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ANTI-INFLAMMATORY EFFECTS OF ETHANOL EXTRACT FROM *HOMALOMENA PIERREANA* RHIZOME

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Summary

Anti-Inflammatory Effects of Ethanol Extract from *Homalomena pierreana* Rhizome

Homalomena has been used in traditional medicine as pain relief in rheumatic diseases. *Homalomena pierreana* (HP) is a rare species of the Araceae family found in Vietnam. This study aimed to investigate the anti-inflammatory effects of ethanol extract from HP rhizome by using lipopolysaccharide (LPS)-induced nitric oxide (NO) production in murine macrophage cell line RAW 264.7 and a carrageenan-induced paw edema test in mice. The results revealed that HP extract inhibited NO production (up to 68.7%) at 100 µg/mL in a concentration-dependent manner in LPS-stimulated RAW 264.7 macrophages. The NO production inhibitory activity of HP extract was equivalent to a positive control, dexamethasone, at the concentration of 50 µg/mL. Furthermore, the extract at doses of 390 mg/kg and 780 mg/kg (equivalent to 1.25 and 2.5 g raw materials) attenuated 25.9% to 35.6% of paw inflammation after 3 hours of carrageenan injection as compared to control. In conclusion, this is a first report to determine the anti-inflammatory effects of ethanol extract from HP rhizome. The follow-up studies should aim at elucidating the anti-inflammatory mechanisms of HP rhizome to achieve beneficial effects of this plant for medicine usages.

Keywords: *Homalomena pierreana, Lipopolysaccharide-induced NO production, RAW 264.7 macrophages, Carrageenan-induced mouse paw edema.*

1. Introduction

Homalomena has been used in traditional medicine as a bone tonic, rheumatic remedy and pain relief [1]. *Homalomena pierreana* Engl. (HP) [Vietnamese name: Than phuc, another scientific name: *Homalomena griffithii* (Schott) Hook.f.] is a rare species of Araceae family in Vietnam with little research on chemical composition till now. HP has been reported distributed in Bach Ma National Park (Thua Thien-Hue province) and southern Vietnam located in Phu Quoc National Park (Kien Giang province) and identified by DNA barcode sequence (trnL intron and trnL-trnF IGS sequences) [2],[3]. Successful clonal propagation of HP has made this species more attractive to study for their chemical composition as well as potential for medicine usages [4].

Nonetheless, there are no exclusive scientific investigations which have been carried out to search for anti-rheumatic activity of this plant. As rheumatoid arthritis is the most common form of inflammatory arthritis, medications that suppress joint inflammation such as non-steroidal anti-inflammatory drugs and glucocorticoids are frequently used as first-line therapeutic agents for treatment of the symptoms. Therefore, this study has been designed to explore *in vitro* and *in vivo* anti-inflammatory effects of HP in order to provide a scientific evidence for benefit use of this plant.

2. Materials and Methods

2.1. Plant materials and extraction

HP rhizome was collected in Phu Quoc National Park, Kien Giang province on December, 2022. The plant was identified and scientifically named by Mr. Cao Ngọc Giang of the Research Center of Ginseng and Medicinal Materials in Ho Chi Minh City (sample code: ĐD 042023). Dried powdered material was extracted (The ratio is 1: 15 w/v) with 45% ethanol at room temperature for 48 h in a percolator apparatus. The extract was collected at a rate of 1 mL/min and concentrated using a rotary evaporator at 60°C under reduced pressure to obtain crude condensed extract (HP extract) with moisture content of 18.1%. The yield of extraction was 31%. HP extract at oral doses of 390 mg/kg and 780 mg/kg (equivalent to 1.25 and 2.5 g raw materials) were selected for *in vivo* study.

2.2. Animals

Six-week-old male *Swiss albino* mice (25 ± 2 g) were purchased from the Institute of Vaccines and Medical Biologicals, Nha Trang, Vietnam.

The mice were habituated to the laboratory animal room for at least one week before the experiment. Food and water were available *ad libitum*. Housing was thermostatically maintained at 26 ± 1°C and a 12-h light-dark cycle (lights on: 07:00 - 19:00). The administered volume of the extract was 10 mL/kg mouse body weight.

2.3. Cells and Chemicals

RAW 264.7 macrophages were obtained from the American Type Culture Collection (ATCC, TIB-71, BSL 2). Dulbecco's Modified Eagle Medium (DMEM, Gibco) and Griess reagent (Invitrogen) was supplied from Thermo Fisher Scientific (USA). Trypsin 10X (HyClone™ Trypsin Protease) was bought from Cytiva. Lipopolysaccharide (LPS) from *E. coli* 0111: B4, fetal bovine serum, penicillin-streptomycin (10000 units), dexamethasone, and carrageenan were purchased from Sigma-Aldrich (USA). Celecoxib was taken from the commercial drug Celebrex® of Pfizer.

2.4. Cell culture

Cells were grown in DMEM (4.5 g/L of D-glucose, L-glutamine) supplemented with 10% fetal bovine serum (v/v) and 1% P/S (Penicillin [100 U/mL]/Streptomycin [100 µg/mL]) in TC-75 cell culture flasks. Cells were incubated at 37°C in a 5% CO_2 atmosphere and passaged every 24 h. Cultured cells were removed from the culture substrate by treatment with 0.25% trypsin. Next, cells were suspended in new medium and inoculated at a proper density in 96-well plates. Cells at 4th passage were used in the study.

2.5. MTT assay for cell viability

For determination of cell viability, 5 × 10^4 RAW 264.7 cells per well were seeded in 96-well plates (100 µL/well DMEM) and incubated overnight at 37°C and 5% CO_2. On the next day, cells were then treated with various concentrations of HP extract for 24h at 37°C and 5% CO_2. After treatment, HP extract-treated cells were incubated with the MTT solution (0.5mg/mL) for 4h at 37°C and 5% CO_2. After discarding the supernatant, the formazan product that formed in the cell was dissolved in 100 µL of DMSO (0.5%, v/v), and the absorbance was measured at 570nm (reference: 630 nm) using an Epoch microplate spectrometer (BioTek, USA). Untreated cells were performed in parallel and treated with medium without the addition of HP extract. Assays were performed in triplicate [5].

$$\%\ cell\ viability = \left(\frac{Ab_{extract treated\ cell} - Ab_{blank\ control}}{Ab_{untreated\ cell} - Ab_{blank\ control}}\right) \times 100\ (\%)$$

2.6. NO Assay

NO content was analyzed indirectly by measuring the supernatants of cultured RAW 264.7 cells for nitrite using the Griess reagent (1% sulfanilamide in 5% phosphoric acid, 1% α-naphthylamide in H_2O). 5 × 10^4 RAW 264.7 cells per well were seeded in 96-well plates (100 µL/well DMEM) and incubated overnight at 37°C and 5% CO_2. RAW 264.7 cells were then treated with various concentrations of HP extract (50 µL/well) or the positive control dexamethasone (at 50 µg/mL ≈ 127,4 µM) plus 50 µL of LPS (4 µg/mL) for 24h at 37°C and 5% CO_2. After 24 h, 75 µL of the supernatants from each well were transferred to a new 96-well-plate and later used for the analysis of nitrite levels as a marker for nitric oxide (NO·) production in a Griess assay. Cell culture media (75 µL) was mixed with 10 µL of Griess reagent plus 65 µL of distilled water in a 96-well plate, incubated at room temperature for 30 min, and then measured at 548 nm using an Epoch microplate spectrometer (BioTek, USA). LPS-untreated cells were performed in parallel. Assays were performed in triplicate. NO release in cell media was calculated based on linear equation of NO ($y = 267.65x - 11.986$, $R^2 = 0.9962$) in which y value was NO concentration (µM) and x value was absorbance at 548 nm [5].

2.7. Carrageenan-induced mouse paw edema test

Mice were randomly divided into 4 groups (8 mice/group). Each group of animals was orally administered distilled water (control group), HP extract (test groups at the doses of 390 mg/kg and 780 mg/kg), or celecoxib 25 mg/kg (reference group). The administration was performed at 1 h, 5 h and 23 h after carrageenan injection. Mice were received intraplantar injections of 50 µL of carrageenan suspension 1% (w/v in saline) into the hind right paw [6]. The right hind paw was marked in order to always immerge it to the same extent in the measurement chamber. The volume of the mouse right hind paw was measured by using a plethysmometer specially modified for small volumes (Ugo Basile, Italy) immediately before subplantar injection, 3 h, and 24 h thereafter. The increase in paw volume was calculated by subtracting the initial paw volume (basal, V_0) to the paw volume measured at each time point ($V_{3\,h}$, $V_{24\,h}$).

The inhibition of paw inflamed swelling (edema) of test groups or reference group was calculated compared to control as followed:

Inhibition of paw inflamed swelling (%)

= (X-Y)/X ×100

(X: Paw inflamed swelling of control, Y: Paw inflamed swelling of test groups or reference group).

2.8. Statistical analysis

The data were expressed in terms of mean ± SEM (Standard error of the mean). The IC_{50} value was determined based on the equation illustrating the correlation between the test substance concentration and the percentage of NO production inhibitory

activity using Graphpad Prism software (USA). All statistical analyses were conducted using SigmaStat version 3.5 software (USA). One-way analysis of variance (ANOVA) followed by Student-Newman-Keuls Method or t-test were used to examine the significant difference among groups. *P* values of less than 0.05 were considered statistically significant.

3. Results

3.1. Effect of HP extract on cell viability of RAW 264.7 cells

As shown in Figure 1A, compared to the control, the cell viability of RAW 264.7 cells treated with HP extract at concentrations of 12.5 μg/mL up to 1000 μg/mL was 115.29 ± 5.05% and 53.89 ± 1.26% (statistical difference with $p = 0.029$), with concentration-dependent inhibition of cell proliferation. The results in Figure 1B showed that the cell viability of LPS-treated RAW 264.7 cells exposed to HP extract at concentration of 100 μg/mL was 77.32 ± 2.92% (statistical difference with $p = 0.04$ as compared to the control).

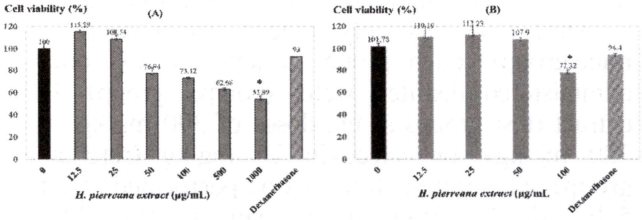

Fig. 1. Effect of HP extract on the cell viability of LPS-untreated RAW 264.7 cells (A) and LPS-treated RAW 264.7 cells (B). Cells were treated with HP extract (0-1000 μg/mL) for 24 h, and cell viability was measured by the cell viability assay. Compared to the control group, $*p < 0.05$.

3.2. HP extract suppressed LPS-induced nitric oxide production in RAW 264.7 cells

The stimulation of RAW 264.7 cells with LPS increased NO production. Figure 2 showed that, as compared to the control group, HP extract significantly inhibited the release of LPS-stimulated NO in the concentration-dependent manner at a concentration range from 12.5-100 μg/mL ($p < 0.05$). The NO production inhibitory activity of HP extract was equivalent to the positive control dexamethasone at the concentration of 50 μg/mL. The IC_{50} value 45.11 μg/mL was determined based on the equation ($y = 24.737\ln(x) - 44.551$, $R^2 = 0.9837$) illustrating the correlation between the test substance concentration and the percentage of NO production inhibitory activity.

3.3. HP extract suppressed carrageenan-induced mouse paw edema

Intraplantar injection of carrageenan in mice resulted in an increase in paw volume [Table 1] after 3 h and 24 h. Administration of the reference drug celecoxib (25 mg/kg) markedly reduced the paw edema at 3 h and 24 h after an injection of carrageenan (inhibition of 42.81% and 32.05%, respectively as compared to control). HP extract at the doses of 390 mg/kg and 780 mg/kg (equivalent to 1.25 and 2.5 g raw materials) exerted significant inhibition of 3 hour-post-carrageenan edema, reached from 25.9% to 35.6% as compared to control. There was no significant difference between the effect of HP extract at the dose of 780 mg/kg and celecoxib. No significant differences were found between two doses of HP extract.

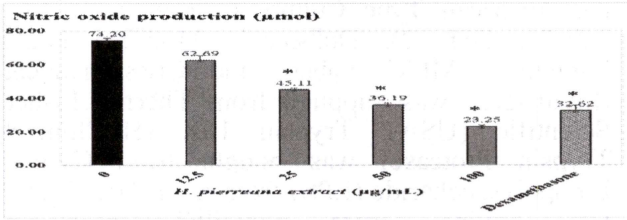

Fig. 2. NO production in LPS-stimulated RAW 264.7 cells after treatment with HP extract. Cells were stimulated with LPS (4 μg/mL) and treated with HP extract at a concentration range from 12.5-100 μg/mL for 24 h. The analysis of nitrite concentration, proportional to the NO released in cell supernatant by the Griess method. Compared to the control group, $*p < 0.05$.

Table 1. Effects of HP extract on hind paw edema induced by carrageenan in mice. (%): Percentage of inhibition of paw inflamed swelling. $***p < 0.001$ compared to the control group; $^{\#\#}p < 0.01$, $^{\#}p < 0.05$ compared to the reference group (one-way ANOVA followed by Student-Newman-Keuls Method).

Group (n= 8)	Doses (mg/kg)	Mouse paw volume (%)	
		3 hours	24 hours
Control	-	103.19 ± 4.62	77.08 ± 4.01
HP extract	390	76.50 ± 3.72**$^{\#\#}$ (25.87%)	68.36 ± 2.90$^{\#}$ (11.32%)
	780	66.45 ± 3.22*** (35.6%)	63.79 ± 5.38$^{\#}$ (17.25%)
Celecoxib	25	59.02 ± 1.70*** (42.81%)	50.84 ± 3.23** (34.05%)

4. Discussion

RAW 264.7 cells are a semi-adherent macrophage-like cell line derived from BALB/c mice, transformed by the Abelson leukemia virus. These cells are commonly used as a model of mouse macrophages for the study of cellular responses [7]. In the study, the survival rate higher than 70% of RAW 264.7 cells in MTT assay was selected for next study. HP extract did not have any cytotoxicity on RAW 264.7 cells upon 24-h exposure at a concentration range from 12.5-100 μg/mL, hence a concentration range less than 100 μg/mL was employed in the following studies.

LPS is a prominent component of Gram-negative bacteria's cell wall that mimics the early phases of the inflammatory response, thereby causing cell to secrete high concentrations of pro-inflammatory cytokines, and inflammatory factors or mediators. Therefore, LPS-induced inflammatory effects in macrophages are widely utilized to screen anti-

inflammatory agents [8]. Since LPS is known to reduce RAW 264.7 cell viability, the cytotoxicity of a mixture of HP extract and LPS was also examined. The results revealed that HP extract at the concentration of 100 µg/mL had no cytotoxic effects on RAW 264.7 cell proliferation but reduced cell viability of LPS-treated RAW 264.7 cells.

When activated by LPS, macrophages release pro-inflammatory mediators and cytokines *via* the toll-like receptor (TLR)4-mediated nuclear factor-B (Nrf2) signaling pathway [9]. LPS-induced macrophages produce excess inflammatory mediators, including cyclooxygenase-2 (COX-2), a key enzyme in prostaglandin E2 (PGE2) synthesis, and inflammatory cytokines such as TNF-α and IL-6 [10]. Dexamethasone, the positive control in this study, is a potent immunosuppressant with the ability to inhibit cytokine responses in activated macrophages, and also inhibits phospholipase A2 in prostaglandin E2 (PGE2) synthesis [11]. In addition, macrophage stimulation by LPS promotes excessive NO release *via* degradation of L-arginine. In the inflammation process, NO is produced by inducible nitric oxide synthase (iNOS) and, as the main pro-inflammatory mediator, plays a key role in the immune system [10]. As a result, LPS-induced NO production in macrophages may be used to evaluate the course of inflammation, and NO production inhibition may have an inhibitory effect on the inflammatory response [12]. In the study, we discovered that HP extract as well as dexamethasone reduced NO production in cells following LPS stimulation, suggesting that HP extract may have a potential anti-inflammatory effect.

IL-6, IL-1β and TNF-α are common pro-inflammatory cytokines produced mainly by macrophages to mediate biological responses related to infection, immunity and inflammation. COX-2 isoform is expressed predominantly in inflammatory cells and upregulated in chronic and acute inflammations, becoming a critical target for many anti-inflammatory agents [13]. It is necessary to find out new agents that could not only alleviate symptoms of inflammatory diseases *via* COX-2 inhibition, but ones which might also reduce gastric epithelial injury. This lead to the further search for HP effects on the cytokine generation of TNF-α, IL-6, and protein expressions of enzymes iNOS and COX-2.

The carrageenan-induced mouse paw edema model is widely used to assess the anti-inflammatory activity of several natural and synthetic compounds. The carrageenan model is typically linked with the activation of the COX pathway since stimulation of phospholipase A2 by carrageenan initiates the early phase of inflammation. Carrageenan-induced edema is caused by dilation of postcapillary venules that result in an exudation of inflammatory fluid and cells and is related to the release of several proinflammatory mediators. The edema developed by carrageenan may be represented by a biphasic curve that develops in the first 6 h, followed by a second phase that starts at 24 h [14]. PGE2 is the main factor for the occurrence of carrageenan-induced inflammation, which occurs in the first phase, up to 6 h after carrageenan injection [14]. Similarly, carrageenan injection induces a significant increased expression of COX-1 and COX-2 between 4 and 24 h afterwards [14]. In the study, HP extract as well as a COX-2 selective inhibitor, celecoxib, markedly reduced paw edema at 3 h after carrageenan injection, suggesting the involvement of COX-2 inhibition. Also, NO release is regulated by both iNOS and eNOS which are both upregulated during the development of the carrageenan-induced paw edema [14]. *In vitro* study on HP extract showed reduced NO production in RAW 264.7 cells following LPS stimulation, suggesting the involvement of NO in the inhibitory effect of HP on paw swelling. Further study is necessary to clarify the mechanism of action of *H. pierreana.*

Chemical investigation of HP resulted in the isolation of six known sesquiterpenoids, namely 1β,4β,6α-trihydroxyeudesmane, 1β,4β,7α-trihydroxyeudesmane, oplodiol, bullatantriol, homalomenol A, and oplopanone [15]. GC (FID) and GC-MS analysis have revealed that α-bisabolol (20.9%), bicyclogermacrene (12.8%), (*E*)-nerolidol (8.0%) as the quantitatively significant compounds of the essential oil (0.2%/fresh weight) from HP rhizome collected in Pu Mat National Park (Nghe An province) [16]. Sesquiterpenes, volatile compounds, have a large range of biological properties and are potent inhibitors and modulators of inflammation, targeting inhibition of NF-kB signaling or disruption of NO production [17]. Therefore, sesquiterpenoids may be active components involved in the anti-inflammatory effect of HP.

Taken together, the findings support the follow-up studies of HP, which may provide a potential scientific evidence for benefit effect in treatment of rheumatic diseases.

5. Conclusion

In conclusion, this study provides the first evidence that ethanol extract from *Homalomena pierreana* rhizome suppresses the inflammatory response as shown using LPS-induced NO production in murine macrophage cell line RAW 264.7 and carrageenan-induced paw edema test in mice. Therefore, *Homalomena pierreana* may be a promising alternative anti-inflammatory agent.

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APPLYING A SOLID DISPERSION SYSTEM FOR ENHANCING THE DISSOLUTION OF LIGNANS-ENRICHED FRACTION FROM *SCHISANDRA SPHENANTHERA* EXTRACT

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Summary

Applying a Solid Dispersion System for Enhancing the Dissolution of Lignans-Enriched Fraction from *Schisandra sphenanthera* Extract

This paper aimed to improve the dissolution of biologically active lignans from *Schisandra sphenanthera* (SS) *via* solid dispersion system (SDS) formulation. The lignans-enriched fraction was obtained from an ethylacetate-soluble extraction, is poorly soluble in water. To ameliorate the dissolution of major lignans from this extract, SD formulation was prepared with the combination of Tween 80 and PVP K30 as carriers by using the solvent evaporation method. The optimal formulation containing 1% Tween 80 and 4% PVP K30 showed the release of over 70% of schisandrin (SC) and gomisin B (GB) contents in dissolution profiles after 30 minutes, the dissolution of schisandrin A (SCA) was simultaneously improved in comparison with pure extract in similar condition testing. The combination of hydrophilic polymer and surfactant in the SDS formulation could be effective in enhancing the dissolution of the active lignans from SS. This is a promising strategy to improve the bioavailability of the drug.

Keywords: *Schisandra sphenanthera, Lignans, Solid dispersion, Dissolution, Formulation, Solubilization.*

1. Introduction

Phytochemical investigations of *Schisandra sphenanthera* Rehd. et Wils (SS) have reported a variety of natural constituents including lignans, triterpenes, volatile oils, and polysaccharides [1]. Pharmacological studies have shown SS possessed wide-range bioactivities, such as antitumor, antioxidant, anti-inflammatory, osteoblastic, immune regulation, neuroprotective, kidney protection, hepatoprotective, and antiviral