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Original Article

Targeting NF-κB Signaling with Naringenin: Molecular Docking and Cellular Insights into Asthma Therapy

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ABSTRACT

Background: Asthma is a chronic inflammatory lung disease where the airways are affected by immune dysregulation, eosinophilic inflammation and activation of NF-κB signaling pathways. Integrated *in silico* and *in vitro* analyses of the therapeutic potential of an endogenous citrus-flavonoid, naringenin, in airway inflammation via NF-κB mediated pathways. **Materials and Methods:** Molecular docking was used to evaluate the naringenin binding to NF-κB p105 subunit, and anti-inflammatory activity was determined by the MTT and ELISA assays in A549 cells stimulated by TNF-α/IL-4, which were used to measure CCL11, CCL26, IL-8, and TSLP. **Results:** Naringenin bound NF-κB p105 with the binding affinity of -7.5 kcal/mol due to hydrogen-bonding and hydrophobic interactions. Non-cytotoxic concentrations (80% or more cells remaining viable) dose-dependently inhibited the production of CCL11, CCL26, IL-8 and TSLP induced by stimulation with TNF-α/IL-4, effects similar to Bay 11-7082. **Conclusion:** Naringenin is an anti-inflammatory agent that inhibits NF-κB activity, which suggests its potential as a natural anti-asthmatic agent.

Keywords: Airway Inflammation, Asthma, Eotaxin, Molecular Docking, Naringenin, NF-κB p105, TSLP.

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INTRODUCTION

Asthma is characterized by airway remodeling, bronchoconstriction, mucus hypersecretion and variable airflow obstruction and affects over 300 million people worldwide (Hough *et al*., 2020; Global Initiative for Asthma, 2023). From a clinical perspective, it manifests as wheezing and dyspnea, chest tightness, and cough, which are due to a combination of genetic predisposition and environmental factors (Hamid and Tulic, 2009; Levy *et al*., 2023). Eosinophils, mast cells, macrophages, dendritic cells, T-helper 2 lymphocytes, neutrophils, and airway epithelial cells are the key cells involved in airway inflammation that produce cytokines and chemokines upon contact with allergens, pollutants, cigarette smoke, or pathogens (Hammad and Lambrecht, 2021; Ogulur *et al*., 2025).

The nuclear factor kappa-B (NF-κB) pathway is a key pathway in asthma, which controls the expression of inflammatory genes. When activated by inflammatory stimuli, NF-κB enters the nucleus and turns on the expression of pro-inflammatory cytokines, chemokines and enzymes such as TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-13, COX-2 and iNOS, which contribute to airway inflammation and disease progression (Ji and Li, 2023). Airway cells from asthmatic patients have consistently been found to be persistently activated by NF-κB (Poynter *et al*., 2004).

Although current asthma treatments (such as inhaled corticosteroids, bronchodilators, leukotriene antagonists, and biologics) are effective, they are not completely effective, may be resistant to corticosteroid treatment, and have adverse side effects (Lim *et al*., 2026). Inhibition of NF-κB is highly appealing as a therapeutic target, as it decreases airway inflammation, eosinophil recruitment, cytokine production and airway hyperresponsiveness (Murphy *et al*., 2010; Guo *et al*., 2024). Curcumin, quercetin, and resveratrol are a few phytochemicals that have anti-inflammatory properties by suppressing NF-κB signaling (Mishra *et al*., 2018).

With the advances in Computational biology and molecular docking, the identification of potential NF-κB inhibitors has been made quick and easy as it helps to predict the protein-ligand interaction before experimental testing (Sliwoski *et al*., 2014; Patel *et al*., 2024). In this study, *in silico* molecular docking was performed with *in vitro* cellular assays to assess the bioactive compounds targeting the NF-κB p105 subunit and to explore their efficacy in blocking inflammatory responses in human bronchial epithelial cells, which showed therapeutic promise for asthma.

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MATERIALS AND METHODS

In silico modelling of target protein

The sequence for human NF-κB p105 (UniProt ID: P19838) was obtained from UniProt, and the model was built using the SWISS-MODEL server, because a complete crystal structure was not available (Waterhouse *et al.* 2018). The best model was minimally energy docked in UCSF Chimera (Pettersen *et al.*, 2004), converted to AutoDock Vina PDBQT format using AutoDock Tools v1.5.7, and docked with ligands with AutoDock Vina (Trott and Olson, 2010).

Preparation of ligand molecules

Fifteen citrus flavanones were found in the literature that have anti-inflammatory and immunomodulatory activities. Their structures were retrieved from PubChem in SDF format, and thus were optimized using Open Babel with force field MMFF94, hydrogen atoms were added and Gasteiger charges were assigned, followed by the definition of the torsional bonds and the conversion to PDBQT format for the molecular docking with AutoDock Vina, performed with PyRx.

Molecular docking

Virtual screening and molecular docking with AutoDock Vina integrated with PyRx were used to look for potential NF-κB p105 inhibitors. The docking was performed in an optimized active site grid with default parameters, except for the exhaustiveness value of 8, and the poses were ranked based on the predicted binding free energy (Trott and Olson, 2010). The best protein-ligand complexes, based on the binding affinity, were analyzed using Discovery Studio Visualizer (v2021) and UCSF Chimera to characterize the hydrogen bonds, hydrophobic, van der Waals, π-π stacking, π-alkyl, and electrostatic interactions (Pettersen *et al.*, 2004).

Cell culture and treatments

Human lung epithelial cell line A549 cells were maintained in DMEM containing 10% fetal bovine serum and 1% penicillin-streptomycin at 37°C in 5% CO_2. Naringenin were dissolved in DMSO (final concentration <0.1%). Cells were stimulated for 24 hr with TNF-α (10 ng/mL) and IL-4 (10 ng/mL) leading to the induction of asthma-like inflammation. Cells were pretreated with Bay 11-7082 (5 μM) or naringenin (50 or 100 μM) for 2 hr, prior to stimulation with cytokines. Untreated and cytokine treated cells were used as control and model groups, respectively, and culture supernatants and cell lysates were harvested for analysis.

MTT Cell viability assay

MTT assays were carried out for the evaluation of the cytotoxicity of naringenin in A549 cells. Cells (1×10^4/well) were treated with naringenin (5-100 μM) for 24 hr, with DMSO (<0.1%) as the vehicle control. The formazan crystals were dissolved in DMSO after incubation with MTT solution (20 μL, 5 mg/mL) for 4 hr and the absorbance recorded at 570 nm. The absorbance of treated cells was divided by the absorbance of untreated cells and then multiplied by 100 to obtain cell viability values. Experiments were replicated three times and concentrations that provided ≥ 80-90% cell viability were chosen for further anti-inflammatory investigations.

Enzyme-Linked Immunosorbent Assay (ELISA)

Commercially available human ELISA kits (Elabscience and R&D Systems, USA) were used to quantify the concentrations of NF-κB p105, eotaxin-1 (CCL11), eotaxin-3 (CCL26), IL-8 (CXCL8), and Thymic Stromal Lymphopoietin (TSLP) in the culture supernatants of A549 cells, following the manufacturers' instructions.

Statistical analysis

All measurements are given as mean ± SD (three independent experiments). One-way ANOVA and Tukey's *post hoc* test were used to analyze the data with IBM SPSS Statistics 21. p-value< 0.05 was defined as statistically significant.

RESULTS

Naringenin exhibits stable binding to NF-κB *in silico*

Using molecular docking, the binding affinity of naringenin to the NF-κB p105 subunit was calculated to be -7.5 kcal/mol, suggesting that naringenin forms a stable protein-ligand complex (Figure 1). The ligand fit well into the active-site binding region showing good shape complementarity, indicating the possibility of modulating NF-κB mediated inflammatory signaling (Figures 1A and 1B). Conventional hydrogen bonds were found with Thr126, Ala137, and Asn138, along with a π-sulfur interaction with Cys123, a π-π T-shaped interaction with His117, π-alkyl interactions with Val125 and Val134, and other van der Waals interactions with Lys116, Ala127, Asp131, Val133, Gly135, Phe136, and Leu139, which all help to stabilize the complex (Figures 1C, 1D).

Naringenin was found to be concentration dependent in reducing cell viability

The cytotoxicity of naringenin to A549 cells was determined after 24 hr of treatment (Figure 2A). Naringenin was found to be concentration-dependently cell-viability reducing. The cell viability was high at 5 μM (94.3%), 10 μM (90.4%) and 25 μM (85.6%) indicating that these were minimally cytotoxic, whereas higher concentrations significantly decreased cell viability to 62.4% at 50 μM and 45.9% at 100 μM. Cells maintained in vehicles with DMSO (0.1%) had a survival rate of 98.7%, indicating little to no toxicity from vehicular DMSO. Based on this criterion of

cell viability (80-90%) 10 µM and 25 µM naringenin were chosen for further anti-inflammatory testing.

Naringenin blocks the production of CCL11, CCL26, IL-8, and TSLP by A549 cells.

Naringenin's effect on production of Eotaxin-1 (CCL11)

Eotaxin-1 (CCL11) was found to be significantly up-regulated by TNF-α/IL-4 (161.2±8.4 pg/mL vs 7.3±0.9 pg/mL in controls) and this was evidence of the induction of inflammatory responses in these cells (Figure B). Production of CCL11 was markedly decreased by Bay 11-7082 (26.4±4.5 pg/mL; *p<0.001), suggesting that NF-κB is responsible for its control. Naringenin also inhibited CCL11 secretion in a dose dependent manner, with the higher dose (100 µM) having an effect similar to Bay 11-7082 and reducing its secretion to 36.2±1.2 pg/mL.

Effect of Naringenin on Eotaxin-3 (CCL26) Production

Eosinophil inflammatory mediators were significantly increased following stimulation with TNF-α/IL-4, as compared to the control group (Eotaxin-3, CCL26, 635.4±7.3 vs 4.5±0.6 pg/mL, respectively, Figure 3A), showing increased eosinophilic inflammation. Bay 11-7082 significantly reduced CCL26 production (**104.2±3.8 pg/mL; *p<0.001), supporting NF-κB-dependent regulation. In addition, the secretion of CCL26 was also inhibited in a dose-dependent manner, with the secretion further reduced to 169.4±3.9 pg/mL at 50 µM and 120.1±3.2 pg/mL at 100 µM, suggesting the effect of naringenin in inhibiting eosinophil recruitment in asthma.

Effect of Naringenin on IL-8 Production

The stimulation of A549 with TNF-α/IL-4 led to a significant up-regulation of IL-8 (CXCL8) secretion (7315.6±105.7 vs 583.2±18.6 pg/mL in controls (Figure B), which reflects increased inflammatory signaling. Bay 11-7082 significantly reduced IL-8 levels (**1058.4±39.2 pg/mL; *p<0.001), confirming NF-κB involvement. Naringenin has also shown anti-inflammatory activity by reducing the production of IL-8 in a dose-dependent manner with a decrease to 2284.7±112.6 pg/mL at 50 µM and 1456.3±44.5 pg/mL at 100 µM.

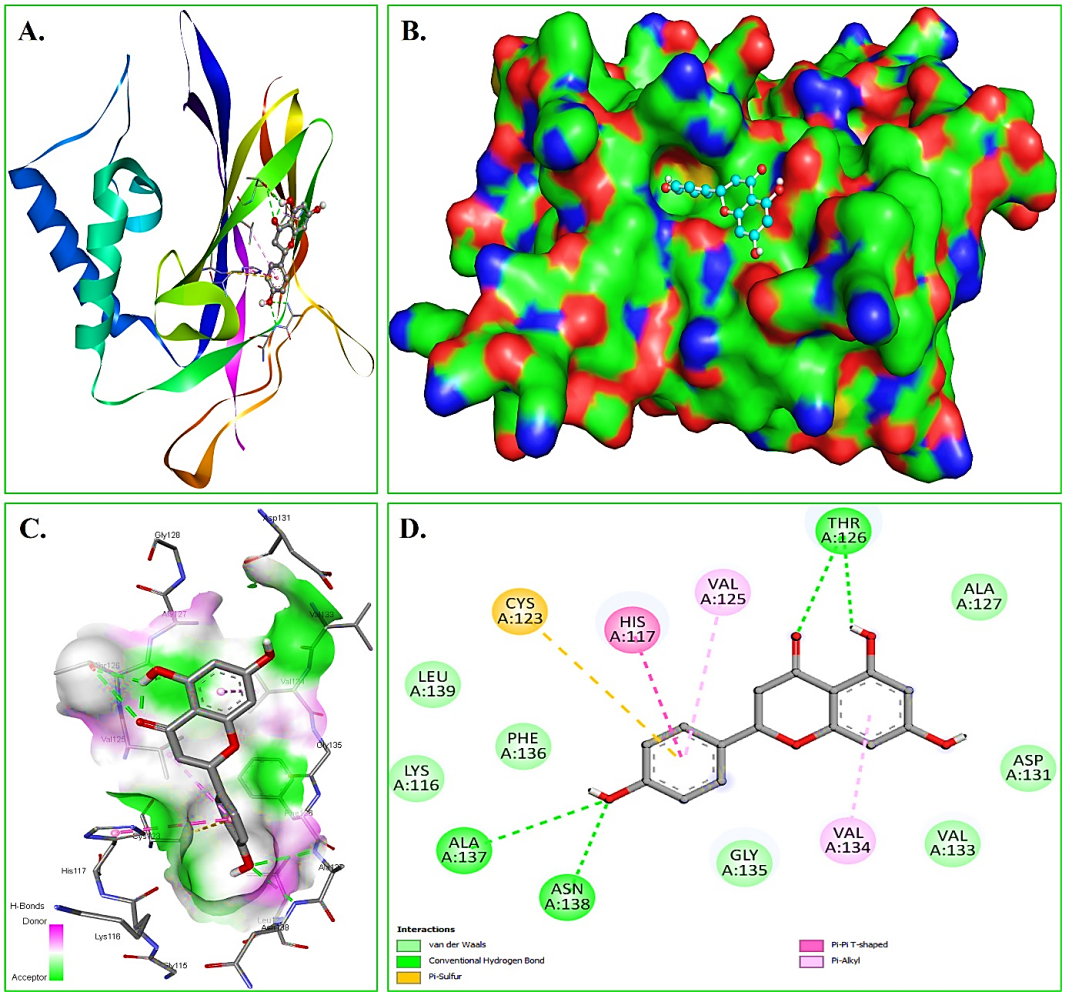


Figure 1: Molecular docking of naringenin with NF-kB p105 subunit. Binding pose in the active site: (A) (B) Top view of the ligand binding. (C) Protein-ligand interactions. Two dimensional interaction map include hydrogen bond, Van der Waals and π-interactions.

Effect of Naringenin on TSLP Production

The production of TSLP was significantly higher when cells were stimulated with both TNF-α and IL-4 (64.1±4.2 pg/mL compared to 3.4±0.4 pg/mL in cells without stimulation; Figure C) suggesting activation of inflammatory signaling pathways in the epithelium. Bay 11-7082 markedly suppressed TSLP secretion (**14.3±1.0 pg/mL; *p<0.001), confirming NF-κB involvement. At 50 µM and 100 µM, the naringenin decreased TSLP levels in a dose-dependent manner, to 32.6±1.8 pg/mL and 17.2±1.1 pg/mL respectively, comparable with the effect of the positive control.

DISCUSSION

Asthma is a chronic inflammatory airway disease in which NF-κB plays a central role by regulating the expression of cytokines, chemokines, adhesion molecules, and alarmins that drive airway inflammation and remodeling (Barnes, 1997; Poynter *et al*., 2004). Targeting this pathway therefore represents a promising therapeutic strategy. In the present study, an integrated *in silico* and *in vitro* approach demonstrated that naringenin binds favorably to the NF-κB p105 subunit and suppresses key inflammatory mediators in cytokine-stimulated A549 cells.

Molecular docking revealed a binding affinity of -7.5 kcal/mol, with hydrogen bonding and hydrophobic interactions stabilizing the NF-κB-naringenin complex, suggesting direct modulation of NF-κB activity. These findings are consistent with previous reports showing that flavonoids, including naringenin, quercetin, hesperetin, and luteolin, inhibit NF-κB signaling through similar molecular interactions (Salehi *et al*., 2019).

Naringenin significantly reduced the eosinophil-associated chemokines CCL11 and CCL26, both of which are critical mediators of eosinophilic airway inflammation and are elevated in asthma (Pease and Williams, 2001). At the higher concentration, its inhibitory effect was comparable to that of the selective NF-κB inhibitor Bay 11-7082, supporting previous evidence that naringenin suppresses NF-κB-dependent inflammatory signaling (Shi *et al*., 2009; Huang *et al*., 2024; Peng *et al*., 2024).

Naringenin also significantly decreased IL-8 (CXCL8) production, indicating its ability to attenuate neutrophil-mediated inflammation, which is particularly relevant to severe and corticosteroid-resistant asthma (Ray and Kolls, 2017). In addition, naringenin markedly suppressed TSLP, a key epithelial alarmin that initiates type-2 immune responses. The reduction in TSLP, together with decreased CCL11, CCL26, and IL-8 levels, demonstrates that naringenin modulates both upstream and downstream inflammatory pathways involved in asthma and supports previous studies linking NF-κB inhibition with reduced TSLP expression (Lee *et al*., 2008; Menzies-Gow *et al*., 2021).

Overall, the coordinated suppression of multiple inflammatory mediators suggests that naringenin exerts broad anti-inflammatory effects through inhibition of NF-κB signaling, providing an advantage over therapies targeting a single cytokine. Nevertheless, this study is limited by its *in vitro* design, and direct assessment of NF-κB activation, including nuclear translocation, IκBα phosphorylation, or reporter assays, was not performed. Future studies using animal models and mechanistic validation are warranted to confirm the therapeutic potential of naringenin in asthma.

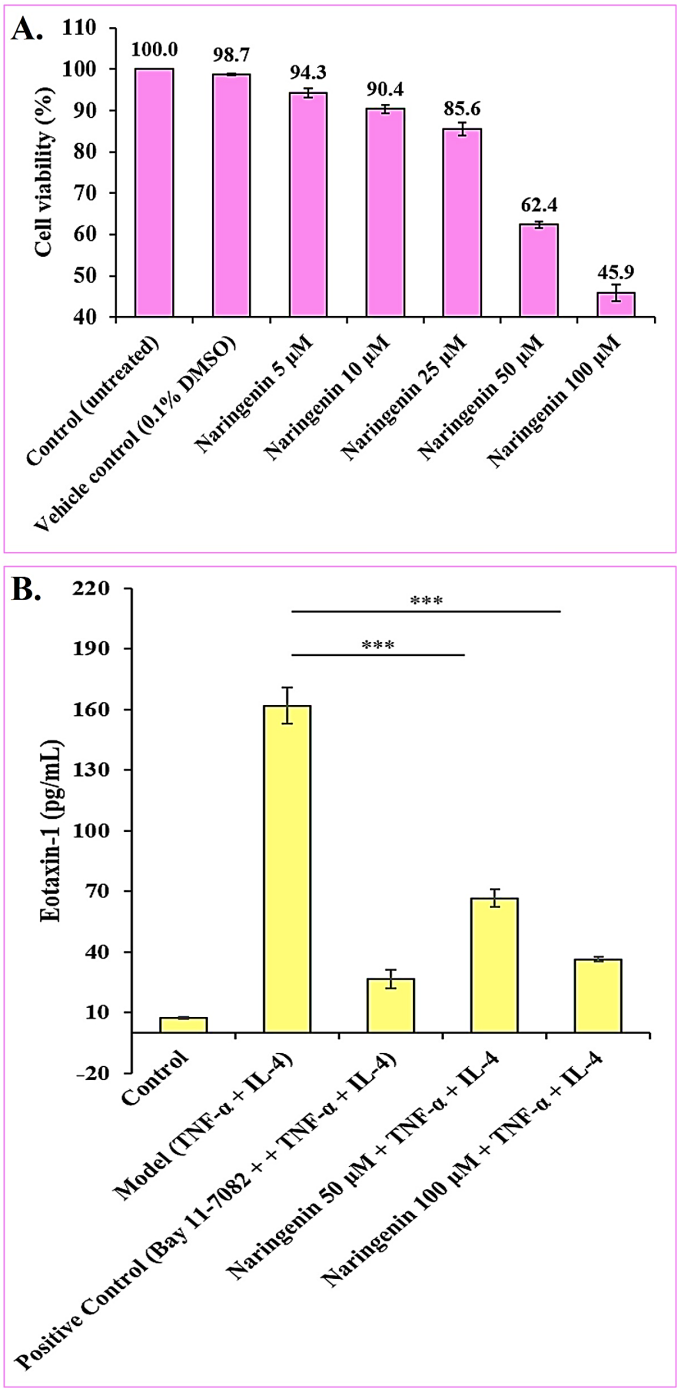


Figure 2: (A) The viability of A549 cells after treatment with naringenin (5-100 µM). (B) Dose-dependent inhibition of CCL11 (Eotaxin-1) production in the A549 cell stimulated with TNF-α/IL-4. Data are mean ± SD (n=3); ***p<0.001.

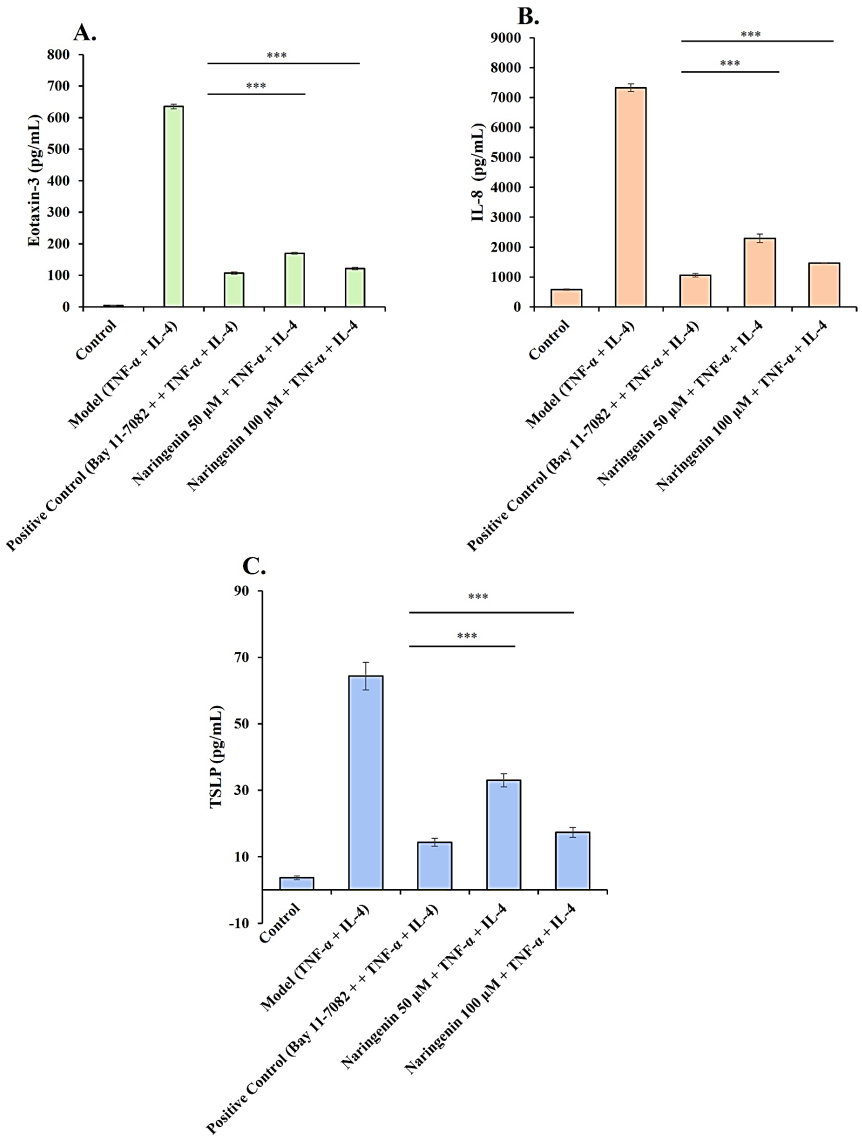


Figure 3: Protein levels of (A) CCL26, (B) IL-8 and (C) TSLP in A549 cells stimulated with TNF?/IL-4 in the presence of naringenin. Naringenin and Bay 11-7082 decreased production of inflammatory mediators in a dose-dependent manner. Data are mean ± SD (n=3); ***p<0.001.

CONCLUSION

From the above, it is concluded that the present results provide both computational and experimental evidence of naringenin as a natural compound that can be used as an asthma drug targeting NF-κB, which can inhibit multiple inflammatory mediators in the pathogenesis of asthma. Naringenin simultaneously blocks eosinophilic chemokines, neutrophil-recruiting cytokines and epithelial-derived alarmins, and might be a promising lead compound for designing novel drugs for anti-asthmatic activity.

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ABBREVIATIONS

NF-κB: Nuclear Factor Kappa B; **TNF-α:** Tumor Necrosis Factor-alpha; **IL-4:** Interleukin-4; **MTT:** 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **CCL11:** C-C Motif Chemokine Ligand 11; **CCL26:** C-C Motif Chemokine Ligand 26; **IL-8:** Interleukin-8; **ELISA:** Enzyme-Linked Immunosorbent Assay; **TSLP:** Thymic Stromal Lymphopoietin; **COX-2:** Cyclooxygenase-2; **3D:** Three-Dimensional; **PDB:** Protein Data Bank; **GMQE:** Global Model Quality Estimation; **QMEAN:** Qualitative Model Energy Analysis; **PROCHECK:** Protein Structure Checking Tool; **ERRAT:** Error Assessment of Protein Structures; **UCSF:** University of California, San Francisco; **SDF:** Structure Data File; **PDBQT:** Protein Data Bank, Partial Charge (Q), and Atom

Type (T); **MMFF94:** Merck Molecular Force Field 1994; **LGA:** Lamarckian Genetic Algorithm; **DMEM:** Dulbecco's Modified Eagle Medium; **DMSO:** Dimethyl Sulfoxide; **NCCS:** National Centre for Cell Science; **SD:** Standard Deviation; **ANOVA:** Analysis of Variance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Abdulrahman Alzahrani helped to conceptualize the study, design experiments, analyze data, prepare the manuscript and approved the final manuscript.

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