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In vivo Anti-Inflammatory Activity of *Derris reticulata* Ethanol Extract

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ABSTRACT

Derris reticulata Craib. has been used in Thai traditional medicine to treat various inflammatory diseases. Recently, *D. reticulata* extract has been reported to exert anti-inflammatory activity by inhibiting nitric oxide (NO) secretion and the expression of various mRNAs in stimulated macrophage cells. However, studies of its anti-inflammatory effects in an animal model have not been performed. The study evaluated the *in vivo* anti-inflammatory activity of an ethanol extract of the wood of *D. reticulata* (DRE). The anti-inflammatory effect of DRE on ethyl phenylpropiolate (EPP)-induced ear edema and carrageenan-induced paw edema in rats was studied. Furthermore, the NO scavenging activity and phytochemical contents of the DRE were determined. The results showed that the most abundant phytochemical compound was lupinifolin, followed by total proanthocyanidin, total phenolic compounds, and total flavonoids. DRE also exhibited NO scavenging activity (15.8 - 49.7%) while 1%, 5%, and 10% DRE promoted a significant reduction of inflammation in EPP-induced rat ear edema (35.0 - 52.5%) and carrageenan-induced rat paw edema (28.1 - 41.0%). The study revealed that DRE possesses potent anti-inflammatory properties in animal models. The results confirm the efficacy of the traditional use of *D. reticulata* in the treatment of inflammatory diseases.

Keywords: *Derris reticulata*, Anti-inflammatory activity, Ear edema, Paw edema, *In vivo* studies

Introduction

Inflammation is one of the body's most important physiological responses, by which it protects itself against infection and injurious stimuli.[1-2] Normally, inflammatory processes develop through the production of proinflammatory agents, such as IL-1β, TNF-α, and prostaglandin E2 (PGE_2).[3] Reactive oxygen and nitrogen species are also released during the process of inflammation and play a central role in the protective effect against invading pathogens.[4-7] It is widely known that excessive or chronic inflammation leads to a number of pathological conditions.[8-10] Nowadays, there is a growing interest in the anti-inflammatory capability of materials with natural origin especially plant-derived substances.

Derris reticulata Craib. (Leguminosae) is a medicinal plant known locally in Thai as cha-em-nuea. The wood of this plant has been used in Thai folk medicine for throat diseases and diabetes, and as a cough suppressant, expectorant, and tonic agent.[11-12] Previous studies have shown that this plant also exerts estrogenic,[13] anticariogenic,[14] antibacterial, antiviral, anti-cancer, α-glucosidase inhibitory, antidiabetic, and antioxidant activities.[11, 15-16] Moreover, it has also been shown that ethanol extract from the stem of *D. reticulata* significantly reduces nitric oxide (NO) production and the mRNA expression of pro-inflammatory cytokines of macrophages, which reveals its anti-inflammatory effect.[17]

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To the best of our knowledge, no previous pharmacological study has investigated the anti-inflammatory potential of *D. reticulata* in an animal model. The study evaluated the *in vivo* anti-inflammatory effect of an ethanol extract of the wood of *D. reticulata* (DRE). The study also examined the phytochemical contents and the NO scavenging activity of DRE.

Materials and Methods

Preparation of DRE

The stem woods of *D. reticulata* were collected from Bangkok, Thailand in October 2016. The plant was identified by a botanist, Dr. Oratai Neamsuvan. A voucher specimen (CB-C26) was deposited at the Faculty of Traditional Thai Medicine, Prince of Songkla University (Songkhla, Thailand). The wood of *D. reticulata* was washed, cut into smaller pieces, and oven-dried at 60°C for 120 h. The dried wood of *D. reticulata* was ground into a fine powder (500 g) and extracted by maceration in ethanol (5 L) at room temperature for 7 days. The filtrate was collected and concentrated under reduced pressure in a rotary evaporator at 60°C. The concentrated extract was dried in a water bath at 45°C. The percentage yield of the DRE was recorded.

HPLC analysis of lupinifolin content

The HPLC method used to analyze the lupinifolin content in the DRE was modified from a previous study.[18] The purification method of lupinifolin was mentioned previously.[19] The DRE was dissolved in methanol (HPLC grade, Merck, Darmstadt, Germany) at a concentration of 300 mg/mL. The DRE solution was filtered through a nylon membrane. The HPLC analysis was performed using an Agilent Technologies (Karlsruhe, Germany) system with a binary pump, auto injector, column thermostat, and variable wavelength detector. The stationary phase was a Hypersil ODS (4.0 × 250 mm i.d., 5 µm) connected to a cartridge guard column (Agilent Technologies, Karlsruhe, Germany). The compounds were eluted with an isocratic

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system consisting of methanol (HPLC grade, Merck, Darmstadt, Germany) and 15% glacial acetic acid (AR grade, Lab scan) in DI water (80:20, v/v) at a flow rate of 1.0 mL/min. The column temperature was 25°C with the detector wavelength at 254 nm. The injection volume of each sample was 10 µL. The chromatograms were processed by Chemstation software (Agilent Technologies, Karlsruhe, Germany).

Determination of total phenolic content

The total phenolic content was determined using the Folin-Ciocalteu method.[20] The absorbance was detected at 760 nm using a Sunrise™ Microplate reader (Tecan Group Ltd, Switzerland). The results were expressed as mg gallic acid (Sigma-Aldrich, USA) equivalent per gram of extract.

Determination of total flavonoids content

The total flavonoid content was determined according to the method in previous study.[21] The absorbance was measured at 510 nm. The total flavonoid content in the DRE was determined using a standard curve prepared with catechin (Sigma-Aldrich, USA). The total flavonoid content of the DRE was reported as mg catechin equivalent per gram of extract.

Determination of total proanthocyanidin content

The total proanthocyanidin content was assessed using the method mentioned previously.[22] The absorbance was detected at 500 nm. The total content of proanthocyanidin in the DRE was reported as mg per gram catechin equivalent.

NO scavenging assay

The method described by Basu and Hazra [23] was used to assess the NO scavenging effect of DRE. The absorbance was measured at 540 nm. The nitrite generated, in the presence or absence of the DRE solution was compared to a sodium nitrite calibration curve.

In vivo anti-inflammatory activity

Experimental animals

Male Wistar rats (90-140 g) were used in the study. Five rats were housed in each cage with free access to food and water. The rats were kept in a temperature controlled room (22 ± 2°C), with 12:12 h light and dark cycle and relative humidity of 55 ± 10%. The animals were acclimatized to the laboratory condition for one week before conducting any studies. All experimental procedures were approved by the Animals Ethical Committee of Prince of Songkla University (MOE 0521.11/060).

Ethyl phenylpropiolate (EPP)-induced ear edema in rats

Twenty eight male Wistar rats were randomly divided into five groups. Ear edema was induced by topical application of 5% ethyl phenylpropiolate (EPP) (Sigma-Aldrich, USA) in a volume of 20 µL to the inner and outer surfaces of the right ear.[24] Three different treatments, acetone (control group), DRE at concentrations of 1%, 5%, and 10% w/v, and 5% phenylbutazone (Sigma-Aldrich, USA), were applied in the same manner in a volume of 20 µl, 30 min before the EPP treatment. The thickness of the ear was measured using a pocket thickness gauge (Mitutoyo, Japan) prior to treatment and at 30, 60, and 120 min after EPP application. The anti-inflammatory activity was calculated as the inhibition of the ear edema formation compared to that of the control group.

Carrageenan-induced paw edema in rats

Thirty Wistar rats were randomly allocated to five groups of six rats each, comprising a control group (oil base; a mixture of 80% coconut oil and 20% tween 20), the DRE treatment groups (1%, 5%, and 10% w/v in oil base), and a 5% phenylbutazone group. The different treatments were applied topically to their right hind paw to the appropriate groups, 1 h before a subplantar injection of 100 µL of freshly prepared suspension of 1% carrageenan (Sigma-Aldrich, USA) in normal saline. The carrageenan was administered into their right hind paw to induce paw edema. The paw volume was measured by a plethysmometer (Harvard Apparatus, USA) before treatment and at 1, 2, and 3 h after the injection of carrageenan.

Statistical analysis

All data are presented as mean ± standard error of the mean (SEM). The data were assessed by analysis of variance (ANOVA) followed by Dunnett's test. A *P* value of less than 0.05 was considered as statistically significant. All the calculations were performed using the SPSS software package for Windows.

Results and Discussion

Phytochemical contents of DRE

The phytochemical analysis showed that lupinifolin was the most abundant compound in the DRE (Table 1). In addition, the DRE was rich in proanthocyanidins, total phenolics, and total flavonoids. A representative chromatogram of the DRE is shown in Figure 1.

Table 1: Contents of phytochemical compounds in DRE

Phytochemicals	Contents (mg/g)
Total phenolics	182.49 ± 2.61
Total flavonoids	114.98 ± 4.54
Proanthocyanidins	203.47 ± 2.14
Lupinifolin	240.25 ± 0.10

Values are the mean ± SEM (n = 3). Lupinifolin was analyzed by HPLC.

NO scavenging activity of DRE

As shown in Figure 2, DRE at concentrations of 0.0625 - 2.5 mg/mL exhibited NO scavenging activity by 15.8 - 49.7%. The maximum effect of DRE was noted at 0.5 mg/mL; thereafter the NO scavenging activity gradually decreased.

In vivo anti-inflammatory activity of DRE

Topical application of EPP induced a progressive swelling of the rats' ears, reaching a maximum effect at 1 h, after which the ear swelling gradually decreased. Phenylbutazone and DRE significantly suppressed the EPP-induced rat ear edema at various time points: 5% DRE and 5% phenylbutazone significantly reduced ear edema at 1 h whereas 1% DRE significantly reduced ear edema at 1 and 2 h. Interestingly, 10% DRE significantly reduced the ear edema at all the measurement times (Table 2).

The subplantar injection of carrageenan resulted in a cumulative swelling of the rats' paws, the maximum effect of which was reached at 3 h. However, the effect of carrageenan was significantly inhibited by the topical application of 5% phenylbutazone and 1% DRE at all measurement times (Table 3). Topical application of DRE at doses of 5% and 10% also significantly reduced paw edema; however, this effect dissipated within 2 h.

The study of the effect of DRE on acute inflammation revealed that DRE suppressed EPP-induced ear edema and carrageenan-induced paw edema in rats. The application of EPP to the rat ear causes erythema, fluid retention, and edema which are characteristic of acute inflammation. Furthermore, carrageenan induces edema of the rat paw caused by the release of proinflammatory agents including bradykinin, histamine, tachykinins, complement, reactive oxygen and nitrogen species, prostaglandins, and thromboxanes.[25] Effective inhibition of edema formation in both models indicates the topical anti-inflammatory potential of DRE.

During the inflammatory process, NO plays an importance role in vasodilation, which contributes to intensified vascular permeability and extravasation of fluids into the inflamed area [26] and these processes are related to the edema of the inflamed tissue.

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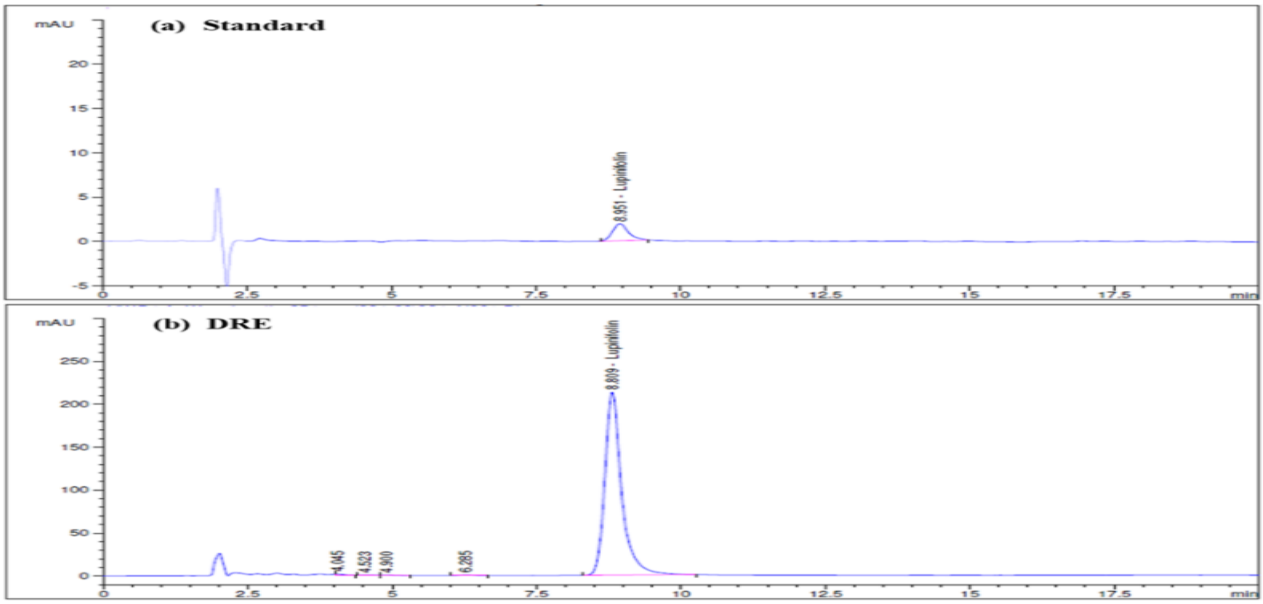

Figure 1: HPLC chromatogram of DRE

Several plant extracts have been shown to exhibit a NO-suppressive effect through direct scavenging of NO radicals, inhibition of nitric oxide synthase (NOS) catalytic activity, and down regulation of NOS protein expression.[27-29] As shown in Figure 2, DRE at concentrations of 0.0625 - 2.5 mg/mL exerted NO scavenging activity of 15.8 - 49.7%. *D. reticulata* has also been shown to exhibit antioxidant activity.[11, 16] It is widely known that inflammatory processes cause an increase in the formation of free radicals.[4-7] In addition, it has been reported that *D. reticulata* extract significantly reduces NO production and the expression of several mRNAs and proteins which are pro-inflammatory cytokines, TNF-α, IL-1 and IL-6, and the enzymes, iNOS and COX-2.[17] These enzymes are responsible for NO and PGE_2 production in macrophage cells. Taken together, it is possible that the anti-inflammatory mechanisms of DRE in animal models are related to the direct scavenging of NO and free radicals and the suppression of the production of NO and pro-inflammatory cytokines at the transcription and translation levels.

The phytochemical analysis revealed that the DRE consisted of lupinifolin, total proanthocyanidins, total phenolic, and total flavonoids (Table 1). Lupinifolin is the major compound found in DRE (Figure 1), and its presence in *D. reticulata* has been previously reported.[30-32] It is widely known that these phytochemical bioactive compounds show anti-inflammatory activities in both *in vitro* and *in vivo* models.[28, 33-35] Moreover, it has been reported that lupinifolin significantly reduces NO secretion and increases the activity of antioxidant enzymes including catalase and superoxide dismutase in castor oil-induced intestinal fluid retention in rats.[36] Therefore, the anti-inflammatory effect of DRE may be related to those phytochemical compounds.

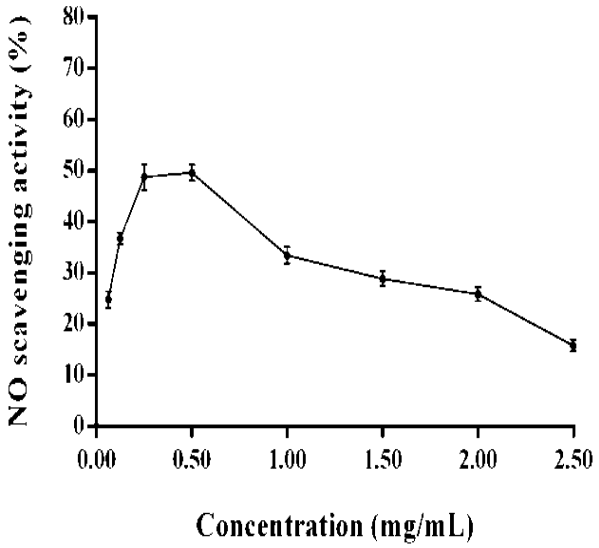

Figure 2: NO scavenging activity of DRE. Values are the mean ± SEM

Table 2: Inhibitory effect of DRE on EPP-induced ear edema

Group	Ear thickness (µm)			Edema inhibition (%)		
	30 min	1 h	2 h	30 min	1 h	2 h
Control (5)	76.0 ± 6.8	118.0 ± 5.8	90.0 ± 9.5	-	-	-
5% Phenylbutazone (6)	63.3 ± 3.3	88.3 ± 4.0*	63.3 ± 4.2	16.7	25.2	29.7
1% DRE (6)	66.7 ± 6.7	68.3 ± 9.5***	58.3 ± 8.3*	12.2	42.1	35.2
5% DRE (6)	53.3 ± 3.3	76.7 ± 4.2**	63.3 ± 10.9	29.9	35.0	29.7
10% DRE (5)	40.0 ± 9.5**	56.0 ± 10.3***	44.0 ± 6.0**	47.4	52.5	51.1

Values are the mean ± SEM, parentheses indicate number of animals. Significantly different from control group: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

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Table 3: Inhibitory effect of DRE on carrageenan-induced paw edema

Group	Edema volume (ml)			Edema inhibition (%)		
	1 h	2 h	3 h	1 h	2 h	3 h
Control (6)	0.24 ± 0.02	0.32 ± 0.03	0.39 ± 0.06	-	-	-
5% Phenylbutazone (6)	0.14 ± 0.01***	0.21 ± 0.01**	0.25 ± 0.01*	41.7	34.4	35.9
1% DRE (6)	0.16 ± 0.01**	0.21 ± 0.03**	0.23 ± 0.03*	33.3	34.4	41.0
5% DRE (6)	0.15 ± 0.02***	0.20 ± 0.02**	0.28 ± 0.03	37.5	37.5	28.2
10% DRE (6)	0.15 ± 0.01***	0.23 ± 0.02*	0.29 ± 0.03	37.5	28.1	25.6

Values are the mean ± SEM, parentheses indicate number of animals. Significantly different from control group: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Conclusion

In summary, an ethanol extract of the wood of *D. reticulata* showed anti-inflammatory activities by the inhibition of EPP-induced ear edema and carrageenan-induced paw edema in rats. This effect of DRE may be related to the lupinifolin, proanthocyanidins, phenolic, and flavonoid compounds which were found in DRE and the mechanism of this effect was related to NO scavenging. Based on these results, DRE represents a potential natural material that will be applicable for the topical healing of inflammatory-related diseases. However, the appropriate topical preparation for therapeutic effect should be further investigated.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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