

Protective effect of corynoline in a murine allergic rhinitis model via inhibition of caspase-1/NF- κ B

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Abstract

Allergic rhinitis (AR) is a serious public health concern worldwide. Therefore, the present study was conducted to scrutinize the protective effect of corynoline (COR) against ovalbumin (OVA)-induced AR in BALB/c mice. The effect of COR was investigated on various parameters, such as nose-rub score, histamine intensity, level of cytokines, and NF- κ B binding activity. It was found that COR causes a significant reduction in the nose-rub score with a reduction in histamine intensity. It also causes reductions in cytokines, such as TNF- α , IL-1 β , and MIP-2, in comparison to OVA-challenged mice. COR reduces the gene expression of active caspase-1 in Western blot analysis, together with inhibition of NF- κ B binding activity. The inhibitory effect on NF- κ B binding was further substantiated by docking analysis, where COR excellently docked into the active site of NF- κ B via the creation of H-bond and π -cation interactions with Lys145. Taken altogether, our results demonstrated that COR could be used as a potential therapeutic agent against AR.

KEYWORDS

allergy, cytokines, docking, histamine, NF- κ B

1 | INTRODUCTION

Allergic rhinitis (AR) is a rising global health concern that currently affects approximately 30% of people across the world.^[1] It is also known as hay fever or allergy, which is commonly triggered by environmental factors and results in exaggerated immune reaction mediated by an IgE-associated response to indoor and outdoor allergens. Patients with AR are clinically characterized by sneezing, running nose, significant increase in eosinophils in the nasal submucosa, and epithelium as well as chronic inflammation of the nasal mucosal membrane. AR has been successfully classified into two forms, such as seasonal, which takes place only at some stage in the year in which certain plants pollinate, and perennial, which occurs year-round.^[2–7] The direct impact of AR on the economic condition of patients has been not fully understood; however, it may lead to substantial indirect cost, which significantly affects individuals and families.

The therapeutic management of AR has been largely dependent on the use of antihistamines, corticosteroids, and mast cell stabilizers, but they are associated with serious side effects, such as, drowsiness, blurred vision, confusion, body ache, insomnia, hypertension and high blood sugar, and so forth.^[8,9] Thus, it is imperative to develop or discover novel agents that are significantly able to provide beneficial effects against AR with fewer or no side effects.

Various plant-based natural products have shown promising results as antiallergic agents and have been found safe in clinical trials after formulation.^[10] These compounds showed an additional benefit upon combination with Western medicines via improving immune response against AR. Corynoline (COR), an alkaloid isolated from *Corydalis bungeana* Turcz., has been widely used in traditional Chinese medicine for treating upper respiratory tract infection.^[11] It also showed anti-inflammatory activity.^[12] However, the effect of COR against AR is yet to be explored; therefore, the present study planned to scrutinize the possible protective effects of COR in an AR animal model.

2 | RESULTS AND DISCUSSION

2.1 | Inhibitory effect of COR on ovalbumin (OVA)-induced AR mice

Allergy is caused by a specific chemical or molecule, which is known as an allergen. It initiates a cascade of events known as an allergic reaction by producing allergic antibodies (IgE).^[13] These antibodies recognize the allergen in the systemic circulation and accompany them to the body's mast cell (a type of white blood cell) for demolition. The activated mast cells in response to allergen secrete preformed proinflammatory mediators, such as histamine, serotonin, nucleotides, proteases, and tumor necrosis factor (TNF)- α , and synthesize and secrete various cytokines, chemokines, and lipid mediators, such as leukotrienes and prostaglandins. These mediators are conclusively responsible for inflammation of tissues, itching, blood vessel enlargement, enhanced secretions, and more importantly, bronchospasm.^[14–17] In the present study, the allergy in mice is induced by OVA, which induces allergic reactions in mice, similar to that of humans. It displayed characteristic allergic behaviors, such as increased sneezing and increased nose rubbing motions.^[18] Initially, the effect of COR was investigated on the physical characteristics in AR mice, such as the frequency of nose rubbing. Toward this, the various concentrations of COR were

administered to OVA-challenged mice, and the frequency of nose rubbing was quantified in 10 min. As shown in Figure 1a, the nose-rub score was found significantly elevated in OVA-challenged mice as compared with the control-treated group. However, in the COR-treated group, the nose-rub score was found significantly reduced. The COR-treated group further showed reduced levels of serum histamine, as compared with the OVA-treated group (Figure 1b). We have further examined the effect of COR on the serum immunoglobulins, such as IgE, IgG1, IgG2a, which corresponds to the immune response against AR. Various clinical studies showed circulating immunoglobulins, such as IgE and IgGs involved in type III hypersensitivity reactions. These immunoglobulins increase eosinophil permeability, which plays a role in the pathogenesis of chronic inflammations.^[19,20] It has been found that COR significantly reduces the serum level of IgE (Figure 1c) and IgG1 (Figure 1d), together with an increase in IgG2a (Figure 1e) in AR mice in a dose-dependent manner as compared with OVA-challenged groups.

2.2 | The effect of COR on levels of thymic stromal lymphopoietin (TSLP) and inflammatory cytokines

In AR, allergens after coming in contact with the mucosal membrane of the nasal cavity induce secretions of a variety of cytokines and

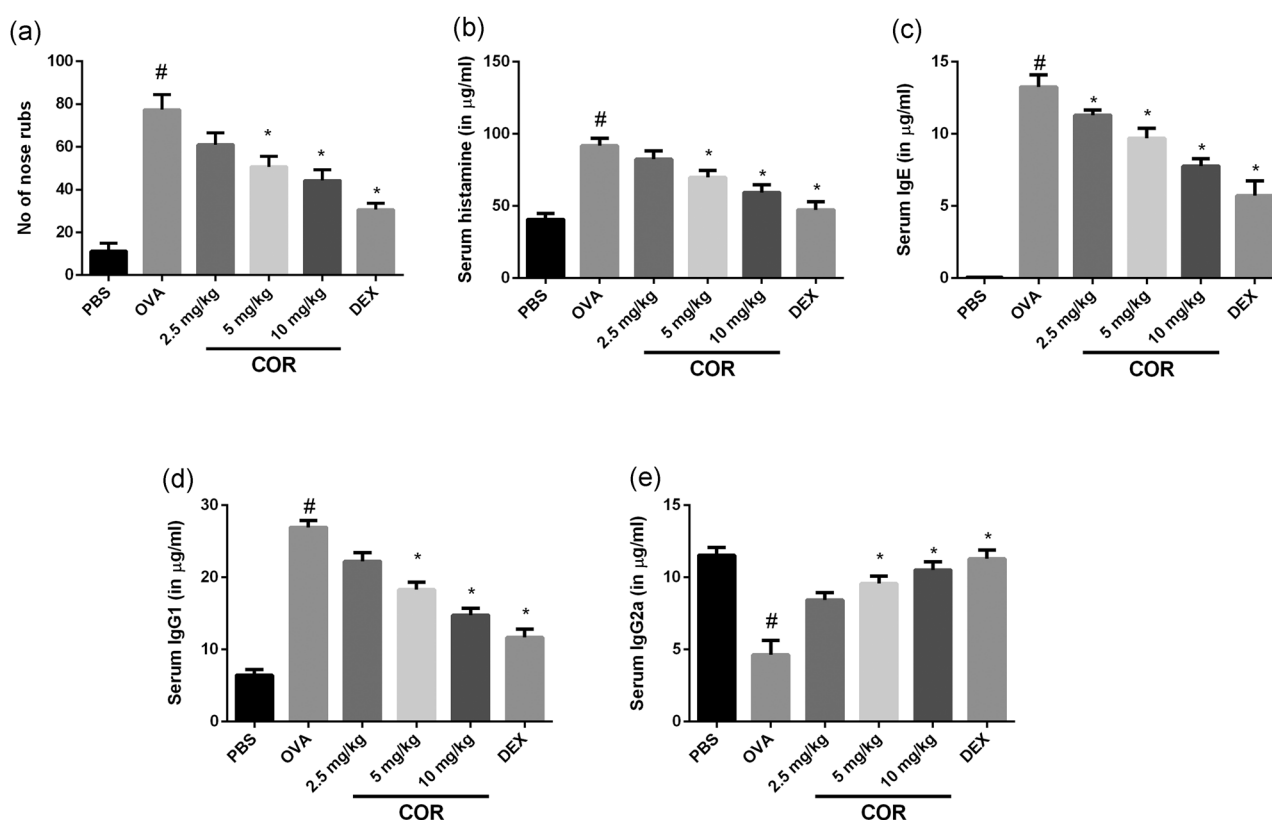


FIGURE 1 The effect of COR on (a) the nose-rub score and serum level of various biomarkers, (b) histamine, (c) IgE, (d) IgG1, and (e) IgG2a. Data are presented as the mean $\pm$ SEM of three independent experiments. COR, corynoline; DEX, dexamethasone; OVA, ovalbumin; PBS, phosphate-buffered saline. # $p < .05$, significantly different from PBS (control); * $p < .05$, significantly different from OVA-challenged mice

chemokines that are involved in driving allergic inflammatory responses. One such product is TSLP.^[21,22] TSLP is an interleukin (IL)-7-like cytokine that triggers dendritic cells and mast cells to induce T-helper (Th)2 inflammatory responses. In humans, TSLP has been linked to the pathogenesis of asthma, atopic dermatitis, and eosinophilic esophagitis.^[23,24] Numerous studies have found a good correlation between TSLP expression and AR.^[25] As presented in Figure 2a, OVA-challenged mice showed a higher level of TSLP as compared with control (phosphate-buffered saline [PBS]). However, upon administration of COR, the level of TSLP was found significantly reduced in a dose-dependent manner as compared with the OVA-treated group. In the next instance, we examined the effect of COR on various cytokines in the nasal mucosa of AR mice. It has been found that the level of IL-1 β , TNF- α , and MIP-2 was significantly elevated in the OVA-challenged group as compared with PBS (control). Moreover, a significant reduction in the level of these cytokines was observed in the COR-treated group in a concentration-dependent manner, with the maximal inhibitory activity being observed in 10 mg/kg-treated group. However, none of the COR doses showed a better effect than dexamethasone (DEX) as standard.

As shown in Figure 3a, OVA-challenged mice showed an increased level of eosinophil infiltration in the nasal mucosa of AR mice in comparison with PBS (control). Surprisingly, the enhanced

infiltration of eosinophil into the nasal mucosa was found significantly lowered in COR-treated mice. To further understand the mechanism behind this event, we further examined the effect of COR on ICAM-1 in the nasal mucosa of AR mice. ICAM-1 is deemed to be responsible for promoting the eosinophil infiltration in AR. It has been found that COR administration significantly reduces the level of ICAM-1 as compared with OVA-challenged mice (Figure 3b).

2.3 | The effect of COR on caspase-1 and NF- κ B

Inflammation is a characteristic hallmark of AR and is associated with the activation of the canonical NF- κ B signaling pathway. Various studies have reported aberrant activation of NF- κ B via caspase-1 in humans as well as in animals.^[26–31] The activation of NF- κ B triggers the release of cytokines that regulate the immune response, as well as adhesion molecules, which lead to the recruitment of leukocytes to sites of inflammation. To express the antiallergic mechanism underlying the protective effects of COR against AR, in the next instance, we intended to investigate the level of caspase-1 and NF- κ B, which is deemed as a vital regulator of AR. It has been found that COR significantly downregulated the expression of active caspase-1 in a dose-dependent manner as compared with OVA-challenged mice in

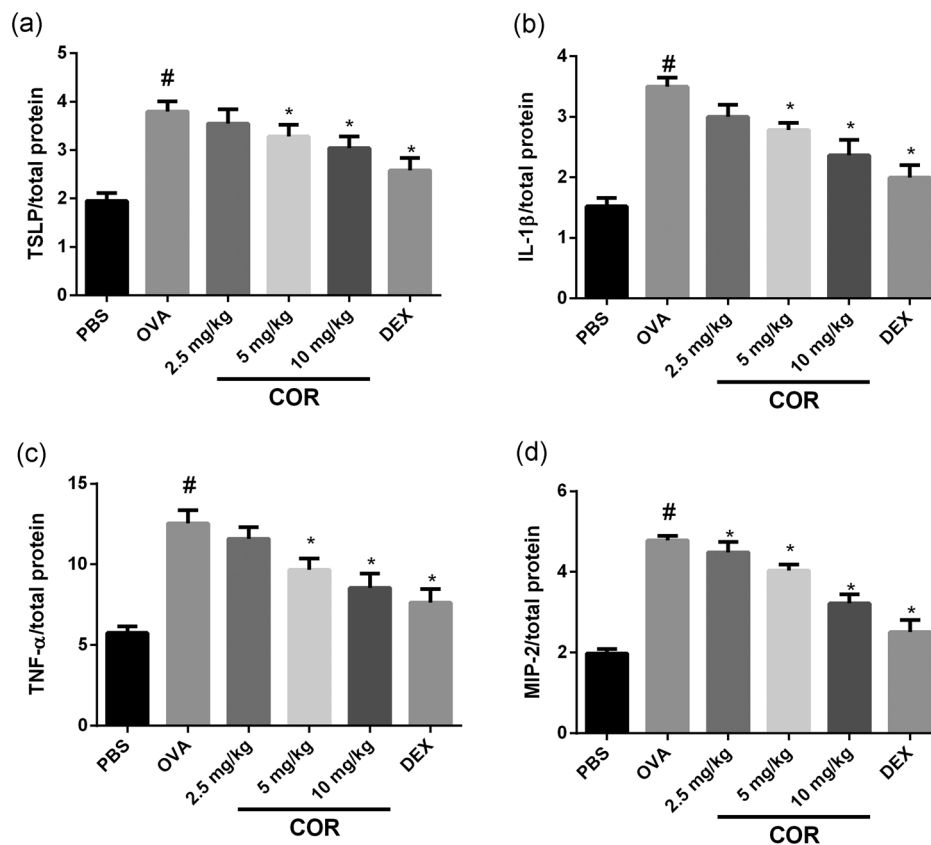


FIGURE 2 The effect of COR on various inflammatory biomarkers. (a) TSLP, (b) IL-1 β , (c) TNF- α , and (d) MIP-2. Data are presented as the mean $\pm$ SEM of three independent experiments. COR, corynoline; DEX, dexamethasone; OVA, ovalbumin; PBS, phosphate-buffered saline; TSLP, thymic stromal lymphopoietin. [#] $p < .05$, significantly different from PBS (control); ^{*} $p < .05$, significantly different from OVA-challenged mice

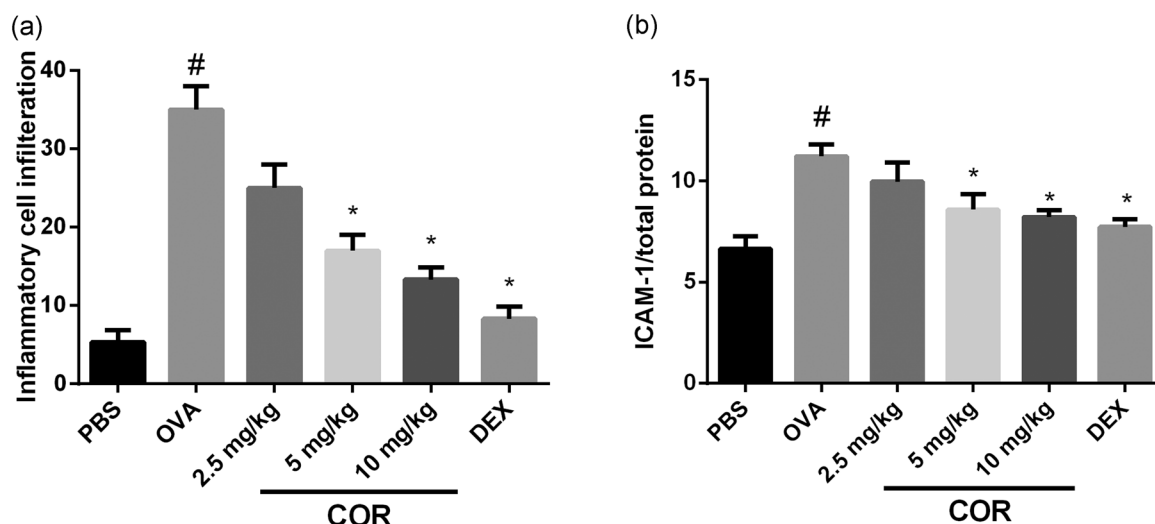


FIGURE 3 The effect of COR on the eosinophil infiltration in the nasal mucosa of AR mice. (a) Eosinophil infiltration, (b) ICAM-1. Data are presented as the mean $\pm$ SEM of three independent experiments. AR, allergic rhinitis; COR, corynoline; DEX, dexamethasone; OVA, ovalbumin; PBS, phosphate-buffered saline. # $p < .05$, significantly different from PBS (control); * $p < .05$, significantly different from OVA-challenged mice

Western blot analysis (Figure 4a). Moreover, COR also significantly inhibited the NF- κ B binding activity, which was found to be elevated in OVA-challenged mice.

2.4 | Toxicity profile of COR on AR mice

In the past decades, many drugs failed to clear clinical trials due to safety concerns, among which toxicity is the main attrition factor for drug molecules.^[32] Impressed by the significant protective effect of COR against AR, the present study is intended to investigate the toxic effect of the COR in mice at the dose of 10 mg/kg. This dose has been selected because COR has shown maximum antiallergic activity at this dose. As shown in Table 1 and Figure 4, the COR-treated mice showed no significant difference in animal body weight at the start and end of the study. Moreover, the weight of heart, lung, liver, spleen, and kidney was further found to have no significant difference after COR administration in comparison to PBS. The effect of COR was also determined on the levels of tissue injury markers lactate dehydrogenase (LDH), serum glutamate oxalate transaminase (SGOT), and creatinine. As presented in Figure 5, the level of these biomarkers was found unchanged in COR-treated group as compared with PBS.

2.5 | Docking analysis of COR in the active site of NF- κ B

Molecular docking analysis is a widely useful tool in drug design and discovery to predict the probable binding mode of ligand (drug molecule) with the protein of interest.^[33,34] The last part of the study was conducted to rationalize the inhibitory effect of COR on NF- κ B

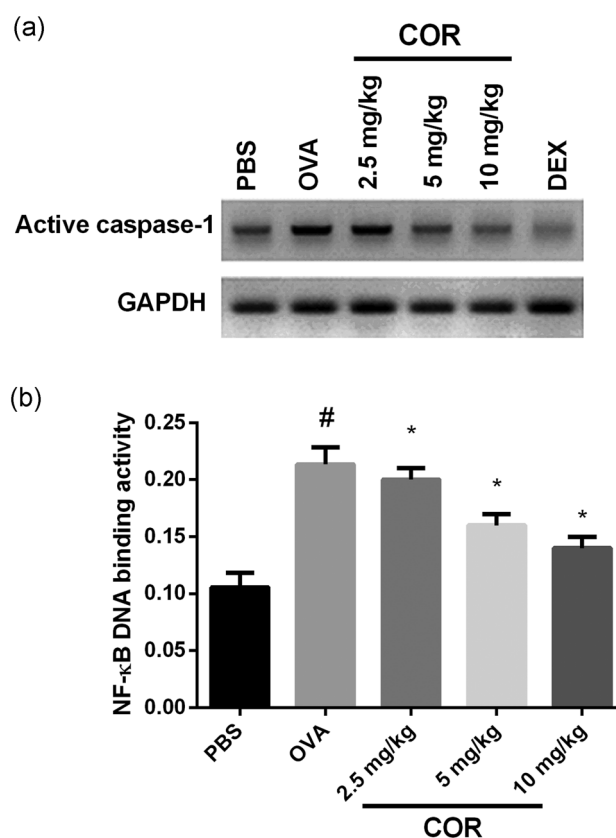


FIGURE 4 The effect of COR on (a) active caspase-1 and (b) NF- κ B binding activity. Data are presented as the mean $\pm$ SEM of three independent experiments. COR, corynoline; DEX, dexamethasone; OVA, ovalbumin; PBS, phosphate-buffered saline. # $p < .05$, significantly different from PBS (control); * $p < .05$, significantly different from OVA-challenged mice

TABLE 1 Effect of COR on the various indices of mice

Parameters	PBS (control)	COR (10 mg/kg)
Initial body weight (g)	18.622 ± 0.22	18.641 ± 0.20
Final body weight (g)	20.15 ± 0.18	20.23 ± 0.15
Heart weight (g)	0.11 ± 0.002	0.12 ± 0.002
Lung weight (g)	0.13 ± 0.003	0.13 ± 0.002
Liver weight (g)	0.85 ± 0.004	0.85 ± 0.003
Spleen weight (g)	0.081 ± 0.001	0.082 ± 0.002
Kidney weight (g)	0.26 ± 0.003	0.27 ± 0.004

Abbreviations: COR, corynoline; PBS, phosphate-buffered saline

binding activity. In this study, the COR has been docked into the active site of the 3D crystal structure of the NF- κ B protein model using computational software (Discovery Studio 3.5). As shown in Table 2 and Figures 6 and 7, COR created an H-bond with Lys145 of Chain A, together with two π -cation interactions with Lys145 of both Chains A and B as a nonbonded interaction. The COR-NF- κ B complex was found to be efficient as shown by excellent CDOCKER energy (24.47) and CDOCKER interaction energy (23.66). Thus, it could be suggested that the inhibition of NF- κ B binding activity of COR might be due to excellent interaction and stable conformation in the active site of NF- κ B.

3 | CONCLUSION

Collectively, our results suggest that COR exerts an anti-inflammatory effect in AR via providing symptomatic relief and inhibition of various proinflammatory cytokines. In addition, COR also inhibited gene expression of caspase-1, together with activation of the NF- κ B signaling cascade in AR mice, as a possible mechanism for its antiallergic effect. Our findings suggest that COR could act as a potential therapeutic drug against AR.

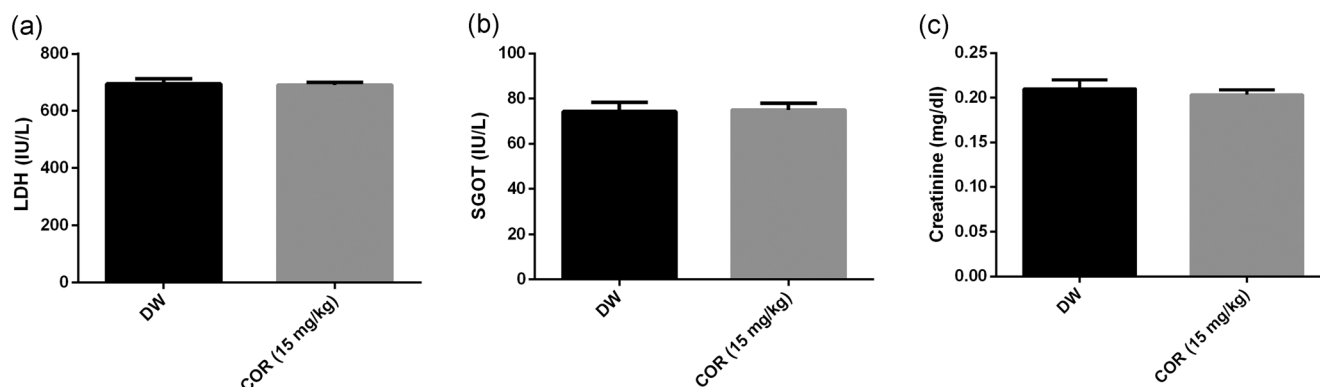
4 | EXPERIMENTAL

4.1 | Chemicals

COR and other chemicals, unless otherwise stated, were procured from Sigma-Aldrich.

4.2 | Induction of AR in mice using OVA

Female BALB/c mice, six-week old, were procured from the central animal house of the institute and housed in strict hygienic conditions with ad libitum supply of food and water. The animal procedure has been approved by the institutional animal ethical committee for biomedical experiments of the First Affiliated Hospital of Xi'an

**FIGURE 5** The effect of COR on (a) LDH, (c) SGOT, and (c) creatinine. COR, corynoline; DW, distilled water; LDH, lactate dehydrogenase; SGOT, serum glutamate oxalate transaminase**TABLE 2** Docking interaction and scoring of corynoline with NF- κ B

Compound	Interaction	Interacting residues	CDOCKER energy	CDOCKER interaction energy
Corynoline	H-bond	Lys145: B chain	24.47	23.66
	π -cation	Lys145: B chain		
		Lys145: A chain		



FIGURE 6 Docked orientation of corynoline in the 3D crystal structure in NF- κ B (PDB:1NFK)

Medical University, China (A-1320/015). The mice were sensitized intraperitoneally with 100 μ g of emulsified OVA and 20 mg of aluminum hydroxide ($\text{Al}(\text{OH})_3$), in 100 μ l of PBS, on Days 1, 5, and 14. Afterward, the OVA (1.5 mg in 2 μ l of PBS) was instilled in the nasal cavity to induce local immunization once a day from 15 days to Day 24. For the OVA-unsensitized mice group, mice were treated intraperitoneally with PBS on Days 1, 5, and 14 and PBS was instilled into the nasal cavity once a day from Day 15 to Day 24. The mice were administered orally with distilled water or COR (in a dose of 2.5, 5, and 10 mg/kg) or DEX (5 mg/kg) into the stomach once a day for 10 days before 1 hr of intranasal OVA challenge. The nose rubbing that occurred in 10 min after OVA intranasal administration was counted from Day 21 to 23 (three times). On the last day of the experiment, that is, Day 25, the blood and nasal tissue samples were collected after anesthesia for biochemical analysis.^[35–37]

4.3 | Preparation of nasal mucosa tissue proteins

Nasal mucosa tissue was homogenized in homogenization buffer (20 mM HEPES, 1.5 mM MgCl_2 , 0.2 mM EDTA, 0.1 M NaCl, 0.2 mM

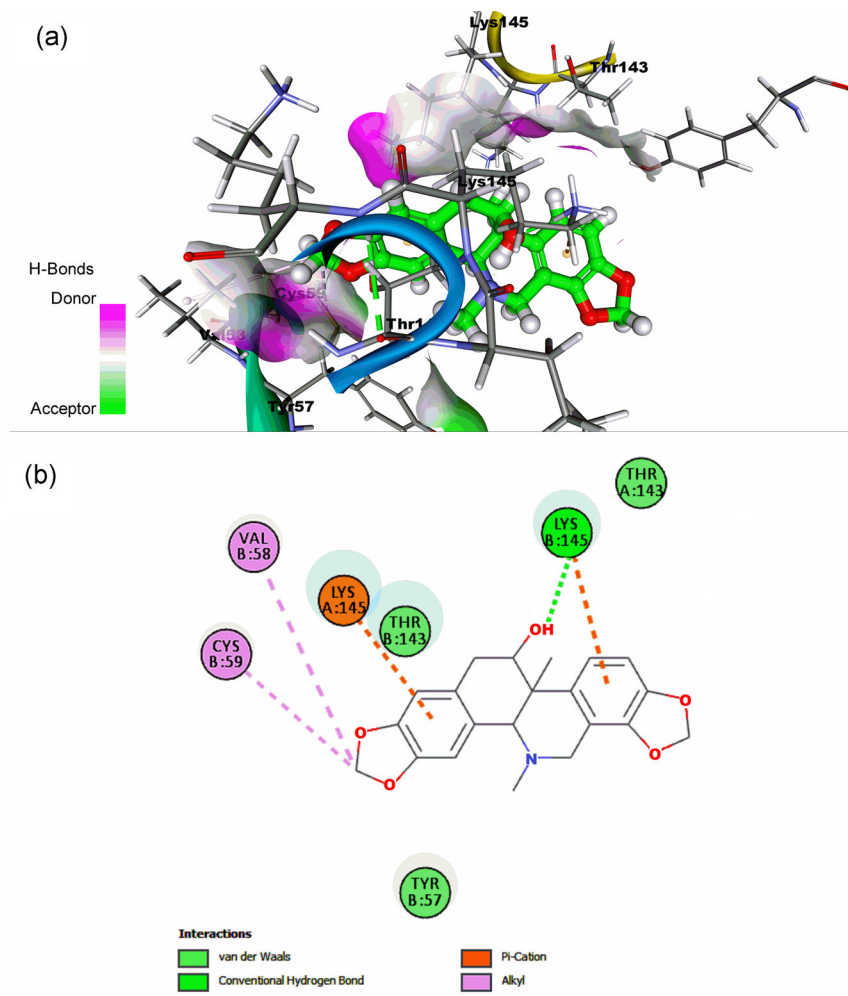


FIGURE 7 Docked orientation of corynoline (COR) in NF- κ B. (a) 3D alignment of COR (carbon skeleton is shown in green) in the active site of NF- κ B, (b) 2D alignment of COR in NF- κ B showing interacting residues. Green, H-bond; orange, π -cation

DTT, 0.5 mM Na₃PO₄, 1% protease inhibitor cocktail) and then centrifuged at 15,000g for 30 min at 4°C. The resulting supernatant was subsequently used for enzyme-linked immunosorbent assay (ELISA), Western blot analysis, and NF-κB DNA binding assay.

4.4 | ELISA analysis

The levels of various biochemical indices were evaluated in the supernatant of homogenized nasal tissues, for instance, TNF-α, IL-1β, TSLP, ICAM-1, and MIP-2 by ELISA kits cat. nos. RTA00, RLB00, MTLP00, MIC100, and SMM200, respectively (R&D Systems Inc., Minneapolis, MN) following the manufacturer's protocol.^[38–40]

4.5 | Western blot analysis

By using an ice-cold radioimmunoprecipitation assay lysis buffer, total protein was extracted. The dissolved proteins were then centrifuged at 12,000 rpm for 5 min at 4°C and bicinchoninic acid protein assay was used to determine the total protein concentration. Isolated proteins were loaded on 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis to separate the proteins and transferred on polyvinylidene fluoride membranes (Millipore, Bedford, MA). The membrane was incubated with primary antibodies (1:1,000; CST or Abcam) after blocking for overnight. The corresponding secondary antibodies (1:2,000; Abcam) were further incubated for 2 hr. The protein bands were observed using enhanced chemiluminescence substrate (Millipore, Billerica, MA), photographed with Image Quant LAS 4000 (GE Healthcare), and analyzed by ImageJ software (NIH, Bethesda, MD).

4.6 | Histamine assay

Histamine levels in the serum of AR mice were determined using o-phthalaldehyde spectrofluorometric analysis as per the previously reported procedure.^[41–43]

4.7 | NF-κB DNA binding assay

In brief, a 96-well ELISA plate was coated by incubation of avidin peroxidase in PBS on a microplate surface overnight at room temperature. The coated plate was then washed with PBS-Tween-20 and blocked with 3% skim milk, after which it was incubated with a 5'-biotinylated 21-single-strand DNA oligonucleotide sequence (1 μg/ml) that contained the previously described NF-κB-binding motif for 1 hr at room temperature (5'-AGTTGAGGGGACTTCCCCAGG-3'). Next, an anti-NF-κB antibody was added to PBS containing 3% BSA for 1 hr at a concentration of 1:500 and the corresponding alkaline phosphatase (AP)-coupled secondary antibody was added. The AP activity was

subsequently detected by the addition of *p*-nitrophenyl phosphate solution. After a 10-min incubation period, the reaction was stopped by the addition of 0.5 M H₂SO₄. Color intensities were measured at 405 nm using a colorimetric microplate reader.^[44]

4.8 | Toxicity study

The COR was administered to BALB/c mice at the dose of 15 mg/kg per day for 14 days. At 24 hr after the last administration, mice were weighed, blood was collected, and various organs (liver, spleen, kidneys, lung, and heart) were weighed. The collected blood was then centrifuged immediately to prepare serum and preserved for biochemical analysis. The following biochemical parameters were measured: lactate dehydrogenase (LDH), serum glutamate oxalate transaminase (SGOT), and creatinine. All biochemical parameters were measured using an automatic biochemical analyzer.

4.9 | Docking study

In the present study, the CDOCKER protocol inbuilt in Discovery Studio 3.0 was selected to perform docking simulation of COR with the 3D crystal structure of the NF-κB p-50 homodimer (PDB code: 1NFK) that was selected as the receptor for docking study. The protein structure was uploaded into the software and the active site was automatically determined using the "find active site protocol" of the software. The active site was defined and selected for docking COR. The water molecule and co-crystallized ligand were removed, and the lost atoms such as hydrogen were added to construct an initial receptor structure for docking. The docking was performed using the default parameters of the CDOCKER protocol.^[45]

4.10 | Statistical analysis

Results were analyzed using the GraphPad Prism software and expressed as the mean ± SEM. Statistical analysis consisted of an independent *t* test and analysis of variance followed by Tukey's post-hoc test. The results were considered significant at a value of *p* < .05.

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CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interests.

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