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Jasmine (*Jasminum grandiflorum*) Flower Extracts Ameliorate Tetradecanoylphorbol Acetate Induced Ear Edema in Mice

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Abstract

Published data from in vitro assays support the anti-inflammatory effects of jasmine (*Jasminum grandiflorum* Linn.) but limited studies are reported in animal models. Herein, the anti-inflammatory effects of jasmine flower extracts (JFEs) including ethanol extract (JF-EE), petroleum ether extract (JF-PEE), ethyl acetate extract (JF-EAE), and *n*-butanol extract (JF-BE) were evaluated in a mouse ear edema model. Acute mouse ear skin inflammation was induced by tetradecanoylphorbol acetate (TPA; 125 μg/mL) and then treated with JFEs (100 mg/mL) or dexamethasone (DEX; 6.25 mg/mL; as a positive control). Jasmine flower extracts alleviated ear edema by reducing TPA-increased ear thickness and ear weight by 30.8% to 64.1% and 24.0% to 47.1%, respectively, whereas DEX showed comparable activity (by 71.8% and 49.1%, respectively). Their anti-inflammatory effects were supported by data from the immunohistochemical assays. Jasmine flower extracts reduced the inflammatory cells (from 5.5- to 9.5-fold) and the expressions of inflammation related enzymes including cyclooxygenase-2 and inhibitor of kappa-B kinase (from 1.9- to 2.8-fold and from 7.1- to 11.0-fold, respectively). Findings from this study showed that JFEs were able to ameliorate TPA-induced mouse skin inflammation. However, future studies on the underlying mechanisms of jasmine flower's anti-inflammatory effects are warranted.

Keywords

jasmine flower, *Jasminum grandiflorum*, phenolics, oleuropein, tetradecanoylphorbol acetate (TPA), anti-inflammation

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Jasmine (*Jasminum grandiflorum* Linn.), a twining evergreen ornamental shrub, is popularly cultivated for its fragrant flowers in many regions of the world including East and South Asia, the Arabian Peninsula, and Northeast Africa.[1] It is one of the most frequently used medicinal herbs as a remedy for many ailments due to its wide spectrum of biological activities including antioxidant, antibacterial, antidiabetic, and anti-inflammatory effects.[1-4] Several published studies have reported the skin beneficial effects of jasimine extracts . For instance, in vitro studies showed that jasmine extracts were able to inhibit the growth of bacteria *Propionibacterium acnes*, which contributed to their anti-acne activity.[5] In addition, in vivo studies showed that ethanolic extracts of jasmine flower were able to enhance wound healing effects by increasing the formulation of granulation tissue and promoting wound contraction in rat models.[6] Although inflammation plays a pivotal role in the pathological development of many skin disorders, only few studies reported the anti-skin-inflammatory activity of jasmine extract.[7]

Our laboratory initiated a program to investigate medicinal plants from Guangdong Lingnan (South of the Nanling Mountains) region in China for their phytochemical constituents and pharmacological activities. One aim of this program was sought to identify Lingnan medicinal and edible plants for dermatological and cosmeceutical applications. During the

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course of bioactivity screening using a panel of in-house bioassays, several plant extracts (including jasmine flower extracts [JFEs]) showed promising anti-inflammatory effects in cellular based assays and in animal models.[8] To further investigate the anti-inflammatory property of jasmine extracts as well as their skin protective effects, 4 JFEs were evaluated for the anti-skin-inflammatory effect in a mouse model. Herein, the ameliorative effects of JFEs against tetradecanoylphorbol acetate (TPA)-induced ear skin inflammation are reported.

Materials and Methods

Chemicals and Reagents

Ethanol, petroleum ether, ethyl acetate, and *n*-butanol are all ACS grade solvents purchased from Sigma-Aldrich (St. Louis, MO, United States). Dexamethasone (DEX; purity >98%), acetic acid, acetone, and formalin solution were purchased from Sigma-Aldrich (St. Louis, MO, United States). Oleuropein, kaempferol, and quercetin were purchased from Aladdin Chemistry (Shanghai, China). Tetradecanoylphorbol acetate (TPA; purity >99.9%) was purchased from Henan Cancer Hospital (Zhengzhou, China). Antibodies for cyclooxygenase-2 (COX-2) and inhibitor of kappa-B (IκB) were purchased from BOSTER Biological Technology (Wuhan, China). Hematoxylin and eosin (H&E) staining reagent was purchased from Beyotime Biotechnology (Shanghai, China).

Preparation of JFEs

Commercially available jasmine flower from "Gulao" mountain (Jiangmen, Guangdong, China) was purchased from local market and stored in the freezer (at −20°C) until extraction. The plant material of jasmine flower was authenticated by Professor Xiaoji Zheng (Guangdong Jiangmen Chinese Traditional Medicine College, Jiangmen, China) and a voucher specimen (FA2004N) was deposited in School of Biotechnology and Health Sciences, Wuyi University (Jiangmen, Guangdong, China). Jasmine flower was air dried at room temperature and pulverized into fine powder (90.0 g). Jasmine flower powder was extracted 3 times with 95% aqueous ethanol (1 L) at 80°C for 2 hours. Ethanol extract was concentrated under vacuo after removal of ethanol to obtain a jasmine flower ethanol extract (JF-EE). Jasmine flower ethanol extract was suspended in distilled water (500 mL) and partitioned sequentially with petroleum ether (500 mL × 3), ethyl acetate (500 mL × 3), and *n*-butanol (500 mL × 3) to afford 4 JFEs including jasmine flower petroleum ether extract (JF-PEE), ethyl acetate extract (JF-EAE), and *n*-butanol extract (JF-BE), respectively, after solvents removal. The extraction yield of JF-EE, JF-PEE, JF-EAE, and JF-BE was 18.7%, 6.9%, 42.2%, and 36.6%, respectively (Table 1).

Characterization of Phenolic Compounds in JFEs

Total phenolic content was analyzed using the Folin-Ciocalteu method with minor modifications.[9] Each JFE (10 mg) was dissolved in ethanol (4 mL) and mixed with Folin-Ciocalteu reagent (1:1 v/v with water; 1 mL). The mixture was allowed to stand for 6 minutes, then sodium carbonate solution (7%; w/v; 5 mL) and distilled water (12 mL) were added. After incubation at room temperature for 90 minutes, the absorbance of the mixture was read at 760 nm. The total phenolic content was expressed as milligrams of gallic acid equivalents per gram of extract (mg GAE/g) using a standard curve prepared with gallic acid. Levels of 3 phenolic compounds including oleuropein, kaempferol, and quercetin were quantified by high performance liquid chromatography (HPLC) method.

Briefly, each JFE (dissolved in methanol; all at equivalent concentrations of 10 mg/mL) was analyzed on a Luna C18 column (250 × 4.6 mm i.d., 5 μM; Phenomenex) with a flow rate of 0.75 mL/min and injection volume of 20 μL for each sample. A linear gradient solvent system consisting of solvent A (0.1% aqueous trifluoroacetic acid) and solvent B (methanol) at room temperature was used as follows: 0 to 30 minutes, 10% to 60% B; 30 to 35 minutes, 60% to 100% B; 35 to 40 minutes, 100% B; and 40 to 42 minutes, 100% to 10% B.

Tetradecanoylphorbol Acetate Induced Mouse Ear Edema Model and Treatments

Protocol for this animal study was approved by the Animal Care & Welfare Committee of Tea Research Institute

Table 1. Characterization of Phenolic Content (by the Folin-Ciocalteu Method) and Levels of Phenolics Including Oleuropein, Kaempferol, and Quercetin (by High Performance Liquid Chromatography Method) in Jasmine Flower Extracts.

		Phytochemical content			
Extracts	Extraction yield (%)	Total phenolics (%)[a]	Oleuropein (%)	Kaempferol (%)	Quercetin (%)
JF-EE	18.7	20.8	23.3	0.1	n.d.
JF-PEE	6.9	12.3	27.5	0.2	n.d.
JF-EAE	42.2	34.5	55.1	1.1	0.4
JF-BE	36.6	31.7	39.5	n.d.	n.d.

JF-BE, jasmine flower *n*-butanol extract ; JF-EAE, jasmine flower ethyl acetate extract; JF-EE, jasmine flower ethanol extract; JF-PEE, jasmine flower petroleum ether extract; n.d., not detected.

[a]Value expressed as in w/w% of gallic acid equivalents.

(Guangdong Academy of Agricultural Sciences; 20161210024). All experimental procedures were performed in strict accordance with the laboratory animal care and use guidelines, and best efforts were made to minimize the pain of experimental animals. Female Kunming mice were obtained from Tea Research Institute of Guangdong Academy of Agricultural Sciences (Guangzhou, China). The animals were housed in standard cages under a 12-hour light/dark cycle with free access to water and chow. Mice were acclimated for 1 week (body weight 28-35 g) and randomly divided into 7 groups (n = 8 per group). Aqueous acetone (50%) was used as a vehicle solvent to dissolve TPA, DEX, and JFEs. All the solvents were externally applied on the skin of mice ears. In the control group, both left ears and right ears of mice were treated with vehicle solvent (50% aqueous acetone; 20 μL). In the model (TPA-treated) group, left ears and right ears of mice were treated with vehicle solvent (20 μL) and TPA (at 125 μg/mL; 20 μL), respectively. In the treatment groups and positive control (DEX-treated) group, right ears of mice were pretreated with JFE (at 100 mg/mL; 20 μL), including JF-EE, JF-PEE, JF-EAE, and JF-BE, or DEX (at 6.25 mg/mL; 20 μL), respectively. After 20 minutes, both left ears and right ears of mice were treated with TPA (at 125 μg/mL; 20 μL). After 8 hours, mice were sacrificed and ear pieces were collected using an electronic rotary microtome (ThermoFisher Scientific, United States). Ear punch biopsies with 6 mm diameter were collected using a metal punch and then weighed. The ear thickness was measured using a digital caliper (Mitutoyo , Japan). Changes (Δ) of ear thickness, ear weight, and percentage of inflammatory cells of each mouse were calculated by comparing differences between the left ear (treated with vehicle solvent first and then with TPA) and the right ear (treated with DEX or JFEs first and then with TPA) in each group (n = 8 per group).

Histological and Immunohistochemical Assays

Collected ear tissue was fixed with formalin solution for histopathological examinations. Hematoxylin and eosin staining assay was performed on mice ear tissues that were fixed in paraffin and sectioned into 4-μm sections using method previously reported.[8] Immunohistochemical staining assays were performed on mice ear tissue sections as we previously reported.[8] Sectioned tissues were incubated with antimouse monoclonal antibodies including COX-2 and IκB, followed by appropriated secondary antibodies. Randomly selected visual fields (n = 10; at 400× magnification) in each group are recorded using a microscopy (AxioScope A1, ZEISS, Germany), and the amount of COX-2 and IκB positive cells were counted with microscopy.

Statistical Analysis

GraphPad prism 6.0 (GraphPad Software, La Jolla, CA, United States) was used to analyze data. All data expressed as mean ± standard deviation. To evaluate the significance, one-way analysis of variance with multiple comparisons and Student-Newman-Keuls (SNK) test were performed. A P-value less than .05 was considered as a statistical significance.

Results

Oleuropein Is a Major Phenolic Compound in JFEs

The chemical constituents of JFEs were characterized by HPLC methods (supplemental Figure S1). The phenolic contents of JFEs were measured by the Folin-Ciocalteu method. The total polyphenol content of JF-EE, JF-PEE, JF-EAE, and JF-BE were 20.8%, 12.3%, 34.5%, and 31.7% (as of mg GAE/g), respectively (Table 1). A major phenolic compound in JFEs was identified as oleuropein by HPLC method and its levels in JF-EE, JF-PEE, JF-EAE, and JF-BE were 23.3%, 27.5%, 55.1%, and 39.5%, respectively. Two flavonoids, namely kaempferol and quercetin, were identified as minor phenolics in JFEs. Kaempferol was detected in JF-EE (0.1%), JF-PEE (0.2%), and JF-EAE (1.1%); and quercetin was detected in JF-EAE (0.4%).

Jasmine Flower Extracts Ameliorate TPA-Induced Ear Erythema and Edema in Mouse

The anti-inflammatory effects of JFEs against TPA-induced acute ear skin inflammation were evaluated. Skin inflammatory characteristics including mouse ear erythema and edema were examined. Topical application of TPA (125 μg/mL; 20 μL) induced ear erythema by causing congestion of blood vessels and vascular permeability, which resulted in increased skin redness (Figure 1(a)). Pretreatment of JFE (100 mg/mL; 20 μL) including JF-EE, JF-PEE, JF-EAE, and JF-BE attenuated TPA-induced ear redness (Figure 1(a)). Dexamethasone, a corticosteroid anti-inflammatory drug, served as a positive control and showed similar effects as of JFE at a lower concentration (6.25 mg/mL; 20 μL). Topical application of JFE treatments also ameliorated mouse ear edema by reducing ear thickness and weight (Table 2). Treatment of JF-PEE showed the most promising anti-inflammatory effect by reducing TPA-increased ear thickness (by 64.1%) and weight (by 47.1%) as compared to the TPA-treated model group. Treatment of DEX had comparable effects by reducing increased mouse ear thickness and weight by 71.8% and 49.1%, respectively. Other JFEs including JF-EE, JF-PEE, JF-EAE, and JF-BE also showed ameliorative effects by reducing ear thickness (by 56.4%, 64.1%, 51.3%, and 30.8%, respectively) and ear weight (by 28.9%, 47.1%, 41.3%, and 24.0%, respectively) as compared to the TPA-treated model group (Table 2). The ameliorative effects of JFE on ear edema were further supported by histopathological assay. As shown in the H&E staining images, application of TPA induced loosening of connective tissue and disorganization of fibers from extracellular matrix (Figure 1(b)). Treatments of JFEs reduced TPA-induced changes of mouse skin thickness and accumulation of granulation tissue. Application of TPA also increased inflammatory cell infiltration (to 19.7%) as

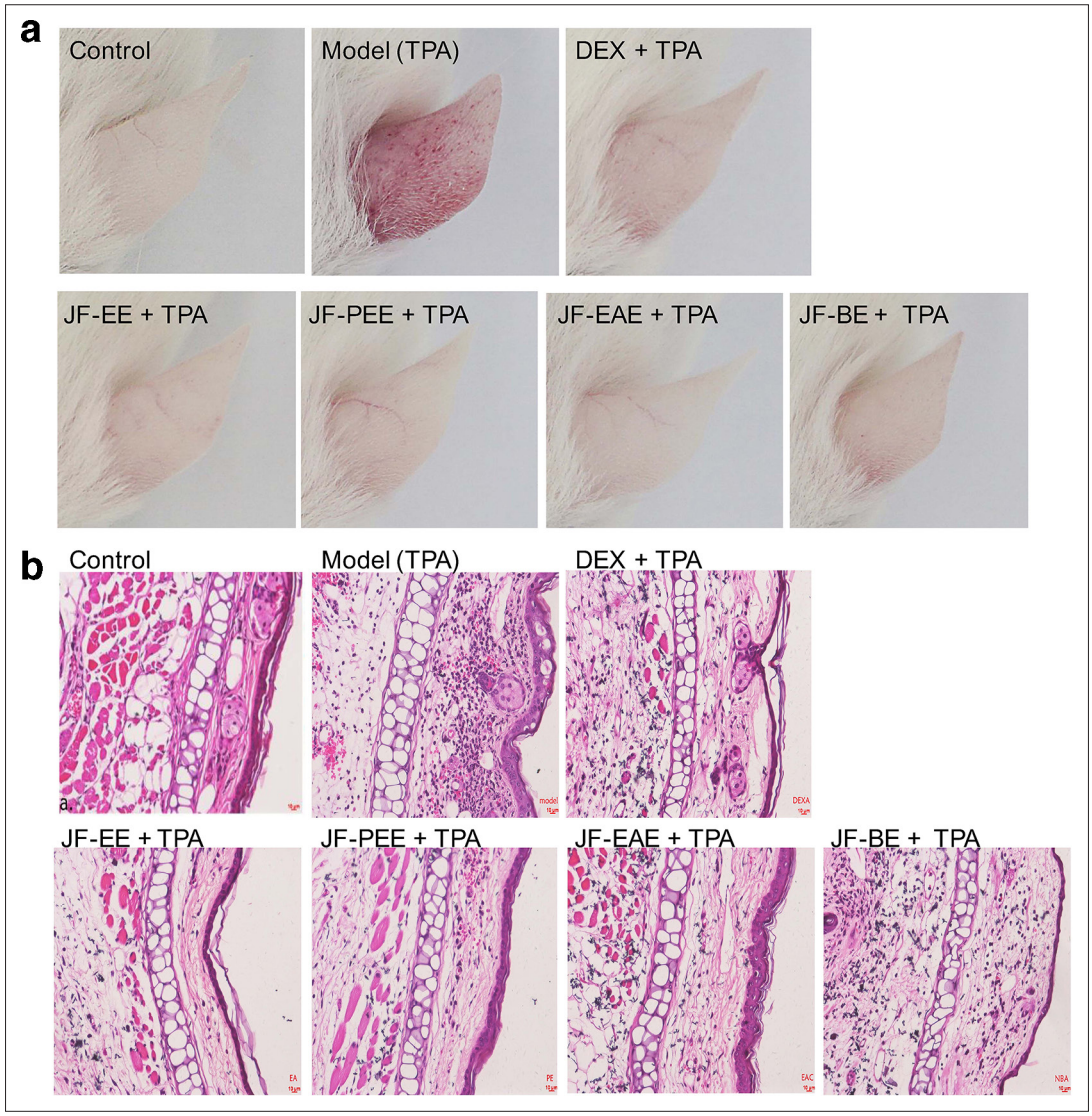

Figure 1. Effects of jasmine flower extracts (jasmine flower ethanol extract, jasmine flower petroleum ether extract, jasmine flower ethyl acetate extract, and jasmine flower *n*-butanol extract; 100 mg/mL; 20 μL) on tetradecanoylphorbol acetate (125 μg/mL; 20 μL) induced mouse ear erythema (n = 8 per group). Representative images of the mouse ears after treatment with 50% aqueous acetone (vehicle solvent; as control group) or tetradecanoylphorbol acetate (as model) with or without jasmine flower extract pretreatment groups (a). Representative images of hematoxylin and eosin staining of mouse ear tissues showing histological changes after acetone or tetradecanoylphorbol acetate treatment with or without jasmine flower extract pretreatments (b). Dexamethasone (6.25 mg/mL; 20 μL) served as a positive control.

compared to the control group, while treatments of JFEs reduced inflammatory cells (5.5%-9.5%) as compared to the TPA-treated group (Table 2).

Jasmine Flower Extracts Downregulated the Expressions of COX-2 and IκB

The anti-inflammatory effects of JFEs were supported by the evaluation of expressions of several inflammation related enzymes including COX-2 and IκB in histopathological assays. As shown in Figure 2, immunochemical staining assay showed that the expressions of COX-2 were significantly increased after topical application of TPA (by 3.4-fold). Treatment of JFEs significantly reduced the expressions of COX-2 in the order of JF-PEE (to 2.3-fold), JF-PEE (to 1.9-fold), JF-EAE (to 2.8-fold), and JF-BE (to 2.1-fold), while the treatment of DEX showed similar effects as the expression of COX-2 reduced to 1.84-fold (Figure 2(upper panel) and (a)). In the development of inflammation, the expression of COX-2 is regulated by a group of transcription factors including nuclear factor-κB (NF-κB), which is stimulated by the kinases of IκB. The effects of TPA induced overexpression of IκB and the downregulatory effects of JFE on the TPA-stimulated expression of IκB were evaluated. The expression of IκB was

Table 2. Effects of Jasmine Flower Extracts on Tetradecanoylphorbol Acetate Induced Changes (Δ) of Mouse Ear Thickness, Ear Weight, and Percentage of Inflammatory Cells.

Group	Dose (mg/mL)	Δ Ear thickness (mm)	Δ Ear weight (mg)	Inflammatory cells (%)
Model	0	0.39 ± 0.03	44.6 ± 7.4	19.7 ± 1.6
DEX	6.25	0.11 ± 0.05**	22.7 ± 8.9**	7.7 ± 1.5**
JF-EE	100	0.17 ± 0.06**	31.7 ± 7.8*	8.7 ± 3.6**
JF-PEE	100	0.14 ± 0.04**	23.6 ± 5.9**	5.5 ± 2.5**
JF-EAE	100	0.19 ± 0.06**	26.2 ± 7.5**	7.2 ± 0.6**
JF-BE	100	0.27 ± 0.05**	33.9 ± 6.9	9.5 ± 2.4**

DEX, dexamethasone; JF-BE, jasmine flower *n*-butanol extract; JFEs, jasmine flower extracts; JF-EAE, jasmine flower ethyl acetate extract; JF-EE, jasmine flower ethanol extract; JF-PEE, jasmine flower petroleum ether extract.
Changes (Δ) of ear thickness, ear weight, and percentage of inflammatory cells of each mouse were calculated by differences between the left ear (pretreated with vehicle solvent and then with TPA) and the right ear (pretreated with JFEs or DEX, and then with TPA) of mice in each group ($n = 8$ per group). Data are shown as mean ± standard deviation. *$P < .05$ and **$P < .01$ as left ear (pretreated with vehicle solvent and then with TPA) vs right ear (pretreated with JFEs or DEX, and then with TPA) of mice in each group.

significantly increased after topical application of TPA (to 14.5-fold). Treatment of JF-EE, JF-PEE, JF-EAE, and JF-BE significantly decreased the expressions of IκB to 7.9-, 7.4-, 7.1-, and 11.0-fold, respectively, which is comparable to the activity of DEX (to 5.9-fold; Figure 2(upper panel) and (b)).

Discussion

Jasmine is a widely used ingredient in cosmeceutical industry. Published studies showed that jasmine extracts can exert a broad range of biological activities including antioxidant and

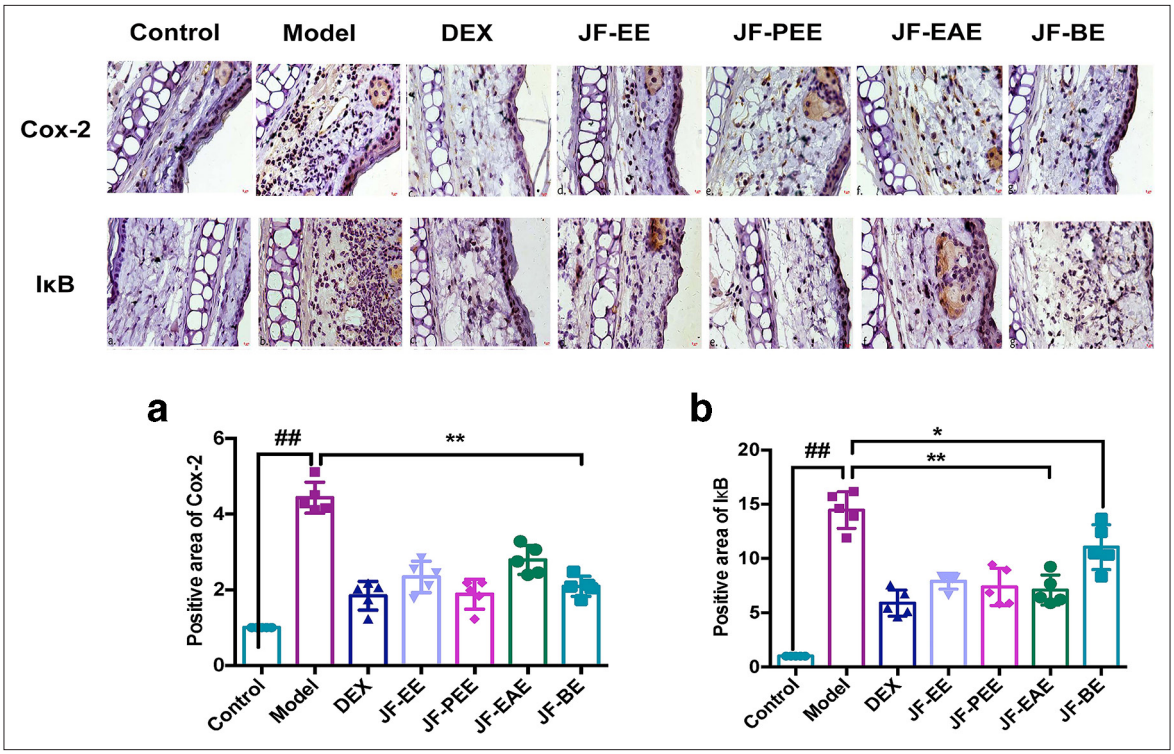

Figure 2. Effect of jasmine flower extract on tetradecanoylphorbol acetate induced expressions of cyclooxygenase-2 and inhibitor of kappa-B. Immunohisotogical staining images showing the expression of cyclooxygenase-2 and inhibitor of kappa-B in mouse ear tissue from different jasmine flower extract treatment groups after 8 hours of tetradecanoylphorbol acetate application (upper panel). Inhibitory effects of jasmine flower extracts treatment on the expression of cyclooxygenase-2 (a) and inhibitor of kappa-B (b). Dexamethasone served as a positive control. $n = 8$ per group, *$P < .05$, **$P < .01$, as the left ear (treated with vehicle solvent first and then with tetradecanoylphorbol acetate; model) vs the right ear (treated with dexamethasone or jasmine flower extracts first and then with tetradecanoylphorbol acetate) in each group; $^{\#\#}P < .01$, as ears only treated with vehicle solvent (control) vs ears treated with tetradecanoylphorbol acetate; model.

antimicrobial effects, which may partially contribute to their skin beneficial effects.[4,5] However, only limited data are reported to show the skin protective and anti-inflammatory effects of jasmine.[7] Herein, we evaluated the anti-inflammatory effects of 4 JFEs in a TPA-induced mouse ear edema model. Data from our current study showed that 4 JFEs were able to ameliorate TPA-induced skin inflammation biomarkers including skin redness and increased inflammatory cells in mouse ears. This anti-inflammatoryactivity of JFEs was partially attributed to their capacity of downregulating the expression of COX-2 and IκB (Figure 2) in mouse ear tissues. These findings are in agreement with a previously reported study showing that a methanolic extract of jasmine leaves was able to inhibit lipopolysaccharides-induced nitric oxide production in murine macrophage cells and alleviate carrageenan-induced paw edema in a mouse model.[7] Published studies suggested that phenolic contents of jasmine leaves extracts were correlated with their antioxidant and anti-inflammatory activities.[3,4,7] Oleuropein, a phenolic compound that is commonly found in the aerial parts of olive, has been reported to show anti-inflammatory effects and contribute to the overall skin protective effects of olive extracts.[10,11] It is possible that oleuropein and other phytochemicals in JFEs exerted anti-inflammatory activity in additive, synergistic, and/or complementary manners. A limitation of this study is that the underlying mechanism(s) of anti-inflammatory activity of JFEs remain unclear. Although published studies suggest that a downregulated expression of IκB is often observed in response to TPA stimulation,[12,13] the expression of IκB in the TPA-treated group was increased (Figure 2(b)). The level of the phosphorylated IκB, which is critical in response to TPA stimulation by regulating the expression of inflammatory transcription factors, such as NF-κB,[14] in the TPA-treated group was not measured. Therefore, evaluations of effects of TPA and JFE treatments on the expression of phosphorylated IκB level are warranted in the future study. Furthermore, although data from the immunohistological assays showed that JFEs reduced the expression of inflammation related proteins including COX-2 and IκB, other pathways that are involved in the anti-inflammatory effects of JFEs were not thoroughly examined. For example, studies showed that oleuropein was able to attenuate kidney inflammation through the regulation of HO-1/Nrf2 expression and NLRP3 inflammasome signaling pathways.[11] Oleuropein was also reported to suppress inflammatory cytokine expressions and inhibit NLRP3 inflammasomes in human placenta.[15] Therefore, the investigation of the anti-inflammasome activity of JFEs and its major phenolic, oleuropein, is warranted.

In summary, 4 JFEs were evaluated for their protective effects against TPA-induced skin inflammation in a mouse model. Jasmine flower extracts ameliorated TPA-induced ear edema and downregulated inflammation associated enzymes including COX-2 and IκB. Future studies on the isolation and identification of phytochemicals from JFEs with anti-inflammatory activity, as well as their mechanism(s) of action, are warranted.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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