



The ameliorative effect of berberine and coenzyme Q10 in an ovalbumin-induced allergic rhinitis model

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Abstract

Purpose Berberine and coenzyme Q10 (CoQ10) are agents with anti-inflammatory and antioxidant characteristics. The purpose of this study was to investigate the effectiveness of berberine and CoQ10 on allergic rhinitis.

Methods This study involved 30 Sprague–Dawley rats, and allergic rhinitis model was established with induction of ovalbumin. Rats were randomized into five groups. The first represented the control group, in which no allergy was established. The second represented the allergy group, in which allergy was induced but no treatment was given. In the remaining three groups, following induction of allergy, desloratadine at a dose of 10 mg/kg was given to Group 3, 100 mg/kg dose of berberine to Group 4, and 20 mg/kg dose of CoQ10 to Group 5. Nasal symptom scores, and plasma immunoglobulin-E, interleukin (IL)-4, IL-13, malondialdehyde (MDA) and nitric oxide (NO) levels were examined at the end of the study. Rats' nasal tissues were also subjected to histopathological immunohistochemical examination.

Results Nasal symptom scores, and plasma immunoglobulin-E, IL-4, IL-13, MDA and NO levels increased significantly in rats with induced allergic rhinitis. Berberine and CoQ10 significantly reduced these elevated levels. CoQ10 was also found as effective as desloratadin in terms of nasal symptom scores and biochemical parameters. At histopathological examination, severe allergic inflammation was observed in rats from allergic rhinitis group. At all treatment groups, the histopathological changes were significantly improved and only a mild inflammation was determined. Also, immunochemistry showed a significant improvement in all three treatment groups. Coenzyme Q10 and berberine were both effective in suppressing allergy symptoms.

Conclusion We think that berberine and coenzyme Q10 can usefully be employed as therapy due to their antioxidant and anti-inflammatory effects in an experimentally induced allergic rhinitis model.

Keywords Berberine · Coenzyme Q10 · Ovalbumin · Allergic rhinitis · Cyclooxygenase-2

Introduction

Allergic rhinitis (AR) is a disease affecting approximately 10–20% of the population [1]. It is a type 1 hypersensitivity reaction deriving from sensitization of specific allergens, such as domestic dust mites, pets, and pollens.

Immunoglobulin E (Ig-E)-mediated AR is a chronic disease characterized by sneezing, nasal congestion, nasal itching, and rhinorrhea. These symptoms are thought to be caused by various inflammatory mediators released from mast cells, eosinophils, basophils, and T lymphocytes stimulated by Ig-E [2]. Several agents are used in the treatment of AR, such as antihistamines, corticosteroids, antileukotrienes, and nasal decongestants. However, long-term use of these agents in AR can cause undesirable side-effects. In addition, these agents may fail to provide sufficient treatment under some conditions and may result in complications, such as anaphylactic reactions. New research is, therefore, taking place into the use of safe and effective natural products in the treatment of AR.

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Berberine is a medicinal alkaloid obtained from *Coptis chinensis* (Huanglian) and shown to exhibit a broad range of pharmacological activities such as anti-inflammatory, antioxidant, anti-cancer, anti-allergic, antiatherogenic, anti-diabetic, hypolipidemic, and cardioprotective properties [3]. Coenzyme Q10 (CoQ10) is an organic, natural, fat-soluble, vitamin-like substance. It is also known as ubiquinone and is a cofactor in the intercellular electron transport chain. CoQ10 is a very powerful endogenous antioxidant and has been implicated in the pathogenesis of several chronic diseases [4].

The purpose of this study was to perform a biochemical, functional, and histopathological examination of the effects of berberine and CoQ10 in an AR model experimentally induced in rats with ovalbumin.

Materials-methods

Animals

Approval for the study was obtained from the Ataturk University Animal Experiments Ethical Committee (No. E.1700320367-13:159). 30 female Sprague–Dawley rats weighing 200–250 g were included. The principles of the Care and Use of Laboratory Animals guideline were applied throughout the study. Rats were housed in special cages, with ad libitum access to food and water, in an automatically controlled 12-h light-12-h dark lighting system. Room temperature was kept stable at 23 ± 2 °C and humidity at $45 \pm 5\%$.

Experimental protocol

The rats were randomly assigned into five groups of six rats each. The first group was assigned to negative control group. An ovalbumin-induced allergic rhinitis model was established to the remaining 24 rats. The groups were organized as follows:

Group 1 (Control group) No sensitization or provocation was applied to the rats in this group.

Group 2 (Ovalbumin group) Sensitization and provocation were applied with ovalbumin in this group. Saline was administered at provocation stage.

Group 3 (Desloratadine group) Sensitization and provocation were applied with ovalbumin in this group. Treatment was administered with the antihistaminic agent desloratadine at provocation stage.

Group 4 (Berberine group) Sensitization and provocation were applied with ovalbumin, and rats were treated with berberine at provocation stage.

Group 5 (CoQ10 Group) Sensitization and provocation were applied with ovalbumin, and rats were treated with coenzyme Q10 at provocation stage.

Drug administration

The ovalbumin, berberine, and coenzyme Q10 used in the study were obtained from the Sigma-Aldrich Chemical Company. Ovalbumin was used for the induction of an AR model as previously described in the literature [5]. Briefly, 0.3 mg ovalbumin and 30 mg aluminum hydroxide were dissolved in saline solution, and this mixture was administered by the intraperitoneal (ip) route every other day for 14 days. Seven ip doses were thus administered. Following this sensitization stage, provocation was applied once daily for 7 days between days 15 and 21 with the administration by micropipette into each nostril of 20 μ l 10% ovalbumin solution dissolved in 1 ml saline solution.

Other drug administrations commenced following the sensitization stage. 4 ml/kg dose of saline solution was administered to rats in groups 1 and 2 at provocation stage by intragastric lavage. All drugs were dissolved in saline solution. The rats in Group 3 were given desloratadine (Deloday®, Vitalis, Istanbul, Turkey) at 10 mg/kg/day once daily by intragastric gavage, commencing on the 15th day of the study, for 7 days. The rats in Group 4 were given berberine at 100 mg/kg by intragastric lavage once daily for 7 days commencing on the 15th day of the study. Rats in Group 5 received CoQ10 at 20 mg/kg by intragastric lavage for 7 days beginning on day 15 of the study.

Nasal symptom scoring

Nasal scoring was performed on day 22 of the study. For this purpose, rats were placed into separate cages and observed for 10 min by five blinded observers following a 10-min adaptation period. Nose scratching, sneezing, and nasal discharge were observed as previously described elsewhere in the literature during this period [6], and scores were calculated as shown in Table 1.

Biochemical analysis

Following nasal symptom scoring on day 22 of the study, all rats were killed by cervical dislocation under 40 mg/kg ketamine and 10 mg/kg xylazine anesthesia. Intracardiac blood specimens were collected and centrifuged for 10 min at 3000 rpm. Plasma was separated and stored in a deep freeze at -80 °C until the day of study.

Plasma nitric oxide (NO) analysis was performed using NO Detection Kit (Enzo Life Science). NO measurement is based on the enzymatic conversion of nitrate into nitrite, and the calorimetric measurement of nitrite, a colored product

Table 1 The nasal symptom scoring system

Nasal symptoms	0	1	2	3
Number of sneezes per minute	None	1–2	3–5	> 6
Number of nasal rubbing per minute	None	1–2	3–5	> 6
Nasal discharge	None	One nostril	Both nostriles	Out-flowing

of the Griess reaction. Plasma NO levels were expressed as micromole/L.

Plasma malondialdehyde (MDA) levels were determined using the method described by Placer et al. [7]. This method is based on the spectrophotometric measurement at 532 nm of the colored product created by MDA in the presence of thiobarbituric acid. Plasma MDA levels were expressed as nmol/ml.

Plasma total Ig-E and interleukin (IL)-4 and IL-13 levels were measured using ELISA with kits specially produced for rats (Sunredbio, China). Ig-E levels were expressed as KU/L, IL-4 levels as pg/ml, and IL-13 levels as ng/L.

Histopathological analysis

Nasal tissue specimens collected for the purpose of histopathological evaluation were fixed for 48 h in 10% formalin solution. Tissues were then decalcified and embedded in paraffin blocks following routine bone tissue procedures. 4 µm sections were taken from each block. The preparates made ready for histopathological examination were stained with hematoxylin-eosin (HE) and examined under a light microscope on a scale of none (-), slight (+), moderate (++), and severe (+++). According to this scale, ciliary desquamation in the epithelium was defined as a desquamated cell number 0 (-), 5–15 mild (+), 15–20 moderate (++), and > 20 severe (+++). Necrotic-eosinophilic mass in the lumen was classified as the diameter of eosinophilic mass none (-), < 5 µm mild (+), 5–15 µm moderate (++), > 15 µm severe (+++). Proliferation in goblet cells was classified as the number of goblet cells at one section < 7 none (-), 7–10 mild (+), 10–15 moderate (++), and > 15 severe (+++). Edema in the lamina propria was classified as the diameter of the edema none (-), < 5 µm mild (+), 5–15 µm moderate (++), and > 15 µm severe (+++). Mononuclear cell infiltration in the lamina propria was classified as the number of cells none (-), 5–15 cells mild (+), 15–20 cells moderate (++) and > 20 cells severe (+++). Dilatation and hyperemia in vessels was defined as the number of dilated vessels in one section none (-), 3–4 vessels mild (+), 5–10 vessels moderate (++) and > 10 vessels severe (+++).

Immunohistochemical analysis

All sections placed onto adhesive (poly-L-lysine) slides for immunoperoxidase examination were passed through xylol

and alcohol series. After washing with PBS, sections were kept in 3% H₂O₂ for 10 min for endogenous peroxidase activation. After being treated with antigen retrieval solution in a microwave for 2×5 min at 500 Watts to reveal the antigens in tissues, the sections were left to cool. Procedures were carried out in line with the kit protocol (AbcamHRP/DAB Detection IHC Kit). After washing with PBS, the tissues were incubated with COX-2 at 37 °C for 30 min for inflammation detection (Catalog no. RB-9072-R7, ready-to-use Thermo Scientific, USA). 3–3' diaminobenzidine was used as a chromogen. Sections were washed with distilled water and classified on the basis of immune positivity as none (-), mild (+), moderate (++) and severe (+++) which was defined as a positive cell number of 0 (-), 3–5 (+), 6–10 (++) and ≥ 10 (+++).

Statistical analysis

Statistical analysis was performed on SPSS 17.0 software. Following analysis of distribution using the Shapiro–Wilk test, normally distributed quantitative values were analyzed using One-Way ANOVA and the post-hoc Tukey test. Analysis of semi-quantitative histopathological data was performed using the Kruskal–Wallis test and the Mann Whitney *U* test was used for two-way comparisons when significant differences were determined with the Kruskal–Wallis test. *p* values < 0.05 were regarded as significant.

Results

Nasal symptom scores

Nasal symptom scores were significantly higher in the group receiving ovalbumin than in the control group (*p* < 0.001). Nasal symptom scores decreased in the berberine and CoQ10 treatment groups and were similar to those of the control group. In terms of nasal symptom scores, while berberine exhibited similar efficacy to desloratadine (*p* > 0.05), CoQ10 showed better efficacy than desloratadine (Fig. 1).

Biochemical results

Total Ig-E levels among the rats in the control group were 1.18 KU/l, approximately twice as high in the ovalbumin group at 2.15 KU/l (*p* < 0.001). Total Ig-E levels were

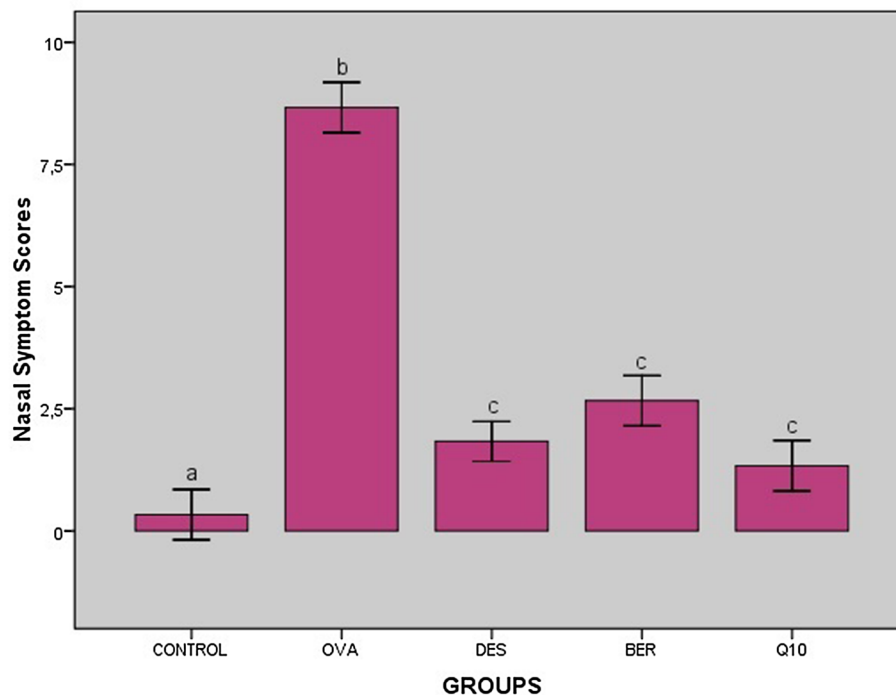


Fig. 1 Nasal symptom score results. Data are expressed as mean values, with standard deviation values shown above each bar. Statistical comparison was performed with one-way ANOVA and post-hoc Tukey test. $p < 0.05$ was accepted as statistically significant. The letters above each bar show statistical comparisons. Different letters indicate significance at the $p < 0.05$ level, while the same letters indicate no significant difference. Group Ova was significantly higher (b)

and group control was significantly lower (a) than other groups while there was no significant difference between treatment groups (c). *Ova* The rats that allergic rhinitis was induced and received no treatment. *Des* The rats that allergic rhinitis induced and treated with desloratadine. *Ber* The rats that allergic rhinitis induced and treated with berberine. *CoQ10* The rats that allergic rhinitis induced and treated with Coenzyme Q10

1.72 KU/l in the rats receiving berberine and 1.5 KU/L in those receiving CoQ10. Berberine and CoQ10 significantly reduced total Ig-E levels ($p < 0.001$). In addition, CoQ10 was determined to be as effective as desloratadine in terms of effects on Ig-E levels ($p > 0.05$) (Fig. 2).

IL-13 and IL-4 levels were significantly higher in the ovalbumin than in the control group ($p < 0.001$). IL-13 and IL-4 levels decreased significantly in the groups receiving berberine and CoQ10 compared to the allergy group ($p < 0.001$). In addition, CoQ10 was also determined to be as effective as desloratadine in terms of effects on IL-4 ($p > 0.05$) (Fig. 2).

Plasma levels of the oxidant parameters MDA and NO were higher in the ovalbumin group than in the control group ($p < 0.001$). Administration of CoQ10 and berberine caused a decrease in the parameters by reducing oxidative stress. Additionally, CoQ10 exhibited similar efficacy to desloratadine in terms of both values ($p > 0.05$) (Fig. 3).

Histopathological findings

Histopathological findings are summarized in Table 2 and Fig. 4.

Group 1 (Control) Histopathological examination of the nasal cavity in the rats in this group revealed a normal histological structure in the mucosa and submucosa (Fig. 4a).

Group 2 (Ova) Histopathological examination of the nasal cavity in this group revealed proliferation in goblet cells, ciliary desquamation in the nasal epithelium, severe eosinophilic cell infiltration, and a necrotic eosinophilic mass in the nasal cavity. Severe edema, severe vascular dilatation and congestion were observed in the submucosa (Fig. 4b).

Group 3 (Des) Histopathological examination of the nasal cavity in this group revealed very mild proliferation in goblet cells, mild edema and vascular dilatation and congestion in the submucosa (Fig. 4c).

Group 4 (Ber) Histopathological examination of the nasal cavity in this group revealed moderate proliferation in goblet cells in the lamina epithelialis, eosinophilic cell infiltration, ciliary desquamation in the epithelium, moderate edema in the lamina propria, and vascular congestion (Fig. 4d).

Group 5 (CoQ10) Histopathological examination of the nasal cavity in this group revealed very mild prolifera-

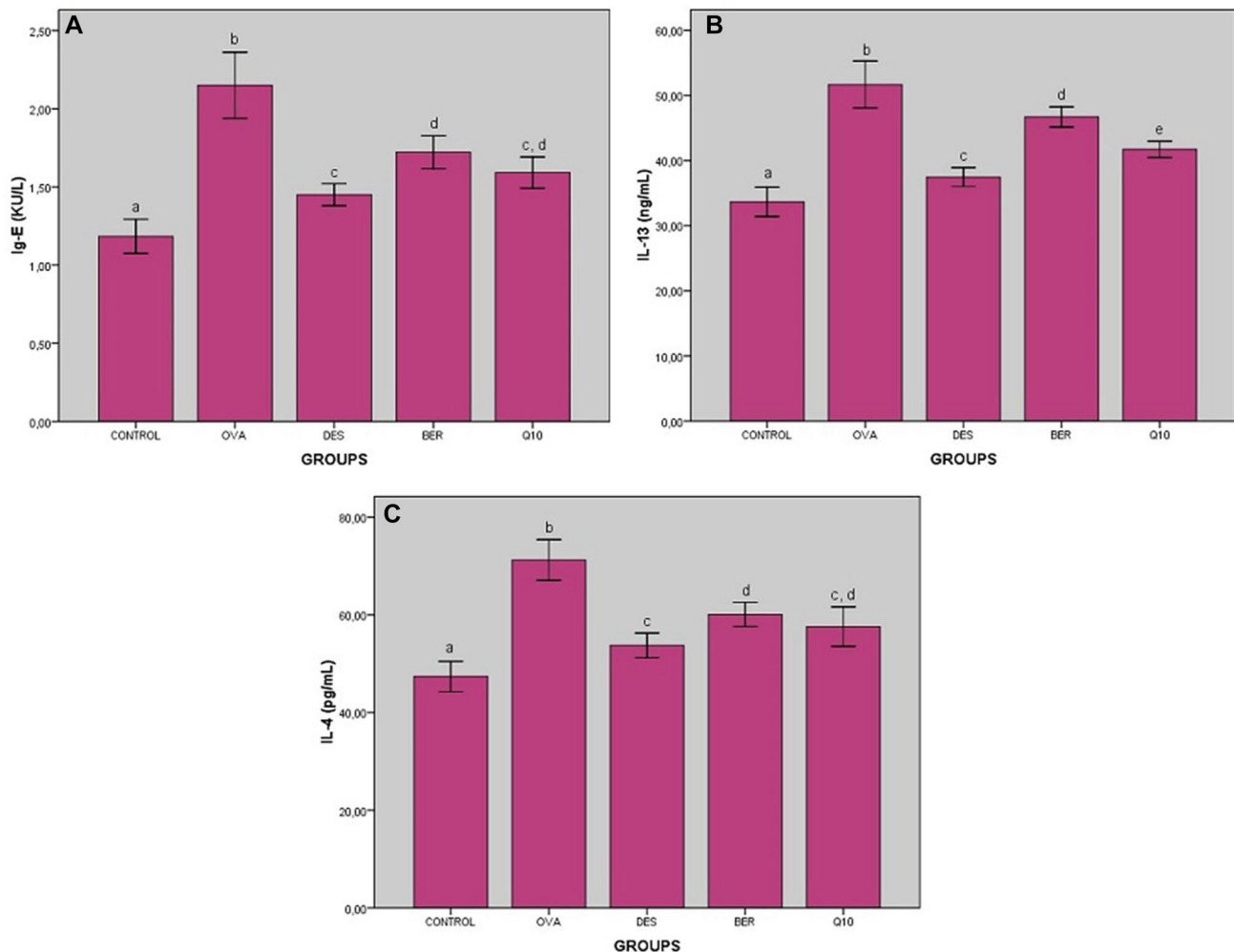


Fig. 2 Comparison of biochemical results between the groups. Data are expressed as mean values, and standard deviation values are shown above each bar. The letters above each bar indicate the statistical comparison. Different letters indicate a significant difference at the $p < 0.05$ level, while the same letters indicate no significant difference. **A** Comparison of total Ig-E results between the groups. Group Ova was significantly higher (b) and Group control was significantly lower (a) than other groups. In treatment groups, Group Ber was significantly higher than Group Des (d). There was no significant difference between groups Des and CoQ10 (c). **B** Comparison of IL-13 results between the groups. Group Ova was significantly higher (b) and Group control was significantly lower (a) than other groups. In

treatment groups, all three groups were significantly different from each other. Group Des was the lowest (c) while Group Ber was the highest (d). **C** Comparison of IL-4 results between the groups. Group Ova was significantly higher (b) and Group control was significantly lower (a) than other groups. In treatment groups, there was no significant difference between groups Des and CoQ10 (c), and Group Ber and Group CoQ10 (d). Group Ber was significantly higher than Group Des (d). *Ova* The rats that allergic rhinitis was induced and received no treatment. *Des* The rats that allergic rhinitis induced and treated with desloratadin. *Ber* The rats that allergic rhinitis induced and treated with berberine. *CoQ10* The rats that allergic rhinitis induced and treated with Coenzyme Q10

tion in goblet cells, mild edema and vascular dilatation and congestion in the submucosa (Fig. 4e).

Immunohistochemical findings

Immunohistochemical findings are summarized in Table 2 and Fig. 5.

Group 1 (Control) Immunohistochemical examination of the nasal cavity in this group revealed negative COX-2 expression (Fig. 5a).

Group 2 (Ova) Immunohistochemical examination of the nasal cavity in this group revealed severe COX-2 expression in the cell infiltration region in both the epithelial region and the lamina propria, and in the eosinophilic mass in the lumen (Fig. 5b).

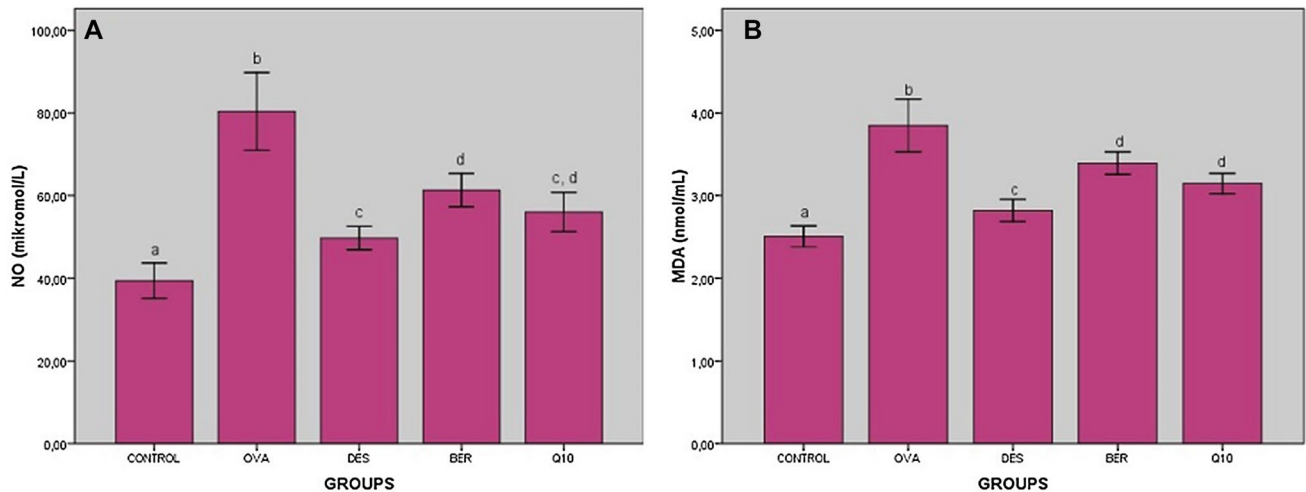


Fig. 3 Comparison of oxidative parameters between the groups. Data are expressed as mean values, and standard deviation values are shown above each bar. The letters above each bar indicate the statistical comparison. Different letters indicate a significant difference at the $p < 0.05$ level, while the same letters indicate no significant difference. **A** Comparison of NO results between the groups. Group Ova was significantly higher (b) and Group control was significantly lower (a) than other groups. In treatment groups, there was no significant difference between groups Des and CoQ10 (c), and Group Ber and Group CoQ10 (d). Group Ber was significantly higher than Group

Des (d). **B** Comparison of MDA results between the groups. Group Ova was significantly higher (b) and Group control was significantly lower (a) than other groups. In treatment groups, there was no significant difference between groups Ber and CoQ10 (d), while Group Des was significantly lower (c). *Ova* The rats that allergic rhinitis was induced and received no treatment. *Des* The rats that allergic rhinitis induced and treated with desloratadin. *Ber* The rats that allergic rhinitis induced and treated with berberine. *CoQ10* The rats that allergic rhinitis induced and treated with Coenzyme Q10

Table 2 Comparison of histopathological findings between the groups

	Control	Ova	Des	Ber	CoQ10
Ciliary desquamation in the epithelium	—	+++	+	++	+
Necrotic-eosinophilic mass in the lumen and erosion in the epithelium	—	+++	+	++	+
Proliferation in goblet cells	—	+++	++	++	++
Edema in the lamina propria	—	+++	+	++	+
Mononuclear cell infiltration in the lamina propria	—	+++	++	++	+
Dilatation and hyperemia in vessels	—	+++	++	++	++
COX-2	—	+++	+	++	+

Group 3 (Des) Immunohistochemical examination of the nasal cavity in this group revealed mild COX-2 expression in the cell infiltration region in both the epithelial region and the lamina propria (Fig. 5c).

Group 4 (Ber) Immunohistochemical examination of the nasal cavity in this group revealed moderate COX-2 expression in the cell infiltration region in both the epithelial region and the lamina propria (Fig. 5d).

Group 5 (CoQ10) Immunohistochemical examination of the nasal cavity in this group revealed mild COX-2 expression in the mucosal interepithelial spaces in the epithelial region and in the lamina propria (Fig. 5e)

Discussion

The nasal epithelium is a region in which pro-inflammatory mediators and cytokines, which play an important role in allergic reactions, are synthesized and released. AR is a hypersensitivity condition associated with Ig-E resulting from the inhalation of allergens. The physiopathology of the disease consists of sensitization, early, and late stages. In the sensitization stage, the allergen coming into contact with the nasal mucosa is exposed to T lymphocytes, causing the emergence of Th2 lymphocytes. With the activation

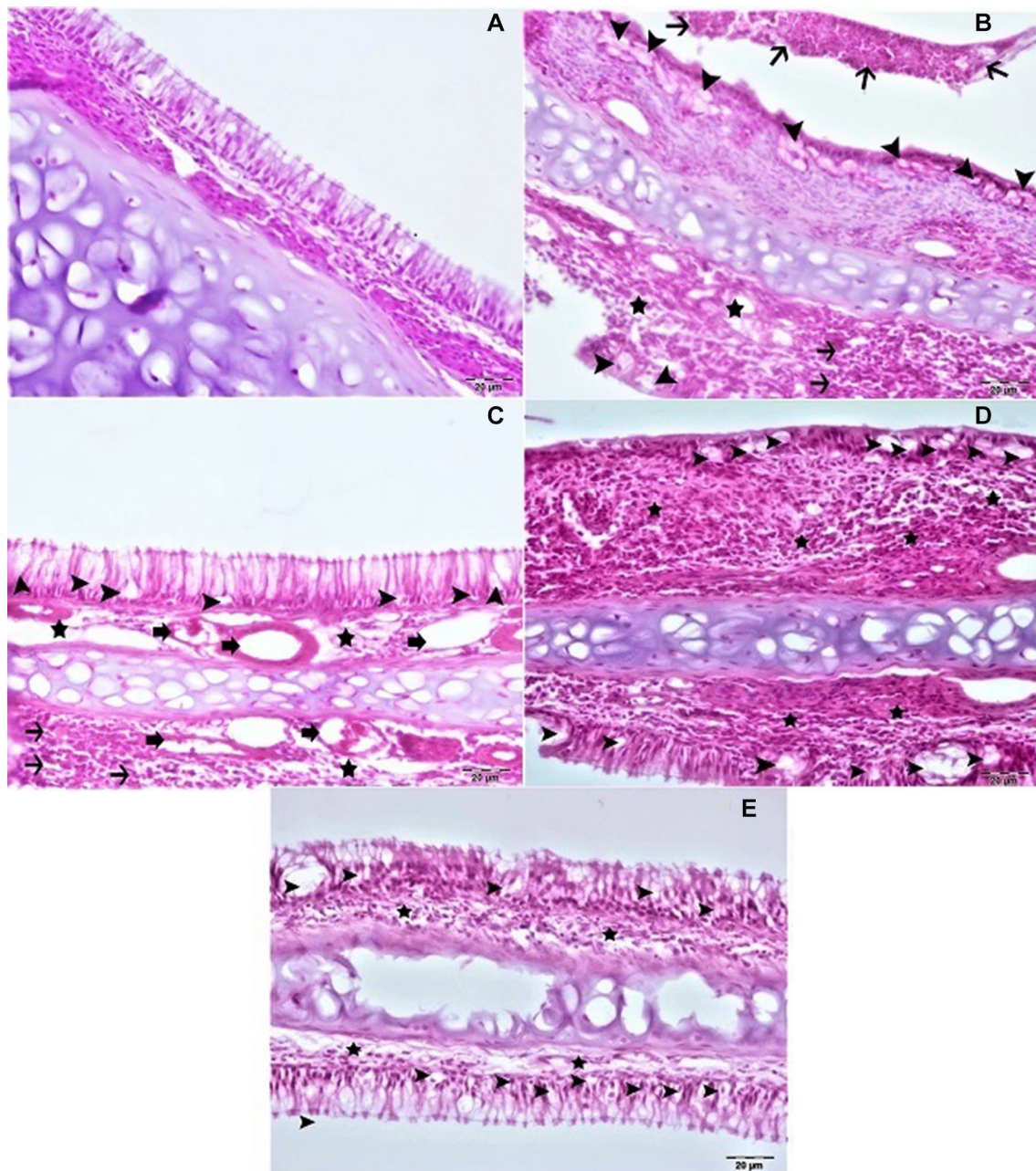


Fig. 4 Histopathological findings (H&E, Bar: 20 μ m). **a** Control group: Nasal cavity—normal histological appearance H&E, Bar: 20 μ m. **b** Ova group: Desquamation in the lamina epithelialis in the nasal cavity, erosion, and proliferation in goblet cells (arrow heads), eosinophilic infiltration in the lumen and the lamina propria (arrows), necrotic mass in the lumen, and edema in the lamina propria (stars), H&E, Bar: 20 μ m. **c** Des group: Mild desquamation in the lamina epithelialis in the nasal cavity, erosion, and proliferation in goblet cells (arrow heads), very mild edema in the lamina propria (stars), eosinophilic leukocyte infiltration (fine arrows), dilatation and congestion in vessels (thick arrows), H&E, Bar: 20 μ m. **d** Ber group: Moderate desquamation in the lamina epithelialis in the nasal cavity, erosion,

and proliferation in goblet cells (arrow heads), moderate edema in the lamina propria and eosinophilic cell infiltration (stars), dilatation and congestion in vessels, H&E, Bar: 20 μ m. **e** CoQ10 group: Very mild degeneration in the lamina epithelialis in the nasal cavity, ciliary desquamation, mild proliferation in goblet cells (arrow heads), mild edema in the lamina propria (stars) and a very low level of eosinophilic infiltration, H&E, Bar: 20 μ m. *Ova* The rats that allergic rhinitis was induced and received no treatment. *Des* The rats that allergic rhinitis induced and treated with desloratadin. *Ber* The rats that allergic rhinitis induced and treated with berberine. *CoQ10* The rats that allergic rhinitis induced and treated with Coenzyme Q10

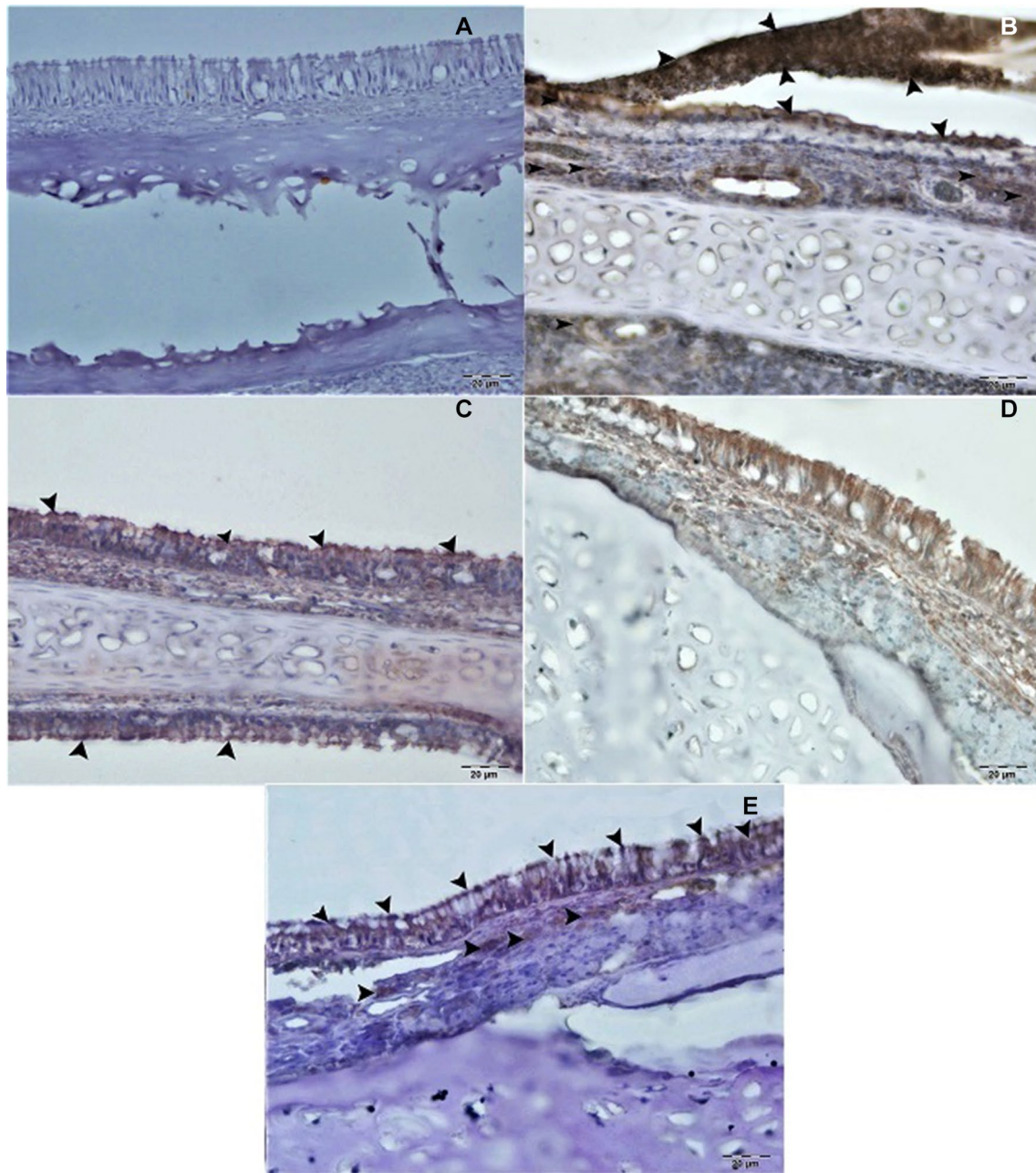


Fig. 5 Immunohistochemical findings (IP-IHC, Bar: 20 µm). **a** Control group: Nasal cavity, negative COX-2 expression, IP-IHC, Bar: 20 µm. **b** Ova group: Nasal cavity, a severe level of COX-2 expression (arrowheads) in the region of mononuclear cell infiltration in the eosinophilic mass in the lumen, the lamina epithelialis, and the lamina propria, IP-IHC, Bar: 20 µm. **c** Des group: Nasal cavity, mild COX-2 expression in the lamina epithelialis and lamina propria (arrow heads), IP-IHC, Bar: 20 µm. **d** Ber group: Nasal cavity, mod-

erate COX-2 expression in the lamina epithelialis and lamina propria (arrow heads), IP-IHC, Bar: 20 µm. **e** CoQ10 group: Nasal cavity, mild COX-2 expression in the lamina epithelialis and lamina propria (arrow heads), IP-IHC, Bar: 20 µm. *Ova* The rats that allergic rhinitis was induced and received no treatment. *Des* The rats that allergic rhinitis induced and treated with desloratadin. *Ber* The rats that allergic rhinitis induced and treated with berberine. *CoQ10* The rats that allergic rhinitis induced and treated with Coenzyme Q10

of Th2 lymphocytes, cytokines leading to Ig-E synthesis and mast cell proliferation are produced, such as IL-3, IL-4, IL-5, IL-9, IL-10, and IL-13 [8]. When the allergen on the surface of the mast cells encounters its own specific Ig-E, an early inflammatory reaction causes the release of

mediators from mast cells and basophils. These include mediators such as IL-4, IL-6, and cyclooxygenase (COX)-2, which give rise to the inflammatory process in the nasal cavity. COX enzymes (COX-1 and COX-2) account for the generation of eicosanoids from arachidonic acid and

are important components and markers of an inflammatory response [9]. Immunohistochemical staining in our study revealed significantly increased COX-2 expression in the cell infiltration region in both the epithelial region and the lamina propria, and in the eosinophilic mass in the lumen in the allergy group compared to the rats in the control group. Inflammatory changes lead to nasal symptoms such as rhinorrhea, itching, and sneezing. This is followed by a later phase involving migration to the nasal mucosa of neutrophils, eosinophils, macrophages, and T and B lymphocytes [5]. Within this cell flow, eosinophils in particular increase the production of reactive oxygen radicals (ROS). Increased ROS production, which plays an important role in AR, increases the permeability of the nasal mucosa and mucus production and reduces the functioning and numbers of the epithelial cilia, while compromising the expression of adhesion molecules and the release of inflammatory mediators. In this way, eosinophils, important allergic inflammatory cells, contribute to the development of AR via oxidative stress [10].

High Ig-E levels are an important marker of the presence of allergic diseases. The presence of Ig-E has been reported as a specific diagnostic method for use in allergic diseases [11]. Winther et al. showed that Ig-E levels increase in patients with seasonal AR and that this is correlated with the severity of rhinitis [12]. One study involving an ovalbumin-induced AR model showed that serum Ig-E levels increased in rats [6]. Meng et al. showed that, like serum Ig-E levels, local Ig-E levels also increased in AR and that investigation of local Ig-E can represent an alternative non-invasive method in diagnosis [13]. Ig-E levels in our study were significantly higher in the groups with induced AR compared to the control group. The use of berberine and CoQ10 lowered Ig-E levels to close to those of the control group.

IL-4 and IL-13 occupy an important place in AR. These interleukins are necessary for the antigen presentation function of lymphocytes. They also contribute to the allergic inflammation by causing Ig-E production [14]. Serum IL-4 and IL-13 levels in rats with AR have been shown to be significantly higher than those of control and treatment groups [6]. Zhao et al. reported higher serum Ig-E, IL-4, and IL-13 levels in guinea pigs in an AR model compared to a control group [15]. Choi et al. reported that Ig-E, IL-4, and IL-13 values rose in their pollen-induced AR model [16]. Similarly, in our study, IL-13 and IL-4 levels increased significantly in rats with AR compared to the control group. Additionally, IL-4 and IL-13 levels decreased significantly in rats receiving berberine and CoQ10.

IL-13 plays a role in airway hyper-responsiveness, eosinophilic infiltration, and mucociliary differentiation. It has also been shown to stimulate the nasal epithelial cells to synthesize NO [17]. NO is an important cellular signal molecule involved in the vasodilation of blood vessels and

in respiratory tract inflammation. It is synthesized from the nasal epithelial cells by inducible nitric oxide synthase (iNOS) during eosinophilic inflammation of the nasal cavity and is thought to be a marker of the severity of nasal disease [18]. Arnal et al. investigated NO concentrations in patients with AR and reported significantly higher levels in AR than in the control group [19]. Similarly, Suojalehto et al. reported that NO levels can be a practical marker of eosinophilic inflammation in the nasal cavity [20]. However, studies examining the relation between AR and NO are inconsistent. Some report that NO levels remain unchanged in AR, while others report a decrease [21]. We determined significantly higher NO levels in rats with induced AR compared to the control group, which we attribute to inflammation in the nasal epithelium.

Another factor implicated in the pathogenesis of AR is oxidative stress. Systemic oxidative stress has been shown to increase in AR, while antioxidant enzyme activities decrease [22]. Shaoqing Yu et al. showed that oxidative stress plays a significant role in AR, and reported significantly higher serum MDA levels in guinea pigs with AR compared to a control group, and also determined that this condition is reversible [10]. We also determined significantly higher MDA levels in the rats with AR than in the control group.

Since oxidative stress also plays an important role in the pathogenesis of AR, we also examined the antiallergic effect of a known antioxidant, CoQ10. CoQ10, an integral part of the mitochondrial electron transport chain, also serves as an important mitochondrial antioxidant by scavenging free radicals and inhibiting lipid and protein peroxidation [23]. Farraq et al. reported that the administration of CoQ10 lowered MDA levels by increasing resistance to mitochondrial lipid peroxidation [24]. One toxicity study investigating the effectiveness of CoQ10 in rats showed that the application of CoQ10 regulated oxidative status by lowering MDA and NO levels [25]. Since CoQ10 is an antioxidant with anti-inflammatory properties, it has been reported that it may be useful in chronic diseases. The use of CoQ10 in asthma, a chronic inflammatory disease, has been shown to be beneficial by reducing the corticosteroid dosage required [26]. In their rat study, Yakın et al. showed that the application of CoQ10 reduced the levels of pro-inflammatory cytokines such as TNF- α , IL-2, IL-4, IL-6, and IL-10 by exhibiting anti-inflammatory, as well as antioxidant effects [27]. In our study, CoQ10 significantly protected the nasal mucosa through its antioxidant and anti-inflammatory effects compared to the AR group and established an improvement in functional parameters. Nasal symptom scores improved in rats treated with CoQ10, and plasma Ig-E, IL-4, IL-5, MDA, and NO levels decreased. Also, CoQ10 was more effective than desloratadine in term of histopathological and immunohistochemical examinations.

Zhenghao Li et al. showed that berberine is effective against allergic diseases in their ovalbumin-induced experimental allergic asthma model. The authors showed that berberine inhibited the nuclear factor kappa (NF- κ B) signal, lowered the levels of pro-inflammatory cytokine such as IL-1 β , IL-4, IL-5, IL-6, IL-13, and IL-17, and inhibited Ig-E production. Histological analysis also revealed that it significantly reduced inflammatory cell infiltration in pulmonary tissue in an allergic asthma model. In this way, they concluded that berberine exhibits a therapeutic effect on airway inflammation in allergic asthma [28]. Kim et al. also reported that berberine improved nasal symptom scores in an AR model induced with house dust mites and significantly improved inflammation by reducing serum Ig-E, GATA-3 mRNA, T-bet mRNA, and tissue eosinophil numbers compared to the AR group [29]. Mehrzadi et al. determined that berberine preserved the oxidative balance by reducing MDA and NO levels in an induced systemic toxicity model. They also reported that berberine exhibited this effect by directly neutralizing ROS and NO [30]. Xiong et al. also showed that berberine reduced MDA levels by exhibiting a protective effect against ROS damage [31]. In our study, nasal symptom scores improved in rats treated with berberine, plasma Ig-E, IL-4, IL-5, MDA, and NO levels decreased, and the nasal mucosa were protected at the histopathological level.

Conclusion

Both berberine and CoQ10 significantly improved nasal symptom scores, biochemical parameters, and histopathological values in our experimentally induced AR model. Particularly, CoQ10 was as effective as desloratadine in all parameters. On the basis of these data, we think that both these antioxidants can be effective in reducing nasal symptoms in the treatment of AR.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH Guide for the Care and Use of Laboratory Animals, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Ataturk University.

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