

Caffeic acid phenethyl ester attenuates IgE-induced immediate allergic reaction

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Abstract Caffeic acid phenethyl ester (CAPE) is the active component of honey bee propolis extracts. The results of the current study demonstrate that CAPE attenuated immunoglobulin (Ig)E-mediated allergic response in mast cells. Oral administration of CAPE inhibited IgE-mediated passive cutaneous anaphylaxis. CAPE effectively reduced both histamine and serotonin (5-HT)-induced vascular permeability in rats. CAPE also reduced histamine and leukotrienes (LTs) release from isolated rat peritoneal mast cells. Moreover, CAPE suppressed contraction induced by histamine (3×10^{-8} – 3×10^{-5} M), 5-HT (3×10^{-9} – 10^{-6} M) and adenosine (3×10^{-8} – 10^{-5} M) in guinea pig tracheal zigzag. These findings provide evidence that CAPE may serve as an effective therapeutic agent for allergic diseases.

Keywords CAPE · Allergy · IgE · Leukotrienes · Histamine · Mast cell

Introduction

Mast cells are important mediators of inflammatory responses such as allergy and anaphylaxis. Anaphylaxis is mediated by histamine released in response to antigen cross linking of immunoglobulin E (IgE) bound to FcεRI on mast cell. Mast cell activation causes degranulation that result in the release of mediators, such as histamine and an array of inflammatory cytokines (Metcalf et al. 1981; Miyajima

et al. 1997). Among the inflammatory mediators released from mast cells, histamine remains the best-characterized and most potent vasoactive mediator implicated in the acute phase of immediate hypersensitivity (Petersen et al. 1996).

The signaling pathway leading to degranulation of mast cells has been extensively characterized (Beaven et al. 1984; Beaven and Metzger 1993). Activation of mast cells leads to phosphorylation of tyrosine kinase and mobilization of internal Ca^{+2} . This is followed by activation of protein kinase C, mitogen-activated protein kinases (MAPKs), and nuclear factor- κB (NF- κB) and the release of inflammatory cytokines. Activated mast cells release histamine, as well as eicosanoids, proteoglycans, proteases, and several proinflammatory and chemotactic cytokines (Bradding et al. 1993).

Histamine, serotonin (5-HT), neuropeptides, prostaglandins, and leukotrienes (LTs) are inflammatory mediators with potent bronchoconstrictor action, which play an important role in the pathogenesis allergic diseases. Furthermore, acetylcholine and neuropeptides released from nerve terminals of the parasympathetic nervous system cause a variety of symptoms in asthmatic patients (Sato et al. 1996). There is also increasing interest in the involvement of adenosine as a mediator in allergic asthma. Adenosine is reported to be a potent bronchoconstrictor in allergic and non-allergic asthmatic subjects (Cushley et al. 1983; El-Hashim et al. 1996).

Caffeic acid phenethyl ester, a potent flavonoid antioxidant, is the active component of propolis (Paulino et al. 2003). It has been reported that CAPE possess strong antiviral (Fesen et al. 1993), antitumoral (Liao et al. 2003), anti-inflammatory (Orban et al. 2000), antioxidant (Hepsen et al. 1999), neuroprotective (Ilhan et al. 2004), antiatherosclerotic (Hishikawa et al. 2005) activities, and to have

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immunomodulatory properties (Park and Kang 1999). These diverse effects of CAPE may be attributed to its ability to permeate cell membranes (Orsolic et al. 2005) and inhibit certain enzyme activities, including lipoxigenase, cyclooxygenase, glutathione S-transferase, and xanthine oxidase (Michaluart et al. 1999), as well as it is a potent and specific inhibitor of nuclear factor kappa-B (NF- κ B) activation (Natarajan et al. 1996).

Although CAPE has been shown to exert immunomodulatory and anti-inflammatory effects, few researches have been done on its effect on immediate hypersensitivity reaction and its action on smooth muscle contraction. Therefore, in this study, the effects of CAPE in animal models of allergic disease in vivo and in vitro were investigated.

Materials and methods

Animals

The experimental protocol conducted in the study complies with the ethical guidelines and the principals of care, use and handling of experimental animals adopted by “The research Ethics Committee”, Faculty of Pharmacy, Mansoura University, Egypt. The adopted guidelines are in accordance with “Principles of Laboratory Animals Care” (NIH publication No. 85-23, revised 1985). The study protocol was approved by members of “The Research Ethics Committee” and by the head of Pharmacology and Toxicology department, Faculty of Pharmacy, Mansoura University, Egypt. Adult male Wistar rats (8 weeks age and 180–230 g weight) and adult male Dunkin Hartley guinea-pigs (2–3 month age and 300–800 g weight) were obtained from Urology and Nephrology Center, Mansoura University, Egypt. They were maintained under standard conditions of temperature 30 ± 2 °C with regular 12 h light/12 h dark cycle and allowed free access to standard laboratory food and water.

Chemicals

Evans blue dye, ovalbumin (OVA)-grade V, aluminum hydroxide, di-orthophthaldehyde, histamine diphosphate monohydrate, 5-HT, CAPE, and adenosine (Sigma Co., St. Louis, MO, USA). Disodium cromoglycate (DSCG): as a gift from Pharco pharmaceuticals (Alexandria, Egypt).

Study design

Passive cutaneous anaphylaxis in rats

Sensitization protocols were performed according to the method described by Coleman et al. (1983) and modified

by Portela et al. (2002). Briefly, animals were actively sensitized by I.P. injection of 0.66 ml of a suspension of 1 mg OVA plus 300 mg aluminum hydroxide in normal saline (aluminum-precipitated OVA). This was considered zero day of sensitization. Seven days later, the animals were boosted S.C. with an identical injection of aluminum-precipitated OVA. The aluminum precipitate acts as an adjuvant to promote IgE production. Fourteen days later, rats were anesthetized with thiopental sodium and blood was withdrawn from the retro-orbital venous plexus of the eye, then rat anti-OVA serum was separated. The anti-OVA IgE antibody was determined by passive cutaneous anaphylaxis (PCA) in rats. Sera were adjusted to the concentration that produced extravasations from (10–20 mm) in diameter (Park et al. 2002). The diluted anti-sera (100 μ L) were injected intradermally into two sites into the shaved dorsal skin of naïve rats. After that, rats were challenged with 1 ml of a solution containing 500 μ g of OVA + 2.5 mg of Evans blue via the tail vein (Park et al. 2002). CAPE (7 mg/kg, orally), drug vehicle (0.5 CMA, orally) or DSCG (100 mg/kg, I.P.) were administered 1 h before the OVA challenge. Thirty minutes later, rats were killed by cervical dislocation and the dye content of the shaved dorsal skin of rats was determined quantitatively according to the method described by Katayama et al. (1978). Briefly, pieces of the dorsal skin containing extravasated dye were removed, weighed, and soaked overnight in stoppard glass tubes containing 1 ml of 1 N KOH at 37 °C. Then, 9 ml of mixed solution of 0.6 N H₃PO₄:acetone (5:13) was added to the tube. The tubes were shaken vigorously for a few seconds and centrifuged at 3,000 rpm for 15 min. Absorbance of supernatant was measured at 620 nm using UV-visible spectrophotometer. The concentration of the dye in shaved dorsal skin was determined from the standard curve of Evans blue dye content (0.025–0.15 ng/ml) and expressed as ng/g tissue.

Histamine and 5-HT-induced skin reactions in rats

Histamine- and 5-HT-induced cutaneous reaction was carried out as previously described by Kimata et al. (2000). Briefly, 50 μ L of histamine (2 μ g) and 5-HT (0.02 μ g) were intradermally injected into the spots on the shaved dorsal skin of rats, respectively. Thereafter, 1 ml of physiological saline containing 5 mg of Evans blue was immediately injected into the tail vein. CAPE (7 mg/kg) and prednisolone (20 mg/kg) were orally administered 1 h before injection of histamine and 5-HT. Animals were killed 30 min after the induction of reactions and the skin surrounding each reaction spot was cut off, from which the extravasated dye was extracted and assayed using the method described in rat PCA.

OVA-induced histamine release from isolated rat peritoneal mast cells

Sensitization protocols were performed according to the method previously described. Rat peritoneal mast cells (RPMCs) were isolated 18–21 days later according to the method described by Shin et al. (1997). In brief, rats were anesthetized by ether, and injected with 20 ml of Tyrode buffer B (137 mM NaCl, 5.6 mM glucose, 12 mM NaHCO₃, 2.7 mM KCl, 0.3 mM NaH₂PO₄, and 0.1 % gelatin), into the peritoneal cavity, and the abdomen was gently massaged for about 90s. The peritoneal cavity was carefully opened, and the fluid containing peritoneal cells was aspirated by a Pasteur pipette. Then, the peritoneal cells were allowed to sediment by centrifugation at 150 g for 10 min at room temperature and they were resuspended in Tyrode buffer A (10 mM HEPES, 130 mM NaCl, 5 mM KCl, 1.4 mM CaCl₂, 1 mM MgCl₂, 5.6 mM glucose and 0.1 % BSA). Further purification of mast cells was not performed (Shuto et al. 1999). RPMCs (2×10^5 cells/ml) were resuspended in Tyrode buffer A and pre-incubated for 10 min at 37 °C. Then CAPE (10 µM), media alone and DSCG (40 µM) were added 20 min before activation by OVA (100 µM). The reaction was stopped 30 min later by chilling the test tube in ice. The cells were separated from the released histamine by centrifugation at 400g for 5 min at 4 °C. After centrifugation, 1 ml of the top layer was transferred to a tube containing 375 mg solid NaCl and 2.5 ml *n*-butanol. This was followed by alkalization to extract histamine into butanol by addition of 0.5 ml of 5 N NaOH, shaking and then centrifugation for 5 min. Two milliliters of the top layer (butanol) was transferred to another tube containing 4 ml *n*-heptane and 2 ml of 0.12 N HCl. This mixture was mixed by inverting several times. After separation into aqueous and organic phases, 2 ml of the aqueous layer (bottom layer) was transferred to another tube. Induction of diorthophthaldehyde condensation and fluorometric assay of histamine was done according to the procedure described by Shore et al. (1959). The fluorescence intensity was measured at excitation wavelength 350 nm and emission wavelength 450 nm using a Perkin-Elmer spectrofluorimeter, model LS 45. A calibration curve was constructed using serial dilutions of standard histamine (0.25–160 ng/ml). The histamine concentration was determined from the standard curve, and it was expressed as (ng/ml).

Biosynthesis of LTs in isolated RPMCs

Suspension of RPMCs (2×10^5 cells/ml) separated from sensitized rats was done in Tyrode buffer A. RPMCs were incubated with CAPE (10 µM), media alone or NDGA (10 µM) for 20 min at 37 °C before addition of OVA

(100 µM) and incubation for additional 10 min. The biological assays of LTB₄ and LTC₄ levels were performed using enzyme-linked immunosorbent assay (ELISA) kits (R&D system, Minneapolis, MN, USA), according to the manufacturer's instructions.

In vitro assays

Guinea pigs were anesthetized and euthanized by cervical dislocation. The trachea was rapidly removed; freed from connective tissue, each trachea was cut into six transverse rings (3–4 mm wide), containing three cartilages as described previously by Emmerson and Mackay (1979). The rings were opened and suspended in individual 15 ml jacketed organ bath containing Krebs-Henseleit solution (KHS) of the following composition in (mM): NaCl 118.4, KCl 4.7, CaCl₂ 2.5, NaHCO₃ 25, MgSO₄ 1.2, KH₂PO₄ 1.2, and glucose 11.7, maintained at 37 °C, pH 7.2, gassed with a mixture of 95 % O₂ and 5 % CO₂. Tissues were allowed to equilibrate for at least 60 min before drug addition, with the buffer solution being renewed every 15 min, under a resting tension of 1 g. Isometric tension generated by the smooth muscle was measured using a force displacement transducer (K30, Hugosachs Elektronik, March, Germany) and recorded with a Powerlab unit linked to a PC running Chart v4.2 software (AD Instruments Ltd., Chalgrove, Oxfordshire, UK). The software was adjusted to record 20 samples per second at 2 mV sensitivity and a 20 Hz filter was applied to remove any noises. After equilibration period, each tracheal zigzag was initially contracted with histamine (10 µM) to check its functional integrity, then washed until the tension returned to the baseline. Cumulative concentration response curves for LTD₄ (3×10^{-11} – 10^{-8} M), histamine (3×10^{-8} – 3×10^{-5} M), 5-HT (3×10^{-9} – 10^{-6} M) or adenosine (3×10^{-8} – 10^{-5} M) were constructed before and after incubation with CAPE (100 µM) for 30 min.

Statistical analysis

For the in vivo studies, the results are presented as the mean $\pm$ standard error of mean (SEM), where (*n*) equals the number of animals. For the in vitro studies, smooth muscle contraction was calculated as % of maximal steady state contraction induced by 10 µM histamine. The concentration–response curve for each experimental condition was plotted; from which, the values of maximal-agonist-induced response ($E_{\max}$) and the concentration of the agonist (expressed as negative log molar) producing 50 % of $E_{\max}$ (pD₂) were deduced. The highest response obtained was considered as the maximum response ($E_{\max}$). Non-linear regression analysis (4-parameter curve fit) was

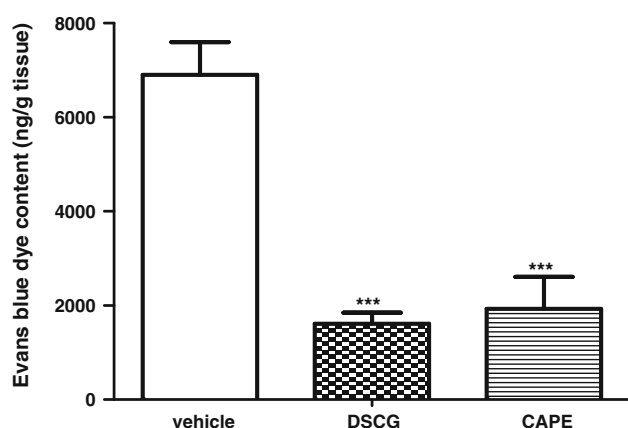


Fig. 1 Effect of CAPE on Evans blue dye contents in PCA in rats. Data are expressed as mean $\pm$ SEM. $n = 6$. *** $p < 0.001$ when compared with vehicle-treated group using one-way ANOVA

carried out using Graphpad Prism software (Graphpad Software Inc., San Diego, CA, USA) and significant differences between groups were determined with paired Student's t test or one-way ANOVA with Dunnett's post hoc test as appropriate.

Results

Effect on PCA in rats

Local extravasation was induced by local injection of IgE followed by an antigenic challenge (Fig. 1). The reference drug DSCG, injected 1 h before challenge, potently inhibited PCA ($p < 0.001$). CAPE orally administered 1 h before the antigen challenge caused a significant inhibition in PCA when compared with vehicle treated group ($p < 0.001$).

Effect on cutaneous reactions induced by histamine and 5-HT

Cutaneous reactions were elicited by an intradermal injection of histamine (Fig. 2a) and 5-HT (Fig. 2b), respectively. CAPE (7 mg/kg) significantly reduced the skin reaction induced by both histamine ($p < 0.001$) and 5-HT ($p < 0.01$). Prednisolone markedly inhibited both reactions at $p < 0.001$.

Effect on OVA-induced histamine release from RPMCs

As shown in Fig. 3, OVA (100 μ M) challenge produced significant release of histamine from RPMCs. Pre-incubation of RPMCs with both CAPE ($p < 0.01$) and DSCG ($p < 0.001$) significantly inhibited OVA-induced histamine release.

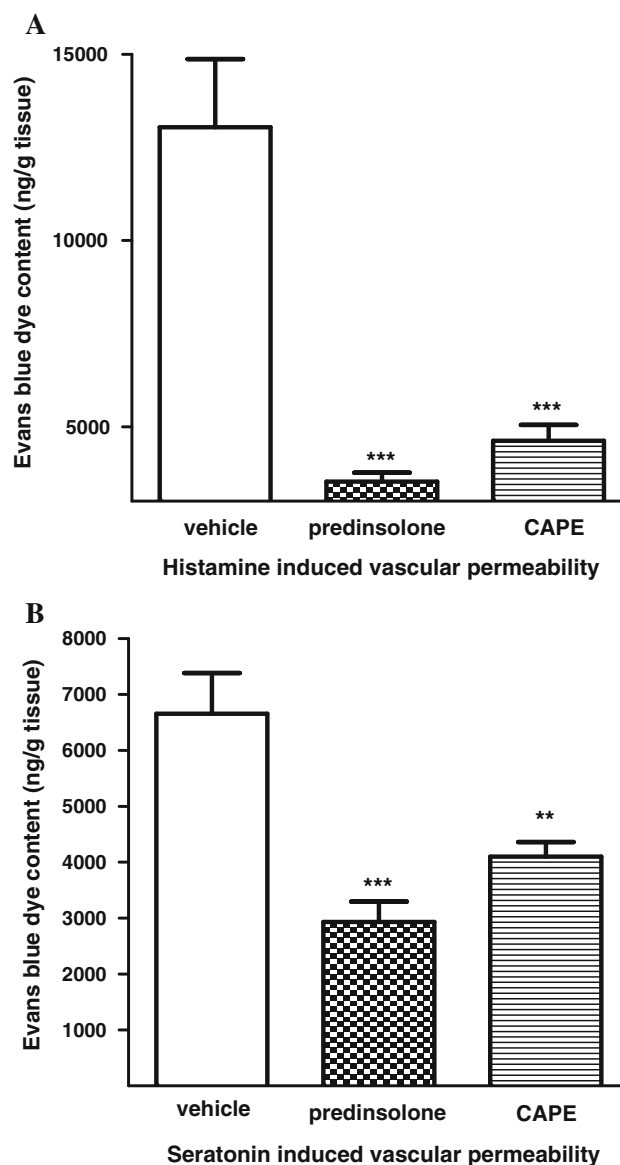


Fig. 2 Effect of CAPE on Evans blue dye contents in vascular permeability induced in rats by **a** histamine or **b** 5-HT. Data are expressed as mean $\pm$ SEM. $n = 6$. ** $p < 0.01$; *** $p < 0.001$ when compared with vehicle-treated group using one-way ANOVA

Effect on OVA-induced leukotrienes release from RPMCs

The spontaneous release of LTD₄ from the isolated RPMCs was found to be minimal. In OVA group, LTB₄ and LTC₄ significantly increased when compared with spontaneous release group (Fig. 4a, b, respectively). RPMCs pre-incubated with NDGA (10 μ M) for 30 min showed a significant reduction in LTD₄ ($p < 0.05$) and LTC₄ ($p < 0.01$) levels when compared with OVA group. CAPE also inhibited both LTD₄ ($p < 0.01$) and LTC₄ ($p < 0.01$) levels at concentration (10 μ M).

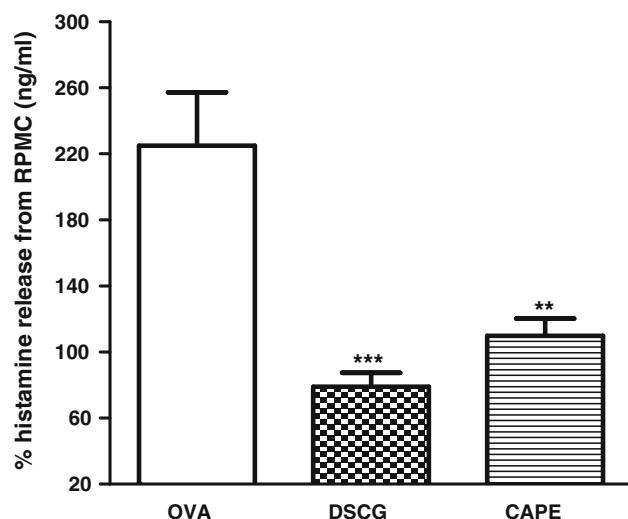


Fig. 3 Effect of CAPE on IgE-induced histamine release in RBMCs. Data are expressed as mean $\pm$ SEM. $n = 6$. ** $p < 0.01$; *** $p < 0.001$ when compared with vehicle treated group using one-way ANOVA

In vitro assays

Incubation of 10 μ M CAPE with tracheal zigzag preparations produced significant reduction in histamine (Fig. 5a), adenosine (Fig. 5b), 5-HT (Fig. 5c)-induced contraction ($p < 0.001$; $p < 0.001$; $p < 0.01$, respectively). $E_{\max}$ was significantly reduced by 39.4 ± 4.39 , 17.4 ± 0.93 , 43.6 ± 2.34 , and 61.5 ± 3.47 % for histamine, adenosine, and 5-HT, respectively, compared to their initial values with only significant decrease in pD_2 value of histamine-induced tracheal contraction ($P < 0.01$) (Table 1).

Discussion

Using in vitro and in vivo models, this work evaluated the efficacy of CAPE against allergic reactions. In vivo, CAPE clearly reduced PCA reaction, histamine, and 5-HT induced vascular permeability in rats and in vitro CAPE reduced histamine and LTs release from mast RPMCs. Also, CAPE had potent inhibitory effect on histamine-, 5-HT-, and adenosine-induced tracheal contraction. These findings suggest that CAPE exhibit antiallergic activities, probably mediated by reduction of the release of mediators such as histamine and LTs from mast cells and weakening the inflammatory action of these mediators.

Passive cutaneous anaphylaxis in rats is one of the most important in vivo models of anaphylaxis in local allergic skin reactions (Kim et al. 2005). The release of vasoactive substances, induced locally in naïve animals using sera from the actively sensitized rats, is subsequent to the antigen–antibody reaction resulting in a dramatic local

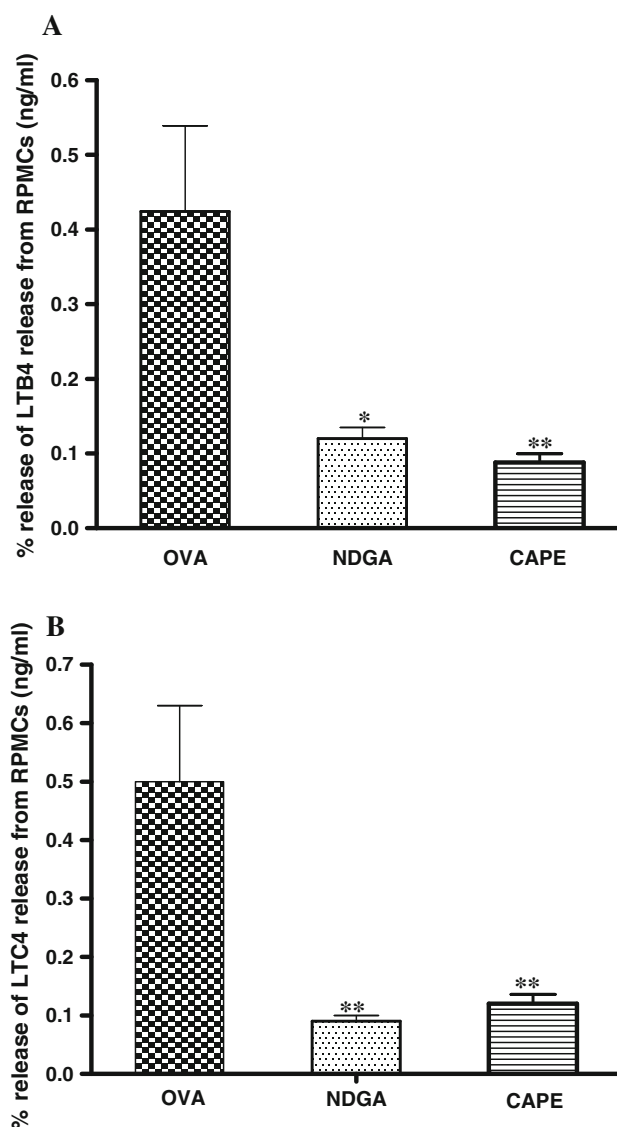


Fig. 4 Effect of CAPE on IgE-induced leukotrienes, **a** LTB4 and **b** LTC4, release in RBMCs. Data are expressed as mean $\pm$ SEM. $n = 6$. * $p < 0.05$; ** $p < 0.01$ when compared with vehicle treated group using one-way ANOVA

increase in vascular permeability. In mast cells, TNF- α is known to be released with histamine and other preformed mediators within minutes after antigenic stimulation, thereby suggesting its potential role in early inflammation (Park et al. 2008). In the present study, pretreatment with CAPE improved manifestations of the PCA reaction as it significantly reduced the dorsal skin Evans blue dye content in rats. So CAPE has the ability to reduce the release of vasoactive substances induced locally.

In order to explore the mechanisms by which CAPE reduced immediate allergic reactions, its effects on histamine release from mast cells and the inflammatory action of mediators were investigated.

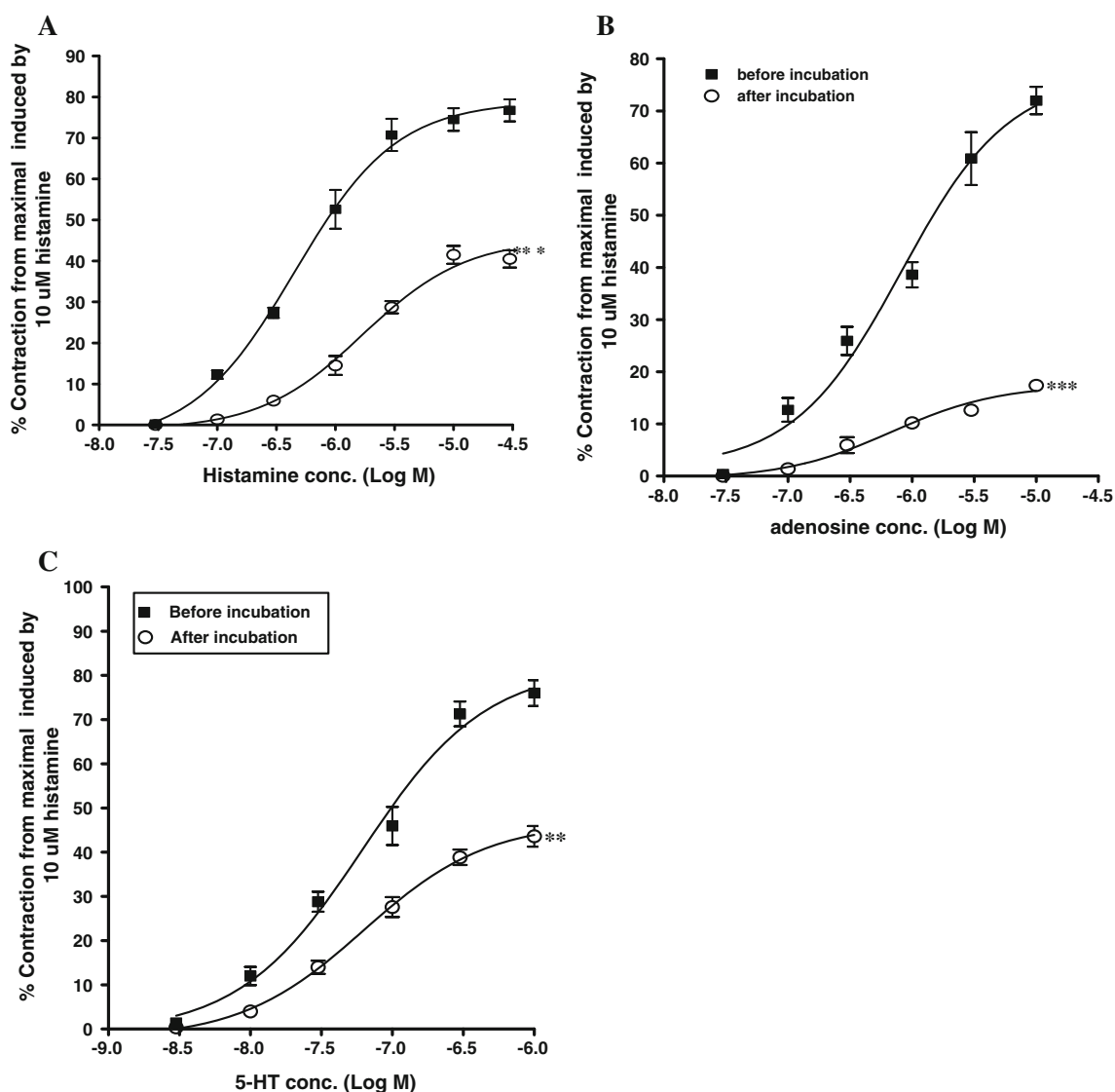


Fig. 5 Effect of CAPE on histamine guinea pig isolated tracheal zigzag contraction induced by **a** histamine, **b** adenosine, and **c** 5-HT. $^{**}p < 0.01$; $^{***}p < 0.001$ when compared with their initial values using paired Student's *t* test. Data are expressed as mean $\pm$ SEM. *n* = 5

Table 1 Effect of CAPE on $E_{\max}$ and pD_{50} for histamine, adenosine, and 5-HT-induced contraction in isolated guinea pig trachea zigzag

CAPE (10 μ g/mL)	pD_{50} (μ M)		$E_{\max}$ (%)	
	Before incubation	After incubation	Before incubation	After incubation
Histamine	6.28 ± 0.07	$5.77 \pm 0.04^{**}$	83 ± 2.65	$39.4 \pm 4.39^{***}$
Adenosine	6.45 ± 0.13	6.43 ± 0.14	72 ± 2.6	$17.4 \pm 0.93^{***}$
5-HT	7.15 ± 0.053	7.12 ± 0.058	76 ± 2.9	$43.6 \pm 2.34^{**}$

Data are expressed as mean $\pm$ SEM. *n* = 5

$^{**}p < 0.01$; $^{***}p < 0.001$ when compared with their initial value using paired Student's *t* test

Results showed that in vitro CAPE (100 μ M) exhibited a significant inhibition on histamine release from RBMCs triggered by OVA and in vivo CAPE clearly reduced the skin reactions induced by histamine and 5-HT in rats at dose 7 mg/kg. Increased permeability of the microvasculature

to macromolecules is one of the earliest events of acute inflammation (Malaviya et al. 2000). Mediators (e.g., histamine, 5-HT, and prostaglandins) that are secreted from mast cells play pivotal roles in the onset and development of inflammation and increased vascular permeability in

various species (Sud'ina et al. 1993). One of the consequences of increased vascular permeability is edema, which is the accumulation of plasma proteins, water, and electrolytes in the interstitium (Jiang et al. 2007). Such effects of CAPE indicate that it exhibits an inhibitory effect on immediate allergic reactions.

In the current study, there was a significant increase in LTs release from OVA-sensitized RPMCs following OVA challenge. CAPE pretreatment; down-regulated LTB₄ and LTC₄ release from the isolated cells. LTB₄ and LTC₄ promote chemotaxis and chemokinesis of eosinophils in mice and human (McEwen et al. 1990), thus contributing to airway inflammation. So, it can be concluded that the anti-inflammatory effect of CAPE in the allergic lung is mediated, at least in part, by inhibition of LTs synthesis. These findings suggest that the antiallergic activity of CAPE is probably mediated by reduction of the release of inflammatory mediators, LTs, from mast cells.

One of the most important cell types involved in pulmonary airway disease are smooth muscle cells. The tracheal epithelium has an important role in modulating responses to several agonists in the pulmonary airway smooth muscle (Macêdo et al. 2011). The potential inhibiting action of CAPE on histamine-, 5-HT-, and adenosine-induced tracheal contraction was investigated. CAPE significantly reduces agonists-induced contraction at all tested concentrations with significant decrease in $E_{\max}$ of histamine, 5-HT, and adenosine. Also, for histamine, CAPE was able to reduce the affinity of histamine contractile effect on tracheal smooth muscle by reducing pD₂ value. The contraction of the smooth muscles of the guinea pig trachea by histamine, 5-HT, and adenosine mediate the opening of calcium channels. Cicala et al. (2003) reported that CAPE demonstrated vascular effect that is partially dependent on nitric oxide and at high concentrations, CAPE vasorelaxant effect occurs in absence of endothelium and it is likely due to an inhibitory effect on calcium. CAPE showed vasorelaxant effect on guinea pig trachea, which may involve Ca²⁺ mobilization.

In conclusion, CAPE shows inhibitory effects on immediate allergic reactions mediated by IgE. This potential could be mediated by reducing the release of inflammatory mediators such as histamine and LTs from mast cells and weakening the inflammatory action of these mediators. Further work is necessary to clarify the possibility that CAPE could be in the treatment of human allergic disorders.

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