one. These demonstrate that, at both tested regimen doses of 24.96 and 74.88 g/kg/day x 7 consecutive days, the HG liquid extract had remarkable anti-inflammatory effects, and these were equivalent to that of diclofenac sodium 24 mg/kg/day.

No studies have been published on the anti-inflammatory effects of a combination of the five medicinal herbs mentioned above like HG liquid extract. Our results are consistent with several studies evaluating the anti-inflammatory effects of medicinal ingredients when used individually. For instance, oral administration of *Dracaena cochinchinensis* at doses of 0.14, 0.56, and 1.12 g/kg inhibited rat paws' edema, increased pain sensation, cyclooxygenase-2 (COX-2) protein expression, or preprotachykinin-A mRNA expression with carrageenan-induced inflammation or sciatic nerve damage (chronic spasm damage) [3]. Lawsone, an active compound isolated from *Lawsonia inermis* leaves, had similar analgesic and anti-inflammatory effects to aspirin in reducing carrageenan-induced hind leg edema in rats [5]. Vo Thi Thu Ha (2018) demonstrated the good anti-inflammatory effects of some flavonoid isolated from *Artemisia vulgaris,* on a mouse paw edema model [7]. Nguyen Thi Hong Ngoc et al. in 2023 demonstrated that turmeric extract had anti-inflammatory effects on a carrageenan-induced mouse paw edema model at doses of 0.4 and 0.8 g/kg. The dose of 0.8 g/kg showed equivalent anti-inflammatory effects to that of diclofenac 0.05 g/kg [9].

The formation of cotton-pellet-induced granulomas is the most appropriate method for studying the efficacy of drugs against the proliferative phase of inflammation. Subcutaneous implantation of a cotton pellet in rodents leads to granulomatous formation at the implantation site. Initially, fluid and protein substances accumulate along with infiltration of macrophages, neutrophils, and fibroblasts, and proliferation of small blood vessels, which are the basic origin of the red, highly vascular mass known as granulation tissue. The granuloma formed by day 7 is characterized by the formation of a vascularized fibrous capsule containing fibroblasts and infiltrating mononuclear cells which are rich in N-acetyl-β-d-glycosaminidase (NAG). This method has been widely used to assess the infiltration, secretion, and proliferative phases of subacute inflammation. The amount of fluid absorbed by the cotton pellet significantly affects the wet weight of the granuloma, while the dry weight correlates well with the amount of granuloma tissue formed. Systemic treatment of animals with a corticosteroid like dexamethasone or an NSAID such as indomethacin resulted in inhibition of granuloma weight gain, NAG activity, and nucleic acid concentrations [14],[15],[18].

In the second experiment, we used prednisolone as the reference drug with the main mechanisms include inhibition of the enzyme phospholipase A2, reduced release of inflammatory mediators (prostaglandins, leukotrienes, cytokines), stabilization of lysosomal membranes, and reduced leukocyte migration to the site of inflammation. The dosage of prednisolone in mice (7.2 mg/kg/day) was extrapolated from its usual therapeutic dose in humans, 5-60 mg/day, and the average human dose (30 mg/day) was chosen [17]. The results revealed that, at doses of 24.96 and 74.88 g/kg/day for 7 consecutive days, HG liquid extract significantly reduced the weights of wet and dry granulomas compared to the control group. This effect was similar to that of prednisolone 7.2 mg/kg/day for 7 days, with insignificant differences among the three groups. This demonstrates that HG liquid extract has high anti-inflammatory effects at the two tested doses, exhibited by reducing the formation of both fluid and protein in the early stages and the amount of tissue in the later stages of granulomas.

Several studies have also evaluated the anti-inflammatory effects of the individual medicinal components on experimental granuloma models when used alone. The anti-inflammatory activities of curcumin and other semisynthetic analogues (sodium curcumin, diacetyl curcumin, triethyl curcumin, and tetrahydro curcumin) were demonstrated by studying carrageenan-induced paw edema and cotton pellet granuloma in

experimental rats [8]. S.K. Afsar et al. (2013) found that the methanolic extract of *Artemisia vulgaris* leaves exhibited significant anti-inflammatory activity at doses of 200 and 400 mg/kg, with the 400 mg/kg dose showing significantly better results compared to the control group ($p<0.05$) [15].

The results from two experiments above suggest that the herbal remedy Huyet giac to moc chi giap hoa thang has its powerful anti-inflammatory effects against both acute and chronic inflammation at doses of 24.96 and 74.88 g/kg/day for 7 consecutive days. Also, using the dose three times higher than the equivalent dose in humans did not result in significant differences in its efficacy.

CONCLUSION

At the two tested doses, 24.96 and 74.88 g/kg/day for 7 days, the HG liquid extract showed impactful anti-inflammatory activities in both carrageenan-induced paw edema and cotton pellet granuloma-induced mouse models. Specifically, the HG extract significantly reduced the level of inflammation and paw edema in mice compared to those of the control group, a similar effect to that of diclofenac sodium 24 mg/kg/day for 7 days. Simultaneously, the HG liquid extract remarkably reduced the weight of both dry and wet granuloma nodules compared to those of the control group, akin to the effect of prednisolone 7.2 mg/kg/day for 7 days. Increasing the HG extract dose threefold (74.88 g/kg/day) resulted in no significant differences in the anti-inflammatory effect compared to the 24.96 g/kg/day dose and was similar to those of the reference drugs. These results provide a basis for further research and development of pharmaceutical products from this herbal combination.

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