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Contributed Paper

Assessment of the Anti-inflammatory Activity of Piceatannol-rich Extract from *Senna garrettiana* Heartwood

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ABSTRACT

Senna garrettiana (F. Caesalpiniaceae) is a Thai medicinal plant. Its heartwood is a rich source of piceatannol. In the present study, piceatannol-rich extract (PRE) from *S. garrettiana* containing 39.2% w/w piceatannol was investigated on inflammatory models in rodents. Topical application (2-8 mg/ear) of the PRE inhibited croton oil-induced mouse ear swelling with a maximal suppression of 45.85% and reduced myeloperoxidase activity by 30.21%. Oral administration of the PRE (10-40 mg/kg) dose-dependently produced a significant suppression of rat paw swelling with 75.81% maximal inhibition at 4 h. The PRE (40 mg/kg) decreased the granuloma weight and attenuated joint swelling at day 13 by 27.93% and 69.25%, respectively. The PRE (40 mg/kg) also suppressed the production of PGE_2, TNF-α and IL-1β in the Complete Freund's adjuvant-injected paw to levels comparable with indomethacin (5 mg/kg). These results demonstrated that the PRE possessed anti-inflammatory effect, and its action might be attributed to inhibition of leukocyte infiltration, as well as modulating the production of PGE_2 and pro-inflammatory cytokines, TNF-α and IL-1β.

Keywords: arthritis, ear edema, inflammation, paw swelling, *Senna garrettiana*

1. INTRODUCTION

Senna garrettiana (*S. garrettiana*) (Craib) Irwin et Barneby or *Cassia garrettiana* Craib is a Thai medicinal plant belonging to the Caesalpiniaceae family and known locally as "Samae-sarn". The heartwood of *S. garrettiana* has been used traditionally for relieving constipation, decreasing body temperature, attenuating muscle pain, nourishing blood, and promoting the menstrual discharge [1].

Previous phytochemical investigations of *S. garrettiana* have identified several

different anthraquinones together with nonanthraquinoid constituents as well as various phenolic compounds [2-3]. Many compounds isolated from *S. garrettiana* e.g., cassialoin, chrysophanol-9-anthrone and piceatannol possess anticancer properties [3].

S. garrettiana is an attractive plant. Its heartwood is a rich source of many bioactive constituents, especially piceatannol (*trans*-3,3′,4,5′-tetrahydroxystilbene), a derivative of phenolic stilbene, which possesses a wide range of biological activity including antioxidant, antitumor, as well as anti-inflammatory activities [4]. Piceatannol, an analogue of resveratrol, has beneficial effects similar to resveratrol [4] but with more metabolic stability [5].

A preliminary study of *S. garrettiana* heartwood extract showed antinociceptive activity on mouse writhing induced by acetic acid [6]. Although anti-inflammatory activity of various plants from the genera *Senna* and *Cassia* have been widely explored [3], to our knowledge, the *in vivo* anti-inflammatory activity of *S. garrettiana* has never been reported. It is expected that *S. garrettiana* with a high piceatannol content probably has significant anti-inflammatory potential. Hence, in the present study, the effects of the piceatannol-rich extract from *S. garrettiana* heartwood were investigated on inflammation in rodent models. The levels of prostaglandin E_2 (PGE_2) and the pro-inflammatory cytokines, tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), were measured to elucidate the mechanisms by which the piceatannol-rich extract exerted its anti-inflammatory activity.

2. MATERIALS AND METHODS

2.1 Materials

The heartwood of *S. garrettiana* was obtained locally and identified by Asst. Prof. Dr. Chatchai Wattanapiromsakul, Department of Pharmacognosy and Pharmaceutical Botany, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Thailand. Voucher samples (No. SKP-098190701) were stored at Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Thailand. The heartwood of *S. garrettiana* was cleaned by removing contaminating materials, then ground by an electric blender to give 10 kg of coarse powder that was stored in airtight containers at room temperature. Piceatannol was purchased from Bio-Techne/TOCRIS Inc., USA. All other reagents used in the study were analytical grade.

2.2 Preparation of Piceatannol-rich Extract from *S. garrettiana* Heartwood

The dried powder of *S. garrettiana* heartwood (10 kg) was extracted three times with methanol (36.0 L) at room temperature. This methanol extract was then filtered and evaporated under reduced pressure to obtain the crude extract (427.1 g). A portion of crude methanol extract (217.3 g) was further partitioned to give four fractions as follows: hexane (7.2 g), dichloromethane (18.4 g), ethyl acetate (104.3 g) and aqueous fractions (85.0 g). Analysis of each fraction by thin layer chromatography found that ethyl acetate fraction contained piceatannol. The ethyl acetate fraction (50.0 g) was then separated using a vacuum liquid chromatography method by silica gel using dichloromethane and methanol (8:2) as the solvent system. Thirty-five fractions (F1-F35) were obtained. All fractions were examined by thin layer chromatography analysis and compared with standard piceatannol. The results found that fractions 13-25 contained piceatannol as a major component. Thus, fractions 13-25 were combined to give the piceatannol-rich extract (23.0 g).

2.3 HPLC Analysis of Piceatannol-rich Extract

Quantification of piceatannol in the piceatannol-rich extract was performed by reversed-phase HPLC with a modified method [7]. The method used the Agilent 1100-quarternary pump system. Separation was carried out in the isocratic mode and accomplished with the HyperClone® ODS C18 column (150 × 4.6 mm, 5 µm). The mobile phase was composed of acetonitrile and 0.01 M potassium hydrogen phosphate (25:75, v/v) and pumped at 1 mL/min flow rate with 50 µL of injection volume. The quantification wavelength was set at 320 nm. Piceatannol was identified by its retention time as compared to authentic standard piceatannol and was quantified using a calibration curve.

2.4 Animals

Male ICR mice and male Wistar rats weighing 25-35 g and 180-220 g, respectively, were used. All experimental animals were purchased from the Southern Laboratory Animal Facility, Prince of Songkla University, Thailand. The animals were housed in standard environmental conditions with controlled temperature of 24 ± 1°C and 12 h light/dark cycles with free access to food and water. The experimental protocols were approved by the Institutional Animal Care and Use Committee (IACUC), Prince of Songkla University (MOE 0521.11/458).

2.5 Croton Oil-induced Mouse Ear Swelling

Croton oil-induced ear swelling was carried out as previously described by Tubaro *et al.* [8]. Ear swelling was provoked by topical application of 2.5% croton oil in acetone (20 µL, 0.5 mg per ear) to the right mouse ear (6 mice per group, 5 groups). Five minutes after applying the irritant, piceatannol-rich extract in propylene glycol (2, 4 and 8 mg/ear each, 20 µL) was topically applied to the right mouse ear. The control group received propylene glycol in the same way. Indomethacin (0.5 mg/ear, 20 µL) was used as a standard control. Swelling was measured as the thickness difference (µm) of the right mouse ear using an electronic caliper (Insize, 1137-150, China) before application and 4 h after applying the irritant. Samples of mouse ear (6 mm in diameter) were removed 24 h after inflammatory induction, and then tissue myeloperoxidase (MPO) activity was determined.

2.6 Assay of MPO Activity

Tissue MPO activity was measured as previously described [9-10]. Briefly, each sample was placed in 1 mL of 80 mM phosphate buffered saline (pH 5.4) containing 0.5% hexadecyltrimethylammonium bromide and homogenized at 0°C. The homogenate was centrifuged at 12000 *g*, 4°C for 15 min. From the resulting supernatant, 20 µL was added to a 96-well plate in triplicate. Then 200 µL of a mixture containing 100 µL of 80 mM phosphate buffered saline (pH 5.4), 85 µL of 0.22 M phosphate buffered saline (pH 5.4) and 15 µL of 0.017 % hydrogen peroxide was added to each sample well and the reaction was initiated by adding 20 µL of 18.4 mM tetramethylbenzidine HCl in dimethylformamide. The plate was incubated at 37°C for 4 min, then placed on ice. The reaction was stopped by adding 30 µL of 1.46 M sodium acetate (pH 3.0). The absorbance was measured at 620 nm to determine the enzyme activity.

2.7 Rat Paw Swelling Induced by Carrageenan

The acute anti-edematous activity of orally administered piceatannol-rich extract was evaluated using the rat paw swelling provoked by carrageenan [11]. The right hind

paw volume of each rat (6 rats per group, 5 groups) was measured using a plethysmometer (Model MK-101CMP, Muromachi Kikai Co., Ltd., Japan). The piceatannol-rich extract of *S. garrettiana* and indomethacin, respectively, were dissolved in cosolvent (propylene glycol: tween 80: distilled water = 4: 1: 4). Thirty minutes after the oral administration of the cosolvent, indomethacin (5 mg/kg), or piceatannol-rich extract (10, 20 and 40 mg/kg) at a constant volume (5 mL/kg), each rat was injected subcutaneously with 0.1 mL of 1% carrageenan in normal saline into the subplantar region of the right hind paw. The right hind paw volume at 0, 0.5, 1, 2, 3, and 4 h after carrageenan injection was determined.

2.8 Cotton Pellet-induced Granuloma Formation in Rats

Cotton pellet-induced granuloma formation was performed by a slightly modified method [12]. Animals (6 rats per group, 5 groups) were anesthetized by intraperitoneal injection of sodium pentobarbital (40 mg/kg) and then implanted with sterile cotton pellets (weighing 20 ± 1 mg) subcutaneously in both sides of the groin area by suturing with sterile catgut. The animals were treated orally with the cosolvent, indomethacin (5 mg/kg) or piceatannol-rich extract (10, 20 and 40 mg/kg), respectively, once daily for 7 days after recovery from anesthesia. On the eighth day, each rat was sacrificed and the cotton pellet granulomas were removed and made free from extraneous tissue, then dried at 60°C for 18 h and weighed to obtain a constant weight. The increase in dry weight of the cotton pellet granulomas was taken as a measure of granuloma formation.

2.9 Complete Freund's Adjuvant-induced Polyarthritis in Rats

Complete Freund's adjuvant (CFA)-induced polyarthritis was evaluated in rats as previously described [13]. CFA (10%, 50 µL) dissolved in corn oil was injected subcutaneously into the rat's subplantar region of the right hind foot (6 rats per group, 5 groups). After injection (day 0), each group was orally administered cosolvent, indomethacin (5 mg/kg), or piceatannol-rich extract (10, 20 and 40 mg/kg), respectively for 14 days. Measurement of paw volume was recorded before and after the injection of CFA and continued on day 4, 7, 10, and 13 using the plethysmometer.

2.10 Assay of PGE_2 and Pro-inflammatory Cytokines TNF-α and IL-1β

Fourteen days after the injection of CFA (day 13), animals were sacrificed, and the subcutaneous plantar tissues were removed from the injected paws. All samples were weighed and kept at -20°C. The levels of PGE_2 and the pro-inflammatory cytokines, TNF-α and IL-1β, production were measured according to the manufacturer's instructions using commercially available ELISA kits (R&D systems, Minneapolis, MN, USA).

2.11 Statistical Analysis

Data obtained were expressed as mean values ± SEM and statistically analyzed by one way analysis of variance (ANOVA) followed by Bonferroni's test. A significant difference was considered at $p < 0.05$.

3. RESULTS

3.1 HPLC Analysis

HPLC chromatograms of authentic piceatannol (A) and piceatannol-rich extract of *S. garrettiana* (B) are displayed in Figure 1. The piceatannol-rich extract contained approximately 39.2% w/w piceatannol.

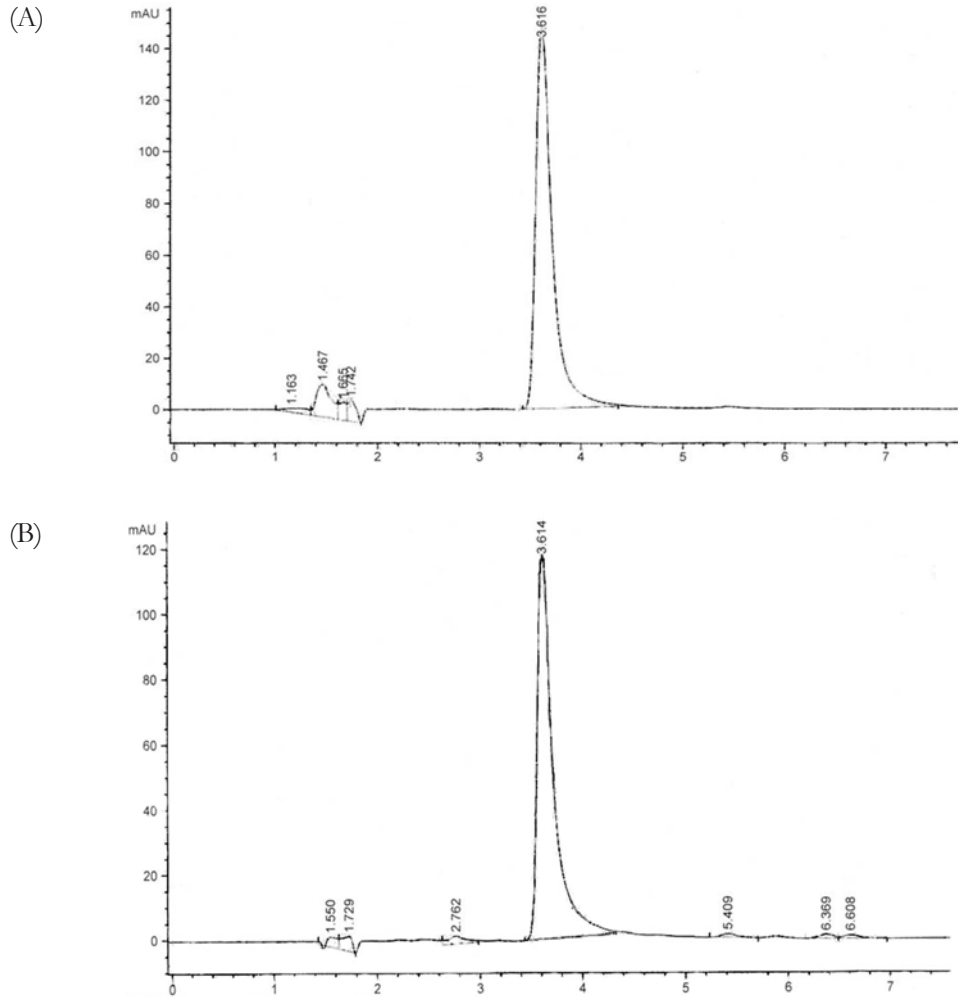

Figure 1. HPLC chromatograms of the authentic piceatannol (A) and piceatannol-rich extract from *S. garrettiana* (B).

3.2 Effects on Mouse Ear Swelling Induced by Croton Oil and Tissue MPO Activity

Cutaneous application of croton oil induced ear swelling in mice elicited a inflammatory response as measured by the thickness increase of the mouse ear and MPO activity of ear tissue. As shown in Figure 2, topical application of piceatannol-rich extract (2, 4 and 8 mg/ear each) dose-dependently suppressed swelling with a maximal inhibition of 45.85% in comparison with the control group (p<0.01). A 0.5 mg/ear dosage of indomethacin also reduced the inflammatory response to croton oil by 69.88%. The piceatannol-rich extract exhibited a significant suppression of ear swelling though less potent than indomethacin, a conventional NSAID. The piceatannol-rich extract dose-dependently reduced tissue MPO activity on croton oil challenge with a maximal effect of 30.21%. The reference drug indomethacin suppressed MPO activity by 43.72% (Figure 3).

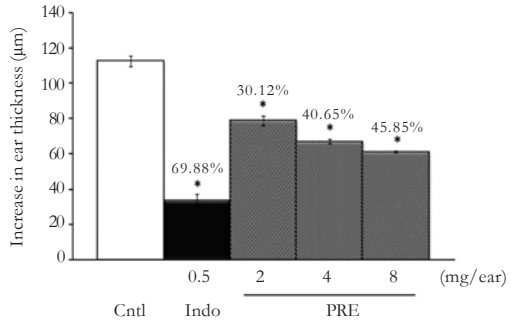

Figure 2. Effects of the piceatannol-rich extract from *S. garrettiana* heartwood on the croton oil-induced ear edema in mice. Values are presented as mean values ± S.E.M (n = 6). *p<0.01, significantly different compared to the control group (Bonferroni's test). Cntl: control; Indo: indomethacin; PRE: piceatannol-rich extract.

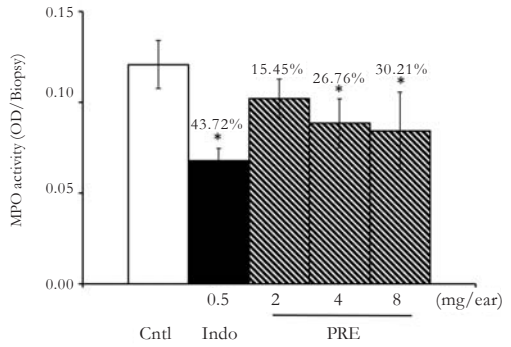

Figure 3. Effects of the piceatannol-rich extract from *S. garrettiana* heartwood on MPO activity in the croton oil-induced mouse ear edema. Values are presented as mean values ± S.E.M (n = 6). *p < 0.01, significantly different compared to the control group (Bonferroni's test). Cntl: control; Indo: indomethacin; PRE: piceatannol-rich extract.

3.3 Effects on Acute Inflammation in the Carrageenan-induced Rat Paw Swelling

The effects of orally administered piceatannol-rich extract and indomethacin, respectively, on inflammation provoked by subcutaneous injection of 1% carrageenan (0.1 mL) into the subplantar region of the right hind paw are summarized in Figure 4. The injected paw volume increased progressively to 1.24 mL at 4 h in the control group. Piceatannol-rich extract displayed a significant reduction of paw swelling in a dose-dependent fashion (10, 20 and 40 mg/kg) with a maximal inhibition of 75.81% at 4 h (p<0.01). At a dose of 5 mg/kg, indomethacin showed a significant suppression of paw swelling at 4 h with a percentage inhibition of 87.90%.

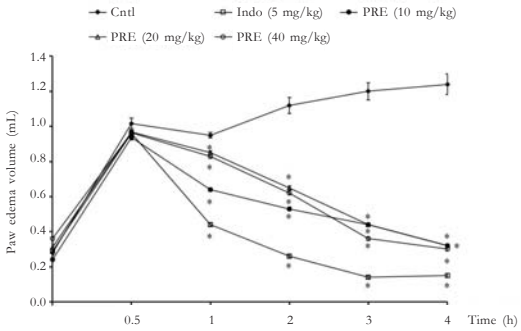

Figure 4. Effects of the piceatannol-rich extract from *S. garrettiana* heartwood on the carrageenan-induced paw edema in rats. Values are presented as mean values ± S.E.M. (n = 6). *p<0.01, significantly different compared to the control group (Bonferroni's test). Cntl: control; Indo: indomethacin; PRE: piceatannol-rich extract.

3.4 Effects on Chronic Inflammation in the Cotton Pellet-induced Rat Granuloma Formation

The results of orally administered piceatannol-rich extract on granuloma formation provoked by cotton pellets are shown in Table 1. Daily doses of piceatannol-rich extract at 10, 20 and 40 mg/kg for 7 days significantly decreased the granuloma weight (2.77 ± 0.02, 2.44 ± 0.01 and 2.40 ± 0.04 mg/ mg cotton pellet, respectively) with a percentage granuloma inhibition of 16.82, 26.73 and 27.93, respectively (p < 0.01). Indomethacin at 5 mg/kg significantly

decreased the granuloma weight (1.99 ± 0.03 mg/ mg cotton pellet) with an inhibition of 40.24%.

3.5 Effects on Chronic Inflammation in the CFA-induced Rat Polyarthritis

Oral administration of piceatannol-rich extract (10, 20, and 40 mg/kg) once daily for 14 days to polyarthritic rats dose-dependently suppressed inflammation on day 7, 10 and 13 (Figure 5). At a dose of 40 mg/kg, piceatannol-rich extract significantly attenuated joint edema at day 13 by 69.25% ($p < 0.01$) and was comparable with indomethacin (5 mg/kg; 69.80%).

Table 1. Effects of the piceatannol-rich extract from *S. garrettiana* heartwood on cotton pellet-induced granuloma formation in rats.

Treatment	Dose (mg/kg)	Granuloma dry weight (mg)	Granuloma weight (mg/mg cotton pellet)	GI (%)
Control	-	66.60 ± 0.79	3.33 ± 0.04	-
Indomethacin	5	39.80 ± 0.60*	1.99 ± 0.03*	40.24
Piceatannol-rich extract	10	55.40 ± 0.46*	2.77 ± 0.02*	16.82
Piceatannol-rich extract	20	48.68 ± 0.23*	2.44 ± 0.01*	26.73
Piceatannol-rich extract	40	48.33 ± 0.38*	2.40 ± 0.04*	27.93

Values are presented as mean values ± S.E.M. (n = 6). *$p < 0.01$, significantly different compared to the control group (Bonferroni's test). GI: Granuloma inhibition.

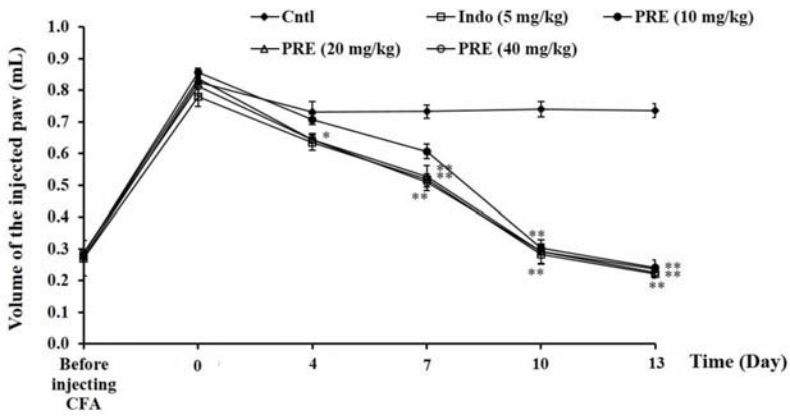

Figure 5. Effects of the piceatannol-rich extract from *S. garrettiana* heartwood on CFA-induced rat polyarthritis. Values are presented as mean values ± S.E.M (n = 6). *$p<0.05$, **$p<0.01$, significantly different compared to the control group (Bonferroni's test). Cntl: control; Indo: indomethacin; PRE: piceatannol-rich extract.

3.6 Effects on Production of PGE_2 and Pro-inflammatory Cytokines

The levels of PGE_2 and pro-inflammatory cytokines, TNF-α and IL-1β, produced in the CFA-induced rat arthritis model were measured to determine the mechanisms of the anti-inflammatory action of piceatannol-rich extract. PGE_2, along with TNF-α and IL-1β levels, dramatically increased in the control groups following CFA injection. Piceatannol-rich extract dose-dependently (10, 20 and 40 mg/kg) suppressed PGE_2 production compared with the control group (p<0.01) (Figure 6A). Piceatannol-rich extract also displayed a significant suppressive effect on TNF-α production at all doses (Figure 6B) and decreased the level of IL-1β, but this was significant only at the highest investigated dose of 40 mg/kg (Figure 6C). Piceatannol-rich extract, at a dose of 40 mg/kg, demonstrated a similar inhibition on these mediators to that of indomethacin (5 mg/kg).

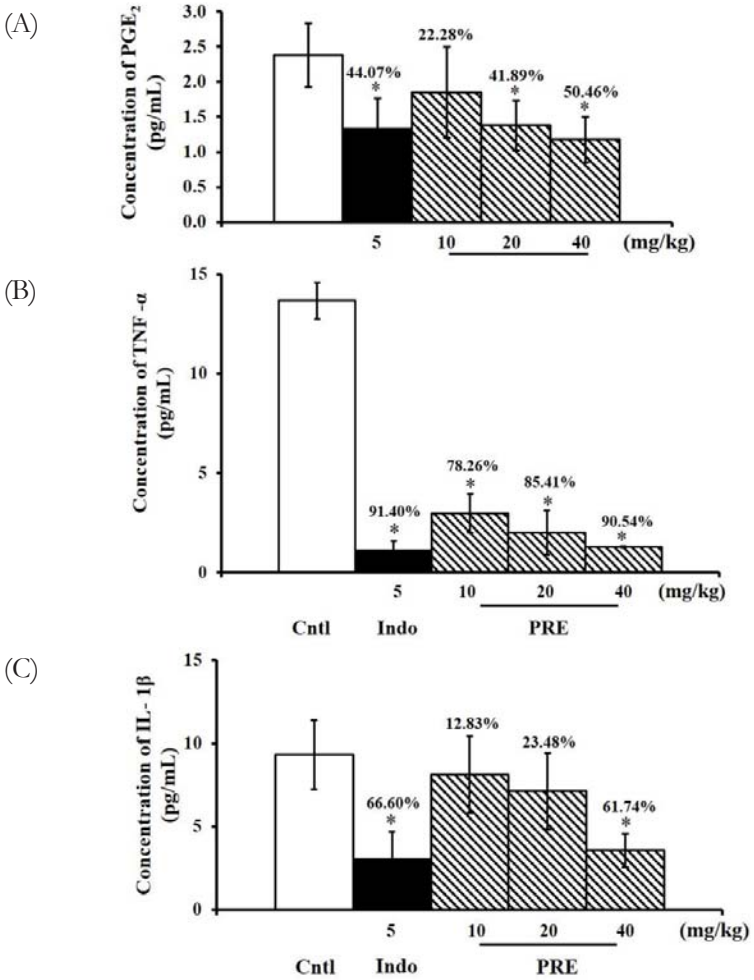

Figure 6. Effects of the piceatannol-rich extract from *S. garrettiana* heartwood on PGE_2 (A), TNF-α (B) and IL-1β (C) production 14 days after CFA injection. Values are presented as mean values ± S.E.M (n = 6). *p<0.01, significantly different compared to the control group (Bonferroni's test). Cntl: control; Indo: indomethacin; PRE: piceatannol-rich extract.

4. DISCUSSION

A methanol extract of *S. garrettiana* heartwood was prepared and then fractionated by chromatographic techniques to obtain a high yield of an ethyl acetate fraction [6]. The ethyl acetate fraction was then further separated to give piceatannol-rich extract that contained 39.2% w/w piceatannol. This piceatannol-rich extract was submitted to a study on the anti-inflammatory activities in rodent models. The results of the *in vivo* studies demonstrated that the piceatannol-rich extract had anti-inflammatory properties on both acute and chronic inflammation.

The croton oil or 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear swelling model is widely used for investigating topical anti-inflammatory activity of compounds [10]. It is a local irritant which produces cutaneous cell injury and activates phospholipase A_2 that results in the release of arachidonic acid from the plasma membrane of the cells. The arachidonic acid metabolites such as leukotrienes and prostaglandins act as inflammatory mediators involved in swelling formation and migration of white blood cells [14]. In addition, TPA also activates the expression of cyclooxygenase (COX)-2 and the inducible NO synthase (iNOS), and up-regulation of COX-2 by nitric oxide (NO) that was mediated by activation of the nuclear factor-kappaB (NF-kB) in the mouse skin [15]. Cutaneous application of piceatannol-rich extract exhibited a suppressive effect on the inflammatory responses provoked by croton oil that produced swelling and infiltration of neutrophils, as demonstrated by the decrease of ear thickness. This suggested that the anti-inflammatory mechanism of the piceatannol-rich extract might involve suppression of COX and iNOS and is also supported by the ability of piceatannol to suppress TPA-induced COX-2 and iNOS expression by blocking the activation of NF-kB and activator protein-1 in mouse skin [16], as well as by suppression of COX-2 expression in human breast epithelial cells [17]. MPO is the marker enzyme present in the intracellular granules of neutrophils which is utilized as a quantitative index of infiltration of white blood cells into inflammatory tissues, and in turn to determine the cutaneous inflammatory intensity [9, 18]. The reduction on the MPO activity of the mouse ear tissue by the piceatannol-rich extract indicated that leukocyte migration during the inflammatory process was diminished by the extract. Taken into consideration, the topical anti-inflammatory effects of piceatannol-rich extract may be attributed to inhibition of neutrophilic infiltration.

Paw swelling induced by carrageenan is one of the most widely used models in experimental animals for evaluation of the acute anti-inflammatory activity of any new compounds [19]. The acute inflammatory responses induced by injection of carrageenan involve three phases attributed to different chemical mediators. The initial phase of 1.5 h is triggered by the release of serotonin and histamine. The second phase is between 1.5 to 2.5 h and is mediated by kinins. The last phase occurs between 2.5 to 6 h and is presumably caused by prostaglandins [20]. Furthermore, production of pro-inflammatory cytokines, including TNF-α and IL-1β is also increased in the paw tissue of the animal after injection of carrageenan [21]. In this model, swelling formation was significantly inhibited by piceatannol-rich extract at 1 h and was maintained throughout the study period of four hours, indicating that the anti-inflammatory activity of the extract might be through the inhibition of both early and late phases of inflammation. Similarly, an inhibitory effect was observed for indomethacin, a standard drug which is a

potent inhibitor of prostaglandin synthesis. The results from this study demonstrated that the inhibitory effects displayed by piceatannol-rich extract against carrageenan-induced paw swelling may be due to the suppression of mediators such as prostaglandins and the pro-inflammatory cytokines that are responsible for the inflammatory response.

The cotton pellet-induced granuloma formation was used extensively as a model for investigating the efficacy of compounds against the proliferative phase of chronic inflammation [12]. Cotton pellets implanted subcutaneously in rats provoked the formation of foreign body granulomas, characterized by three phases of inflammatory response including transudative, exudative, and proliferative phases [12]. An increase in dry pellet granuloma weight represents the proliferative phase of the inflammatory response. In our study, the piceatannol-rich extract significantly suppressed the granuloma formation, comparing with the control group. Therefore, inhibition of granuloma formation by this extract indicated the suppression of the proliferative phase of the inflammatory response to the cotton pellet and was probably due to the antiproliferative activity of piceatannol [4].

Polyarthritis provoked by CFA is a standard animal model that mimics the human pathophysiological state [22]. Polyarthritis is developed and mostly urged by the assembly of macrophages and T-lymphocytes into the paw, giving rise to rat paw swelling and infiltration of numerous leukocytes into the synovial membrane, resulting in osteolytic lesions and chronic inflammation [23]. Macrophage activation results in generation of pro-inflammatory cytokines such as TNF-α and IL-1β, growth factors and other mediators of inflammation, including PGE_2 and an increase in the level of lysosomal enzymes [24]. Furthermore, the activation of iNOS and augmentation of neutrophil response to inflammatory stimuli is caused by TNF-α induced NO synthesis [24].

In the present study, the piceatannol-rich extract displayed an antiarthritic activity against the CFA-induced polyarthritis. At a dose of 40 mg/kg, the extract exhibited a comparable efficacy to indomethacin on day 13 as well as a suppression of PGE_2 elevation and the levels of pro-inflammatory cytokines TNF-α and IL-1β. Therefore, the therapeutic effects of the piceatannol-rich extract on polyarthritis induced by CFA may be partly ascribed to the down-regulation of PGE_2 and pro-inflammatory cytokines (TNF-α and IL-1β). This was also supported by an *in vitro* study. It was found that piceatannol reduced the production of pro-inflammatory cytokines on the expression of heme oxigenase-1 [25] and inhibited PGE_2 and NO production on inflammation induced by lipopolysaccharide of RAW 264.7 macrophages [26]. It also attenuated the expression of COX-2 mRNA and inducible NO synthase (iNOS) and protein levels [27]. Moreover, it accelerated the apoptosis of neutrophils as a part of its enhancing effect on the resolution of inflammation [28].

5. CONCLUSIONS

The results obtained from the present study revealed that either topical or oral administration of piceatannol-rich extract from *S. garrettiana* heartwood had therapeutic potential on acute and chronic inflammation, and its actions might be partly due to inhibition of leukocyte infiltration and modulation of PGE_2 and pro-inflammatory cytokines, TNF-α and IL-1β.

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