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Paeoniflorin inhibits mast cell-mediated allergic inflammation in allergic rhinitis

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Abstract

Paeoniflorin (PF), one of the main effective ingredients from the root of *Paeonia lactiflora* Pall., was reported to possess antitumor, anti-inflammatory, and antiallergic properties. However, the roles of PF in activated human mast cell line, HMC-1 cells, have not yet been elucidated. Thus, the aim of this study was to examine the antiallergic and anti-inflammatory effects of PF on phorbol-12-myristate 13-acetate plus calcium ionophore (PMACI)-induced human mast cells and to identify the mechanism responsible for these effects. Our results demonstrated that pretreatment with PF effectively attenuated PMACI-induced production of tumor necrosis factor- α and interleukin 1 β in HMC-1 cells. In addition, PF significantly suppressed PMACI-induced histamine release and caspase-1 activation in HMC-1 cells. Furthermore, PF prevented the activation of nuclear factor κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) signaling pathways in activated HMC-1 cells. In conclusion, we showed for the first time that PF attenuated the mast cell-mediated allergic inflammatory response through suppressing the NF- κ B and MAPK signaling pathways.

KEYWORDS

allergic rhinitis, caspase-1, inflammatory response, paeoniflorin

1 | INTRODUCTION

Allergic rhinitis is an allergic inflammatory disease of the upper airway and the prevalence has been increasing in the past few years.¹ It is characterized by one or more nasal symptoms, such as sneezing, itching, nasal discharge, rhinorrhea, postnasal drainage, and nasal obstruction.² In spite of many treatment options for allergic rhinitis, none of the treatments were completely effective. Mast cells are the major effector cells in the progression of allergic rhinitis. Activated mast cells could secrete a variety of bioactive substances, such as histamine, chemokines, cytokines, and growth factors, which promote the local inflammatory response.^{3,4} Thus,

suppression of the mast cell function may be an effective way to alleviate the progression of allergic rhinitis.

The root of *Paeonia lactiflora* Pall. (family Ranunculaceae) has been used in traditional Chinese medicine for the treatment of pain, muscle spasm, inflammation, and degenerative disorders. Paeoniflorin (PF) is one of the main effective ingredients from the root of *P. lactiflora* Pall.⁵ Emerging studies have reported that PF possesses diverse pharmacological activities, such as neuro-protective, anti-inflammatory, antioxidative, immunoregulatory, antitumor, and antiallergic effects.^{6–8} For example, Sun et al⁹ reported that PF treatment dramatically decreased airway hyperresponsiveness to aerosolized methacholine and downregulated the levels of interleukin-5 (IL-5), IL-13, IL-17, and eotaxin in the bronchoalveolar lavage fluid of asthmatic mice. However, the roles of PF in activated human mast cell line, HMC-1 cells, have not yet been elucidated. Thus, the

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aim of this study was to examine the antiallergic and anti-inflammatory effects of PF on phorbol-12-myristate 13-acetate plus calcium ionophore (PMACI)-induced human mast cells and to identify the mechanism responsible for these effects. The results of this study indicated that PF has an antiallergic effect by modulating mast cell-mediated allergic responses in allergic rhinitis.

2 | MATERIALS AND METHODS

2.1 | Reagents and cell culture

PF was purchased from Sigma (St Louis, MO; HPLC $\geq 98\%$). The human mast cell line was purchased from the American Type Culture Collection (ATCC, Manassas, VA). Cells were cultured in Dulbecco modified Eagle medium (DMEM; Life Technologies, Grand Island, NY), supplemented with 10% fetal bovine serum (FBS; Gibco, Rockville, MD) and 100 U/mL penicillin/streptomycin (Sigma) in a 5% CO₂ incubator at 37°C. Passages between 4 and 8 were used in all experiments.

2.2 | Cell viability assay

Cell viability was assessed using the Cell Counting Kit-8 (CCK-8; Dojindo, Kumamoto, Japan) assay, according to the manufacturer's instructions. Briefly, HMC-1 cells were seeded at a density of 1×10^5 cells per well in 96-well culture plates overnight and then incubated with different concentrations of PF (0, 1, 5, 10, and 20 μ M) for 24 hours. Then, 10 μ L of CCK-8 solution was added to each well and incubated for 4 hours at 37°C. Finally, the absorbance was measured at 540 nm with an ELISA reader (Bio-Rad, Hercules, CA). The cell survival rates were expressed as percentages of the value of normal cells.

2.3 | Assessment of TNF- α and IL-1 β production

HMC-1 (1×10^5 cells per well) were pretreated with PF (1, 5, or 10 μ M) for 1 hour before incubation with 25 nM PMA plus 1 μ M A23187 (PMACI) for 2 hours. Then, the cell culture medium was centrifuged, and the supernatant was collected. Subsequently, the levels of tumor necrosis factor- α (TNF- α) and IL-1 β in the supernatant were determined by ELISA kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China), according to the manufacturer's instructions, respectively.

2.4 | Determination of histamine level

After treatment, the histamine content in the supernatant was evaluated using the *o*-phthaldialdehyde fluorometric

procedure.¹⁰ The fluorescence intensity was analyzed using a fluorescence microscope with an excitation wavelength of 353 nm and an emission wavelength of 438 nm.

2.5 | Caspase-1 activity assay

After treatment, the activity of caspase-1 was evaluated using a caspase assay kit (R&D Systems Inc., Minneapolis, MN) according to the manufacturer's instructions.

2.6 | Western blot analysis

HMC-1 cells were collected after washing with ice-cold phosphate-buffered saline and then lysed with RIPA buffer (50 mM Tris-HCl [pH 7.2], 150 mM NaCl, 1% Triton X-100, and 0.1% sodium dodecyl sulfate [SDS]). Protein concentrations were measured with a BCA protein assay kit (Pierce, Rockford, IL). Aliquots (about 30 μ g per lane) were separated by 10% SDS-polyacrylamide gel and transferred to a polyvinylidene difluoride membrane (Millipore, Boston, MA). The membranes were blocked with 5% fat-free milk in Tris-buffer saline for 1 hour at room temperature and incubated with primary antibodies overnight at 4°C. The primary antibodies were anti-p-p65 (1:2500), anti-p65 (1:1500), anti-I κ B α (1:300), anti-p38 (1:1000), anti-phospho-p38 (1:1000), anti-ERK (1:2500), anti-phospho-ERK (1:1500), anti-JNK (1:1000), anti-phospho-JNK (1:1000), and anti-GAPDH (1:2000). After washing, the membranes were incubated with appropriate horseradish peroxidase-conjugated secondary antibody (Santa Cruz Biotechnology, Santa Cruz, CA) for 1 hour at room temperature. Finally, the immunoreactive protein bands were visualized using an enhanced chemiluminescence reagent (GE Healthcare, Buckinghamshire, UK).

2.7 | Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS Inc, Chicago, IL). All values are presented as the mean $\pm$ standard deviation. The statistical significance was assessed using one-way analysis of variance, followed by Tukey post hoc test for multiple-group comparisons. $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Effect of PF on the viability of HMC-1 cells

We examined the effect of PF on cell viability. The results of CCK-8 assay indicated that PF at a concentration of

20 μM caused a significant inhibition of the viability of HMC-1 cells compared with untreated HMC-1 cells. Cell viability was not significantly impaired at PF concentrations of $\leq 10 \mu\text{M}$ (Figure 1); therefore, these concentrations were chosen for additional experiments.

3.2 | PF inhibits PMACI-induced production of TNF- α and IL-1 β in HMC-1 cells

Pro-inflammatory cytokines play important roles in the progression of allergic rhinitis; thus, we examined the effects of PF on the production of TNF- α and IL-1 β in HMC-1 cells exposed to PMACI. As shown in Figure 2A, compared with untreated HMC-1 cells, PMACI treatment significantly induced TNF- α production in HMC-1 cells. However, pretreatment with PF dose-dependently suppressed the production of TNF- α in HMC-1 cells exposed to PMACI. In addition, PMACI-induced IL-1 β production was also prevented by PF (Figure 2B).

3.3 | PF suppresses PMACI-induced histamine release and caspase-1 activation in HMC-1 cells

Histamine is the salient inflammatory mediator released after allergen challenge in allergic rhinitis; thus, we examined the effect of PF on histamine release in PMACI-stimulated HMC-1 cells. As shown in Figure 3A, PMACI treatment significantly induced histamine release in HMC-1 cells, and this effect was potentially reversed by PF. Furthermore, we investigated

the effect of PF on caspase-1 activation in HMC-1 cells in response to PMACI. As shown in Figure 3B, as compared with the control group, caspase-1 activity was dramatically increased in PMACI-stimulated HMC-1 cells. However, pretreatment with PF efficiently prevented PMACI-induced caspase-1 activation in HMC-1 cells, exhibiting dose dependence.

3.4 | PF prevents NF- κB activation in activated HMC-1 cells

NF- κB is an important transcriptional regulator of inflammatory cytokines; thus, to explore the regulatory mechanisms of PF on inflammatory response, we detected the effect of PF on NF- κB activation in

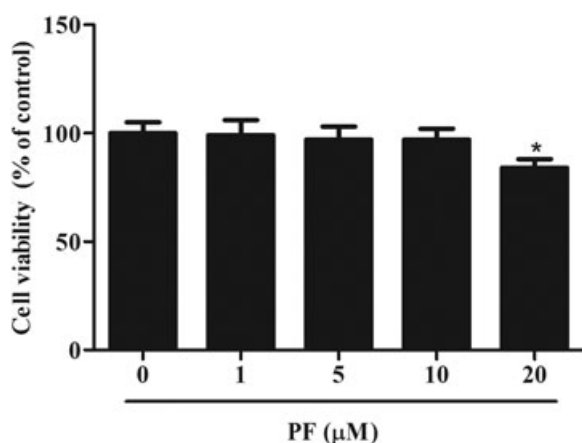


FIGURE 1 Effect of PF on the viability of HMC-1 cells. HMC-1 cells at a density of 1×10^5 cells per well were incubated with different concentrations of PF (0, 1, 5, 10, and 20 μM) for 24 hours. Cell viability was determined using the CCK-8 assay. Data are expressed as mean $\pm$ SD of 3 independent experiments. * $P < .05$ vs control. CCK-8, cell counting kit-8; HMC-1, human mast cell line-1; PF, paeoniflorin; SD, standard deviation

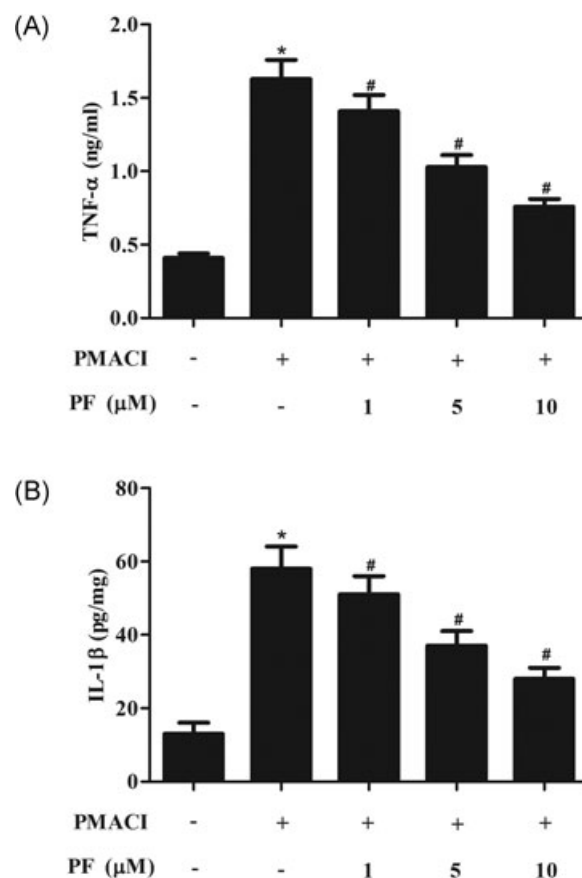


FIGURE 2 PF inhibits PMACI-induced production of TNF- α and IL-1 β in HMC-1 cells. HMC-1 cells (1×10^5 cells per well) were pretreated with PF (1, 5, or 10 μM) for 1 hour before incubation with 25 nM PMA plus 1 μM A23187 (PMACI) for 2 hours. (A,B) The levels of TNF- α and IL-1 β in the supernatant were determined by ELISA kits. Data are expressed as mean $\pm$ SD of 3 independent experiments. * $P < .05$ vs control; # $P < .05$ vs PMACI. ELISA, enzyme-linked immunosorbent assay; HMC-1, human mast cell line-1; IL-1 β , interleukin-1 β ; PF, paeoniflorin; PMACI, phorbol-12-myristate 13-acetate plus calcium ionophore; SD, standard deviation; TNF- α , tumor necrosis factor- α

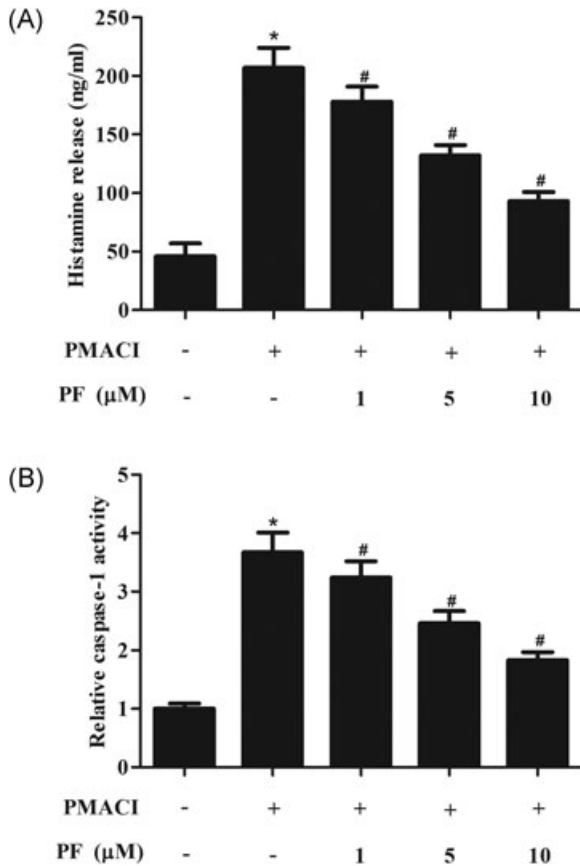


FIGURE 3 PF suppresses PMACI-induced histamine release and caspase-1 activation in HMC-1 cells. HMC-1 cells (1×10^5 cells per well) were pretreated with PF (1, 5, or 10 μ M) for 1 hour before incubation with 25 nM PMA plus 1 μ M A23187 (PMACI) for 2 hours. (A) Histamine content was evaluated using the *o*-phthalaldehyde fluorometric procedure. (B) The activity of caspase-1 was evaluated using a caspase assay kit. Data are expressed as mean $\pm$ SD of 3 independent experiments. * $P < .05$ vs control; # $P < .05$ vs PMACI. HMC-1, human mast cell line-1; PF, paeoniflorin; PMACI, phorbol-12-myristate 13-acetate plus calcium ionophore; SD, standard deviation

HMC-1 cells exposed to PMACI. As shown in Figure 4, PMACI stimulation markedly induced phosphorylation NF- κ B/p65 and degradation of I κ B α in HMC-1 cells when compared with the untreated group; however, the activation of NF- κ B was greatly suppressed by treatment with PF.

3.5 | PF prevents the activation of MAPK pathway in activated HMC-1 cells

Because the mitogen-activated protein kinase (MAPK) pathway is also important for inflammatory response, therefore, we investigated the effect of PF on MAPK pathway activation in PMACI-stimulated HMC-1 cells. Western blot analysis showed that the levels of p-p38, p-ERK, and p-JNK were significantly increased in HMC-1

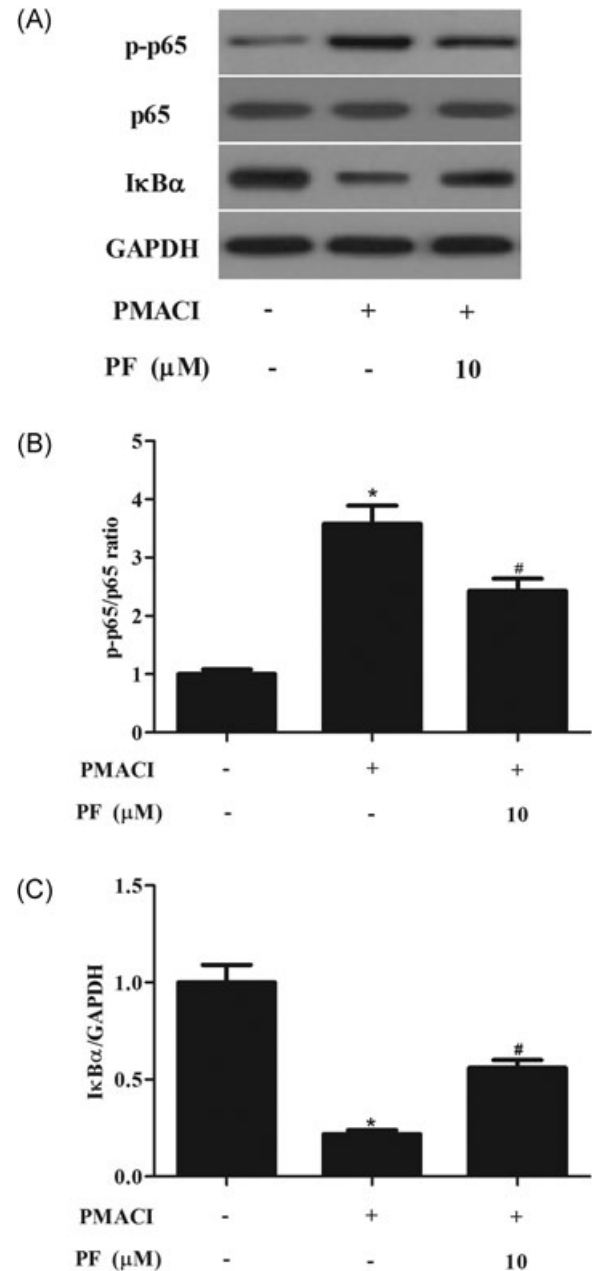


FIGURE 4 PF prevents NF- κ B activation in activated HMC-1 cells. HMC-1 cells (1×10^5 cells per well) were pretreated with 10 μ M PF for 1 hour before incubation with 25 nM PMA plus 1 μ M A23187 (PMACI) for 2 hours. (A) The levels of p-p65, p65, and I κ B α were measured using Western blot analysis. (B,C) Quantification analysis was performed using Gel-Pro Analyzer version 4.0 software. Data are expressed as mean $\pm$ SD of 3 independent experiments. * $P < .05$ vs control; # $P < .05$ vs PMACI. GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HMC-1, human mast cell line-1; NF- κ B, nuclear factor κ B; PF, paeoniflorin; PMACI, phorbol-12-myristate 13-acetate plus calcium ionophore

cells exposed to PMACI compared with the control group. However, pretreatment with PF could attenuate the phosphorylation of p38, ERK, and JNK in activated HMC-1 cells (Figure 5).

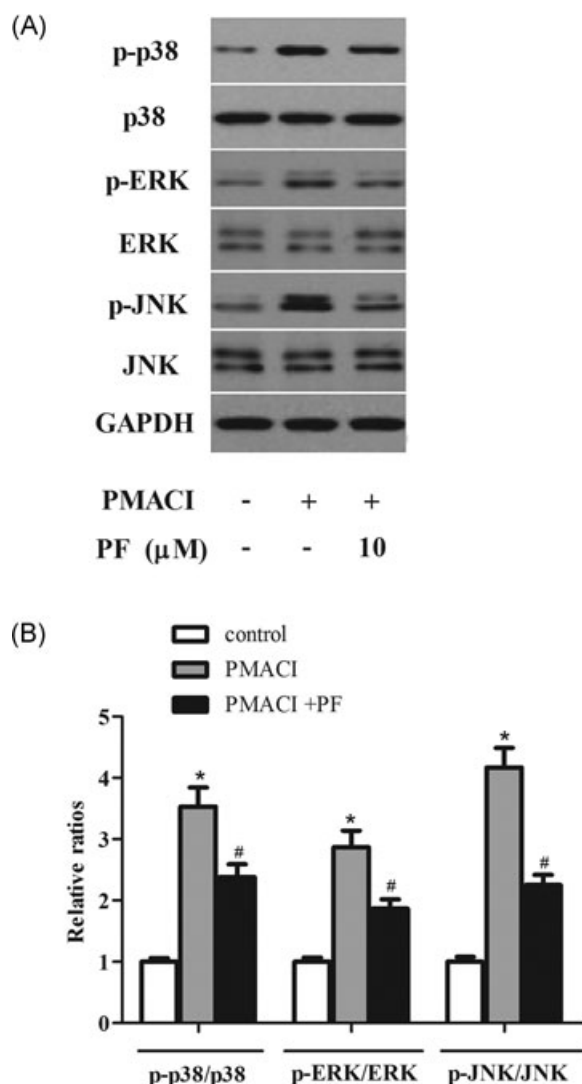


FIGURE 5 PF prevents the activation of mitogen-activated protein kinase pathway in activated HMC-1 cells. HMC-1 cells (1×10^5 cells per well) were pretreated with 10 μ M PF for 1 hour before incubation with 25 nM PMA plus 1 μ M A23187 (PMACI) for 2 hours. (A) The levels of p-p38, p38, p-ERK, ERK, p-JNK, and JNK were detected using Western blot analysis. (B) Quantification analysis was performed using Gel-Pro Analyzer version 4.0 software. Data are expressed as mean $\pm$ SD of 3 independent experiments. * $P < .05$ vs control; # $P < .05$ vs PMACI. GAPDH, glyceraldehyde 3-phosphate dehydrogenase; HMC-1, human mast cell line-1; PF, paeoniflorin; PMACI, phorbol-12-myristate 13-acetate plus calcium ionophore; SD, standard deviation

4 | DISCUSSION

In the current study, we adopted PMACI-stimulated HMC-1 cell injury model to investigate the antiallergic and anti-inflammatory effects of PF on activated mast cells. Our results demonstrated that pretreatment with PF effectively attenuated PMACI-induced production of TNF- α and IL-1 β in HMC-1 cells. In addition,

PF significantly suppressed PMACI-induced histamine release and caspase-1 activation in HMC-1 cells. Furthermore, pretreatment with PF prevented the activation of NF- κ B and MAPK signaling pathways in activated HMC-1 cells.

Pro-inflammatory cytokines play critical roles in triggering allergic inflammation in mast cells. TNF- α is required for both the production of notably T helper 2 cytokines and the migration of T helper 2 cells to the sites of allergic inflammation.¹¹ Several studies showed that the levels of IL-1 β , IL-4, and IL-5 are upregulated in nasal secretions from patients with allergic rhinitis.^{12,13} In addition, a study by Hu et al¹⁴ reported that the blockade of TNF- α and IL-1 β can alleviate pathological allergic inflammation in the nasal mucosa and lung tissues in allergic rhinitis guinea pigs. In this study, we found that PMACI treatment induced the production of TNF- α and IL-1 β in HMC-1 cells. However, these effects were significantly prevented by PF. These results are similar to a previous study showing that PF could reduce the production of IL-1 β , IL-6, and TNF- α in a rat model of high-fat diet-induced atherosclerosis.¹⁵ These data suggest that PF exerts an antiallergic effect in activated HMC-1 cells via downregulation of the production of pro-inflammatory cytokines.

Histamine, an important mediator of allergic reactions, is implicated in the pathogenesis of allergic rhinitis.^{16,17} It was reported that histamine nasal insufflation can induce nasal itch, sneezing, rhinorrhea, and nasal blockage.¹⁸ In the current study, our data showed that PF markedly inhibited PMACI-induced histamine release in HMC-1 cells. These results imply that PF can exert an antiallergic effect in activated HMC-1 cells by the inhibition of histamine release.

Caspase-1 is a member of the caspase family and plays a crucial role in the regulation of inflammatory and immune responses.¹⁹ It was reported that caspase-1 activity was significantly increased in an animal model of allergic rhinitis.²⁰ Herein, we demonstrated that pretreatment with PF efficiently inhibited caspase-1 activation in HMC-1 cells exposed to PMACI. These data suggest that the antiallergic effects of PF are associated with the inhibition of caspase-1 activation in activated mast cells.

The activation of NF- κ B pathway plays an important role in inflammatory response.^{21,22} In response to stimuli, the inhibitory protein I κ B α is phosphorylated by IKK α / β , ubiquitinated, and rapidly degraded by the proteasome, allowing NF- κ B to release from I κ B and translocate to the nucleus and regulate a large number of genes involved in inflammation, including cytokines (eg, TNF, IL-1, IL-8, and IL-6).²³ Recently, a study showed that local NF- κ B inhibition using NF- κ B decoy oligodeoxynucleotides suppressed the

allergic response in a murine model of allergic rhinitis.²⁴ In the current study, we found that pretreatment with PF significantly prevented PMACI-induced phosphorylation of NF- κ B/p65 and degradation of I κ B α in HMC-1 cells, which suggest that the antiallergic effect of PF on inflammatory response in activated HMC-1 cells may be responsible for the regulation of NF- κ B signaling pathway.

The MAPK signaling pathway has been shown to be involved in the synthesis of inflammation mediators.²⁵⁻²⁷ The activation of ERK1/2 is responsible for the production of TNF- α , IL-3, and IL-13 in mast cells.²⁸ Therefore, inhibition of the MAPK pathway might be an effective approach to treat inflammatory response. Our findings showed that PF prevented PMACI-induced MAPK activation in HMC-1 cells. These data imply that PF exerts the antiallergic effect by modulating mast cell-mediated allergic inflammatory response, at least, in part, through the inactivation of MAPK signaling pathway.

In conclusion, these data indicated that PF attenuated the mast cell-mediated allergic inflammatory response through suppressing the NF- κ B and MAPK signaling pathways. These findings suggest that PF would be beneficial for the treatment of mast cell-mediated allergic reactions.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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