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Original Article

Suppressing NF-κB/Caspase-1 Activation is a Mechanism Involved in the Anti-inflammatory Effect of Rubi Fructus in Stimulated HMC-1 Cells

Mi-Ok Yang[1,*] and Noh-Yil Myung[2,†,]**

[1]*Wonkwang Institute of Nature Healthcare Studies, Iksan 54538, Korea*
[2]*Department of Oriental Medicine and Healthcare, Wonkwang Digital University, Iksan 54538, Korea*

Inflammation plays an important role in immune system's response to tissue injury and biological stimuli. However, excessive inflammation can cause tissue damage. Therefore, the development of naturally derived anti-inflammatory agents have received broad attention. In this study, we investigated the anti-inflammatory mechanism of Rubi Fructus (RF) extract on the mast cell-mediated inflammatory response. To determine the regulatory mechanism of RF in inflammatory reaction, we evaluated the effects of RF on secretion of interleukin (IL)-8, IL-6 and tumor necrosis factor (TNF)-α and activation of nuclear factor-κB (NF-κB) and caspase-1 in activated human mast cells-1 (HMC-1). The results showed that RF attenuated IL-8, IL-6 and TNF-α secretion in a concentration-dependent manner. Moreover, RF significantly attenuated caspase-1and NF-κB activation in activated HMC-1. Conclusively, the present results provide evidence that RF may be a promising agent for anti-inflammatory therapy.

Key Words: Rubi Fructus, Mast cells, Inflammatory cytokines, Nuclear factor-κB, Caspase-1

INTRODUCTION

Inflammatory reaction is an important pathological process that occurs during disease development. Inflammatory responses are especially beneficial for protecting against injury and improve wound healing (Lee et al., 2013). However, excessive inflammation can cause tissue damage. Mast cells activation is mandatory for allergic reactions and play an important role in the inflammatory reaction (Solimando et al., 2022). In inflammatory response, mast cells can induce tumor necrosis factor (TNF)-α, tryptase, interleukin (IL)-8, histamine, and other chemokines, leading to tissue damage. Inflammatory cytokines derived from mast cells are linked to various chronic diseases, including atopic dermatitis and asthma (Moon et al., 2019). Therefore, modulating excess inflammatory cytokines may help develop treatments for inflammatory-related diseases.

Nuclear factor-κB (NF-κB) perform a key role in regulating the expression of inflammatory-related genes at transcription level. In inflammatory process, the IκB kinase complex is phosphorylated and degraded. This in turn, activated NF-κB is translocated into the nucleus, leading to induced transcription of inflammatory mediators (Gadaleta et al., 2011).

Caspase-1 is a member of the caspases family and play crucial roles in diverse cellular processes (Broz et al., 2010). Increased caspase-1 will lead to the inducing of active IL-1β and IL-18, contributing to chronic inflammation. It was reported that caspase-1 inhibitor attenuated the inflammatory

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*Ph.D., **Professor.
†Corresponding author: Noh-Yil Myung. Department of Oriental Medicine and Healthcare, Wonkwang Digital University, Iksan 54538, Korea.
Tel: +82-70-5227-3492, Fax: +82-63-843-2856, e-mail: myungnohyil@wdu.ac.kr

response via down-regulation of NF-κB activation, indicating that caspase-1 is an upstream of NF-κB (Moon and Kim, 2011). For this reason, inhibiting of NF-κB and caspase-1 activation is an excellent strategy against treating inflammatory disorders.

Various herbal plants have been used to prevent and treat many diseases. Recent studies have reported that herbal plants have various pharmacological applications. Rubi Fructus (RF), the fruits of Rubus core anus Miquel (Rosaceae), has been reported to have various biological properties, including antioxidant, and anticancer properties as well as effects on impotence (Cha et al., 2001; Jung et al., 2014; Nam et al., 2014). Recently, it was reported that RF alleviates macrophage activation and adipocyte differentiation (Kim et al., 2020). RF contains various functional constituents such as polyphenols, anthocyanins, gallic acid and 23-hydroxytormentic acid (Lee et al., 2003). It has been found that constituents of RF have anti-carcinogenic, antioxidant, and anti-inflammatory effects (Dong et al., 2018). Although numerous and diverse biological activities of RF have been identified, the precise mechanism of RF on mast cell-related inflammatory reaction is not well understood. Hence, the main purpose of this study was to explore the effect of RF on the inducing of histamine, inflammatory cytokine and activation of NF-κB/caspase-1 in activated human mast cells (HMC-1) to determine the possible anti-inflammatory mechanism of RF.

MATERIALS AND METHODS

Reagents

4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), phorbol 12-myristate 13-acetate (PMA), Calcium ionophore A23187, avidin peroxidase (AP), phosphate buffered saline (PBS) and other reagents were supplied by Sigma-Aldrich Co. (St. Louis, USA). The cytokine assay kits for human IL-8/ IL-6/TNF-α were purchased from BD Biosciences (CA, USA). Specific antibody for NF-κB was supplied by Santa Cruz Biotechnology (CA, USA). Fetal bovine serum (FBS), Iscove's Modified Dulbecco's Medium (IMDM), enhanced chemiluminesence (ECL), and bicinchoninic acid (BCA) were supplied by Thermo Fisher Scientific Inc. (IL, USA.). Caspase-1 colorimetric assay kit was purchased from R&D System Inc. (MN, USA).

Preparation of RF extract

Dried fruits of RF (100 g) were extracted in 1 L of a 70% aqueous ethanol solution at room temperature, frozen and lyophilized (Sunileyela, EYELA-FDU-1200, Japan). The powdered RF extracts (yield, 12.7%) were dissolved in PBS and then filtered through 0.22 μm filters (GVS ABLUO, Fisher scientific, USA).

Cell culture

Cells were maintained in IMDM supplemented with 10% FBS, penicillin (100 IU/mL), and streptomycin (100 μg/mL) at 37℃ in 5% CO_2 atmosphere. HMC-1 was activated by 50 nM PMA plus 1 mg/mL calcium ionophore A23187 (PMACI).

MTT assay for cell cytotoxicity

To determine cell viability after treatment with different concentrations of RF, the MTT colorimetric assay was conducted. Briefly, Cells were incubated with RF at various concentrations (0.05, 0.5 and 1 mg/mL) for 12 h and 50 μL MTT solution was added. After incubation for 4 h at 37℃ in 5% CO_2, the crystallized formazan was dissolved and the absorbance was evaluated at 570 nm (Molecular Devices, USA).

Cytokine assay

Concentrations of IL-8, IL-6 and TNF-α derived from cells were measured using ELISA assay kits (BD Biosciences, CA, USA) following the manufacturer's protocols. Briefly, micro plates were coated with anti-human IL-8, IL-6 and TNF-α monoclonal Abs and incubated overnight. After then, the sample or standard solution of IL-8, IL-6 and TNF-α was incubated. After additional washing with PBS-0.05% Tween-20 (PBS-T), the plates were incubated with biotinylated Abs of IL-8, IL-6 and TNF-α for 2 h. After washing the plates, AP and ABTS substrates were sequentially added. Color development was then measured at 405 nm.

Histamine assay

The levels of histamine secreted by cell were determined with Enzyme immunoassay kit (Neogen, USA) according to the manufacturer's protocol.

Nuclear extraction and western blot analysis

The nuclear fraction was isolated by NE-PER Nuclear extraction reagent kit per the manufacturer's instruction. After protein quantification using BCA kit, the protein was separated by gel electrophoresis, and electroblotted to membrane in transfer buffer. The membrane was then blocked with non-fat milk (5%) and blotted with primary Abs. After washing with PBS-T, membrane was reacted with horseradish-peroxidase-conjugated secondary Abs for 1 h. After washing with PBS-T, the protein bands were developed by an ECL detection system.

Luciferase reporter gene assay

NF-κB promoter activity was examined using a luciferase assay. Briefly, cells were transfected by NF-κB-luc DNA for 24 h and transfected cells were treated with different concentrations of RF and activated with PMACI. Activity was evaluated using a luciferase assay kit (Promega, WI, USA) according to the manufacturer's protocols.

Caspase-1 activity assay

The enzymatic activity of caspase-1 was determined following the manufacturer's protocols by a caspase-1 colorimetric assay kit (R&D System Inc., MN, USA).

Statistical analysis

Data were expressed as mean ± standard deviation (S.D). The statistical analyses were conducted using an independent *t*-test and ANOVA analysis. $P < 0.05$ was considered significant for the differences.

RESULTS

Effect of RF on cell viability and histamine increase in activated-HMC-1 cells

Activated mast cells increase inflammatory mediators including histamine, tryptase, and cytokine, leading to allergic inflammation (Theoharides et al., 2015). We firstly explored the effect of RF on cell viability and histamine secretion induced by PMACI. The cells were pretreated with RF (0.05, 0.5 and 1 mg/mL) and the cytotoxic effect of RF was evaluated using an MTT assay. Result showed that RF did not affect cell viability (Fig. 1A). It is known that mast cell-derived histamine initiates allergic inflammation (Thurmond et al., 2008). Thus, we measured the regulatory effect of RF on histamine increase in activated HMC-1 cells. We found that RF decreased PMACI-induced histamine levels in a concentration-dependent manner (Fig. 1B). The suppression rate of the histamine levels by RF (1 mg/mL) was approximately 25.2% ($P < 0.05$). The results indicate that RF can exert an anti-allergic effect through attenuation of histamine increase in activated-mast cells.

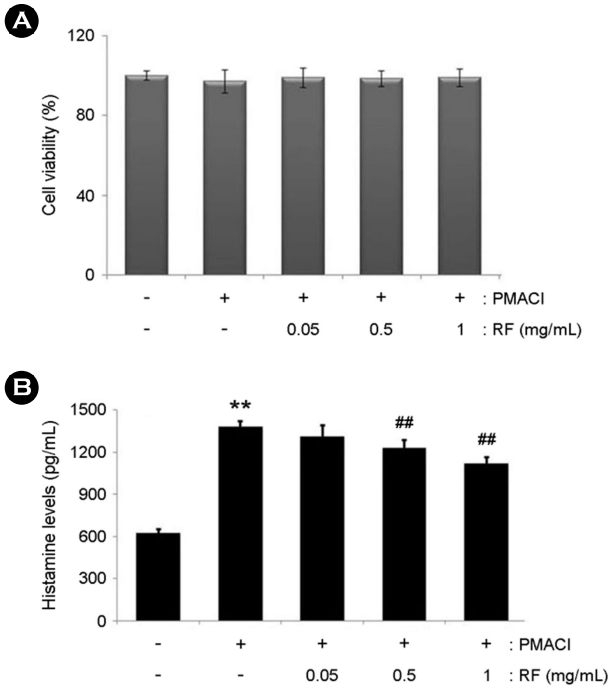

Fig. 1. Effects of RF on cell viability and histamine in activated HMC-1 cells. (A) Cells (3×10^5cells/well) were incubated with different concentration (0.05, 0.5 and 1 mg/mL) of RF for 12 h and cell viability was examined using the MTT assay. (B) Cells (1×10^6 cells/well) were treated with various concentration of RF before stimulation with PMACI for 2 h. Histamine concentration was measured with a histamine assay kit. Values are presented as mean ± standard deviation of independent experiments ($^{**}P < 0.05$ vs. control, $^{\#\#}P < 0.05$ vs. PMACI alone treatment).

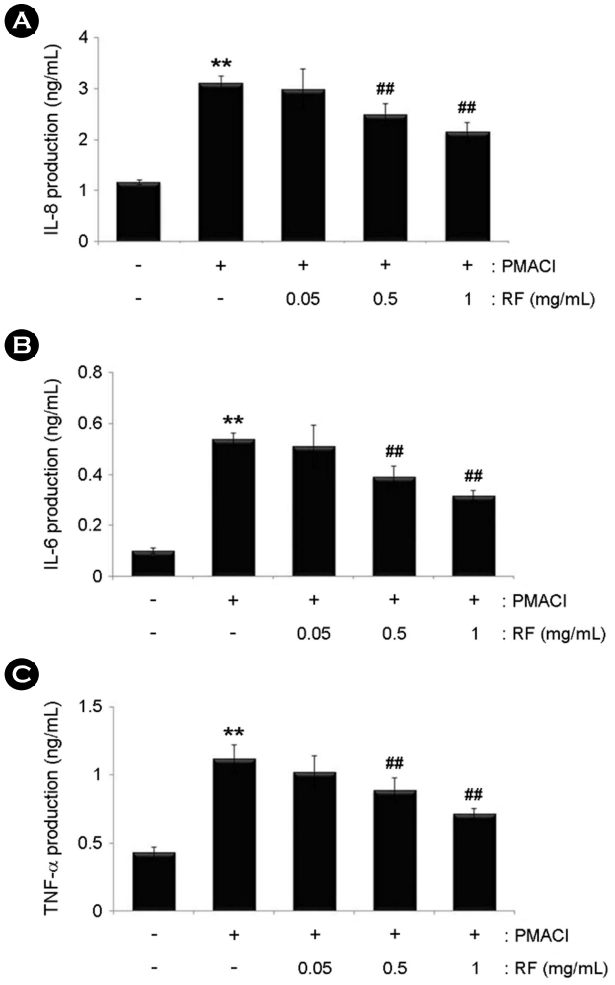

Fig. 2. Effects of RF on IL-8, IL-6 and TNF-α secretion levels in activated HMC-1 cells. (A, B and C) Cells (3×10^5 cells/well) were incubated with different concentration (0.05, 0.5 and 1 mg /mL) of RF for 1 h and stimulation with PMACI for 7 h. IL-8, IL-6, and TNF-α concentrations were determined with ELISA kits. Values are presented as mean ± standard deviation of independent experiments ($^{**}P < 0.05$ vs. control, $^{\#\#}P < 0.05$ vs. PMACI alone treatment).

Effect of RF on inflammatory cytokine increase in activated HMC-1 cells

Inflammatory cytokines are linked to various inflammatory disorders. Thus, attenuation of inflammatory cytokines is a therapeutic strategy against treating inflammation disease (Birrell et al., 2005). In this study, ELISAs were performed to evaluate the anti-inflammatory effect of RF on IL-8, IL-6 and TNF-α release in PMACI-activated HMC-1 cells. Cells were incubated with RF (0.05, 0.5 and 1 mg/mL) and activation with PMACI for 7 h. Results showed that PMACI alone inducedIL-8, IL-6 and TNF-α secretion in activated HMC-1cells. However, RF attenuated the PMACI-induced increase IL-8, IL-6 and TNF-α levels in a concentration-dependent manners (Fig. 2). The suppression rates of IL-8, IL-6 and TNF-α increase by RF (1 mg/mL) were approximately 30.8% ($P < 0.05$), 37.8% ($P < 0.05$), and 34.9% ($P < 0.05$), respectively.

Effect of RF on NF-κB activation in activated HMC-1 cells

Activated NF-κB is a representative factor in the pathogenesis of allergic inflammation and alleviation of NF-κB activation is linked to anti-inflammatory strategy (Hayden and Ghosh, 2008). To investigate the mechanism underlying the anti-inflammatory effect of RF, we examined the potential effect of RF on NF-κB activation in activated HMC-1 cells. Since NF-κB activation requires nuclear NF-κB translocation, we determined the effects of RF on these processes using western blot analysis. Fig. 3A shows RF attenuated PMACI-induced the NF-κB translocation in the nucleus. NF-κB relative level was represented in Fig. 3B. To examine the regulatory effects of RF on NF-κB activation, we determined the effect of RF on NF-κB the promoter activity using a luciferase reporter assay. We found that PMACI considerably increased the luciferase reporter gene activity whereas RF inhibited enhanced these phenomenon (Fig. 3C). The inhibition rate of NF-κB luciferase activity by RF (1 mg/mL) was approximately 33.3% ($P < 0.05$).

Effect of RF on caspase-1 activation in activated HMC-1 cells

Caspase-1 activity is related to the inflammatory response via an increase in inflammatory mediators including IL-1β (Yu et al., 2014). To elucidate the anti-inflammatory mechanisms of RF, we determined the inhibitory effect of RF on caspase-1 catalytic activity in activated HMC-1 cells. Results revealed that the PMACI-enhanced caspase-1 activities were remarkably inhibited by RF in a concentration-dependent manners (Fig. 4). The suppression rates of caspase-1 activity by RF (1 mg/mL) were approximately 29.1% ($P < 0.05$).

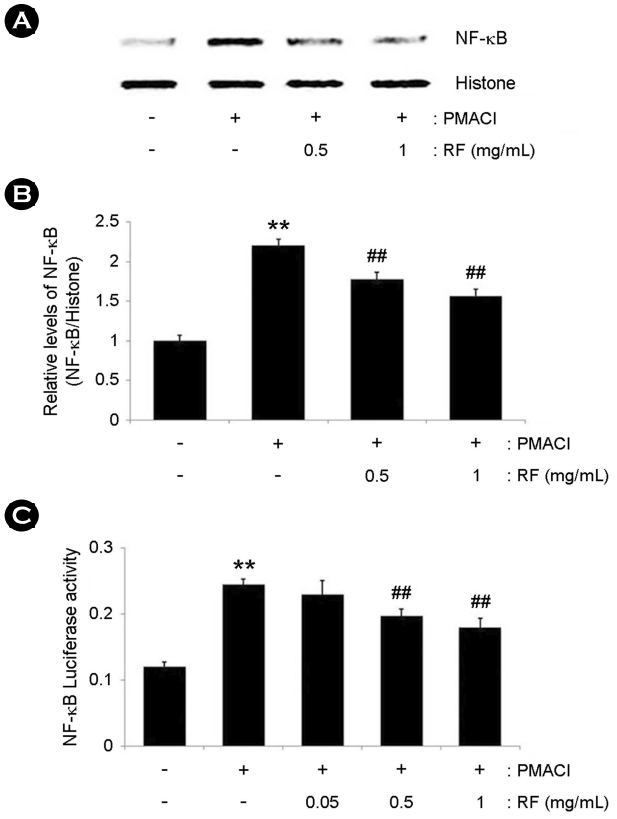

Fig. 3. Effect of RF on NF-κB translocation and promoter activity in activated HMC-1 cells. Cells (5×10^6 cells/well) were incubated with various concentration (0.5 and 1 mg/mL) of RF and then activated with PMACI for 2 h. (A) Nuclear extracts were isolated and measured for NF-κB (RelA/p65) expression by Western blot analysis. (B) Relative NF-κB level was presented. (C) NF-κB promoter activity was examined by a luciferase assay kit. Values are presented as mean ± standard deviation of independent experiments ($^{**}P < 0.05$ vs. control, $^{\#\#}P < 0.05$ vs. PMACI alone treatment).

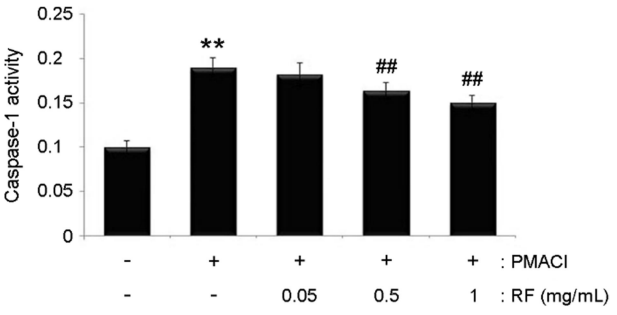

Fig. 4. Effect of RF on caspase-1 activation in activated HMC-1 cells. Cells (5×10^6 cells/well) were pretreated with RF at different concentrations (0.05, 0.5, and 1 mg/mL) for 1 h and activation with PMACI for 4 h. Caspase-1 enzymatic activity was evaluated using a colorimetric assay kit. Values are presented as mean ± standard deviation of independent experiments ($^{**}P < 0.05$ vs. control, $^{\#\#}P < 0.05$ vs. PMACI alone treatment).

DISCUSSION

Natural products as potential treatment options for various diseases have gained growing interest (Huang et al., 2019; Kim et al., 2021). Although natural plants have been used in alternative medicines, information on the anti-inflammatory mechanisms involved in potential effect of natural plants are limited. The present study was conducted to examine the mechanisms involved in the effect of RF in mast cell-related allergic inflammation. Findings of this result showed that RF effectively attenuated PMACI-induced histamine, IL-8, IL-6 and TNF-α secretion in HMC-1cells. Additionally, it was found that the regulatory mechanisms of RF on allergic inflammation involved NF-κB/caspase-1 inhibition in PMACI-activated HMC-1 cells.

Inflammatory reaction is generally a defense response to numerous and various stimuli. A moderate inflammatory response is necessary to attenuate infections, remove damaged cells, and initiate the tissue recovery (Robb et al., 2016; Squiccimarro et al., 2022). However, excessive inflammatory reaction might exacerbate tissues damage or induce inflammatory disorders. Mast cells play important roles in inflammatory process by regulating immune responses through increase of histamine, leukotriene and cytokines (Forsythe, 2016). Emerging evidence indicated that histamine derived from mast cells has a biological role in triggering allergic inflammatory response (Jemima et al., 2014; Tanaka and Furuta, 2021). Therefore, attenuation of histamine release help treat allergic inflammatory disease. Our results revealed that RF considerably suppressed PMACI-enhanced histamine release (Fig. 1B). The suppression rate of histamine production by RF (1 mg/mL) was approximately 25.2% ($P < 0.05$). This results implicated that RF displays anti-allergic activity by inhibiting histamine release in activated HCM-1.

In an inflammatory process, mast cells increased an array of cytokines with the potential to exacerbate allergic inflammation (Caughey, 2016). It was been reported that high levels of IL-6 cause inflammatory response, and induces of IgE release (Olivera et al., 2018). Mast cell-derived IL-8 can act as a chemotactic agent for immune cells, activating inflammatory reaction. TNF-α derived from mast cells can

accumulate neutrophil and eosinophil, resulting in inflammatory disorders (Solimando et al., 2022). In this study, we demonstrated that RF attenuated PMACI-induced the increase levels of IL-8, IL-6 and TNF-α in activated HCM-1. The suppression rate of IL-8, IL-6 and TNF-α by RF (1 mg/mL) was approximately 30.8%, 37.3%, and 34.9%, respectively. These results indicated that RF can exert an anti-inflammatory properties by suppressing the production of inflammatory cytokine.

Recently, a number of studies have showed that activated NF-κB is a major factor in the pathogenesis of allergic inflammation (Barnabei et al., 2021). Deficiencies of NF-κB attenuate the inflammatory reaction by suppression of inflammatory mediators in mast cells (DiDonato et al., 2012). Accumulating evidence has reported that caspase-1 can exert regulatory activity by inducing various inflammatory pathways (Wu et al., 2018). Caspase-1 deficiency led to inhibit the inflammatory response in an allergic rhinitis model (Han et al., 2017). Caspase-1 inhibitor suppressed the NF-κB activation, suggesting NF-κB pathways is regulated by caspase-1 (Moon and Kim, 2011). These studies demonstrated modulating of NF-κB and caspase-1 activation may be helpful in development of treatments for inflammatory -related disease. To explore the anti-inflammatory mechanism of RF, we investigated whether RF could attenuate the PMACI-induced activation of NF-κB//caspase-1 in HMC-1 cells. We found that RF inhibited PMACI-induced the NF-κB translocation into the nucleus and NF-κB the promoter activity. Additionally, we confirmed that RF attenuated the caspase-1 activation induced by PMACI in a concentration-dependent manner. The suppression rate of caspase-1 activity by RF (1 mg/mL) was approximately 29.1% ($P < 0.05$). Taken together, our results indicate that the regulatory effect of RF on mast cell-related inflammation might be resulting from blockage of NF-κB/caspase-1 activation in activated HMC-1 cells.

In summary, the present study indicated that the anti-inflammatory effects of RF can attributed to regulation of histamine and inflammatory cytokines in PMACI-activated HMC-1 cells. Additionally, we suggested that the anti-inflammatory mechanism of RF in mast cells results from attenuation of NF-κB/caspase-1 activation. Our novel results may provide experimental evidence that RF might be potential agent for treating inflammation-related diseases.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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