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Combination treatment for allergic conjunctivitis – Plant derived histidine decarboxylase inhibitor and H1 antihistaminic drug

Anita K. Bakrania, Snehal S. Patel*

Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, 382 481, India

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ABSTRACT

Aim of present investigation was to study the effect of catechin and the combination of catechin and cetirizine in ovalbumin induced animal model of allergic conjunctivitis. Guinea pigs were divided into 5 groups: normal control, disease control, disease treated with catechin 100 mg/kg, disease treated with cetirizine 10 mg/kg, disease treated with combination of catechin and cetirizine, 50 mg/kg & 5 mg/kg respectively. Sensitization was carried out by intraperitoneal injection of ovalbumin for the period of 14 day. Simultaneously, catechin was administered orally for 14 days while, cetirizine was administered at the day of experiment. Determination of clinical scoring, mast cell and blood histamine content, histidine decarboxylase activity from stomach was carried out. Vascular permeability was measured by dye leakage after secondary challenge of allergen and conjunctival tissues were subjected for histopathological examinations. Treatment with catechin, cetirizine and combination showed significant ($P < 0.05$) decrease in clinical scoring and vascular permeability. While, catechin 100 mg/kg and catechin 50 mg/kg showed significant ($P < 0.05$) decrease in histamine content in mast and blood. The treatment also showed significant ($P < 0.05$) decrease in the histidine decarboxylase enzyme activity. However, cetirizine group did not show any difference in enzyme activity as well as histamine content. Histopathological examination also showed improvement in ulceration and decrease in edema and inflammation in all treatment groups. From the present study, we can conclude that catechin exhibits potent anti-allergic activity by histidine decarboxylase enzyme inhibition and combination shown significant anti-allergic activity at reduced dose by both enzyme inhibition as well as inhibition of histamine receptors.

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1. Introduction

Allergic conjunctivitis is abnormal and altered immunological reaction induced by cross linking of allergen with IgE molecules on ocular surface which leads to release of histamine from mast cells and basophils by degranulation (Abelson et al., 1994). Current treatment options include; antihistamines, mast cell stabilizers, non-steroidal anti-inflammatory drugs, corticosteroids and immunosuppressants. These drugs however have a quick onset of action to relieve allergic reactions but lack a longer duration of action as well as associated with CNS (Central Nervous System) and CVS (Cardiovascular System) side effects (Small et al., 2007; Bourdin et al., 2009, Mihaibisca, 1997).

Histamine is a fundamental mediator released during the immediate allergic response from tissue mast cells and during the late

phase response chiefly from recruited basophils. Histidine decarboxylase is an enzyme which catalyzes synthesis of histamine from histidine in mast cell and therefore H1 antagonist can be a choice in the treatment of allergic disease by preventing binding of histamine to the H1 receptors. The histidine decarboxylase inhibitors are agent which inhibits the conversion of histidine to histamine, and so, is thought to be beneficial through reduction of potentially damaging, histamine-related local immune response in allergic diseases. In the view of drawbacks of currently available synthetic antihistaminic drugs, it is reasoned that screening plant derived histidine decarboxylase inhibitor in combination with H1 antihistaminic drug which combines high selectivity with good oral efficacy and absence of CNS side effects could constitute a major therapeutic improvement in treatment of allergic diseases.

Catechin is a flavan-3-ol that is present in several plants such as *Acacia catechu*, *Camellia sinensis*. It has found to have beneficial effect in various diseases and disorders such as; aging, Parkinson's disease, stroke, obesity, diabetes, cancer and viral infection (Yilmaz,

* Corresponding author.

E-mail address: snehalpharma53@gmail.com (S.S. Patel).

2006; Singh et al., 2011). Catechin reported to have enzyme inhibitory actions on histidine decarboxylase in *in vitro* study (Shimamura et al., 2007; Kawai et al., 2003). Therefore, the aim of the present investigation was to study effect of Catechin alone and in combination with cetirizine at reduced dose in animal model of allergic conjunctivitis.

2. Materials and methods

2.1. Materials

Catechin, ovalbumin, histamine hydrochloride, compound 48/80 was purchased from Sigma Aldrich Pvt. Ltd., India, cetirizine was purchased from Balaji drugs Ltd. India, o-phthalaldehyde, L-histidine, other chemicals were of analytical grade.

2.2. Experiment animals

All experiments and protocols described in present study were approved by the Institutional Animal Ethics Committee (IAEC) of Institute of Pharmacy, Nirma University, Ahmedabad. 30 Hearty Guinea pigs (500–600 g) and 24 Balb/C albino mice were procured from Zydus Research Centre, Ahmedabad. Animals have been housed in the animal house of Nirma University, Ahmedabad under controlled conditions of temperature 23 ± 2 °C, relative humidity $55 \pm 5\%$, and 12 h light and dark cycle.

2.3. Experimental protocol

Guinea pigs were divided into 5 groups normal control group, disease control group, disease treated with catechin (100 mg/kg, p.o.), disease treated with cetirizine (10 mg/kg, p.o.), disease treated with combination of catechin and cetirizine (50 mg/kg & 5 mg/kg respectively). Sensitization was carried out by intraperitoneal injection of 100mcg ovalbumin dissolved in 20 mg alum for fourteen days and ovalbumin challenge was given by instillation in conjunctiva on 14th day. Treatment of catechin was started on day of sensitization till 14th day while, cetirizine was administered one hour before ovalbumin challenge. At the end of experiment, clinical scoring for physical characteristics was carried out (Yanni et al., 1999) (Table 1). Determination of vascular permeability was carried out by U V spectrometer of dye leakage from conjunctival tissues by tracing the jugular vein and injecting 0.4 ml Evans blue dye followed by subcutaneous injection of 0.1 ml 0.3% ovalbumin into the conjunctival tissue and measuring the extracted dye by excision of conjunctiva into extraction solution using UV spectrometer (Nakahara et al., 2000). Estimation of mast cell histamine content was done by isolation of mast cells from peritoneal cavity

followed by degranulation with compound 48/80 and estimation of histamine content by spectrofluorimetry at 450 nm emission excited at 360 nm (Kim et al., 2006). Blood histamine content was measured by similar procedure using basophils instead of mast cells for histamine measurement (Barsoum and Gaddam, 1935). Eyes including eyelids and conjunctiva were exenterated and fixed in 4% paraformaldehyde for 24 h. Conjunctival tissues were cut into cross sections of 3-mm thick and stained with toluidine blue for detection of mast cells and eosinophils respectively.

Histidine decarboxylase assay was performed using the stomach homogenate. Homogenate was prepared in ice-cold 0.02 M phosphate buffer (pH 6.2) containing 1 µg/ml pyridoxal-5'-phosphate and 1 µg/ml dithiothreitol. Homogenate was subjected to centrifugation and supernatant obtained was used as the enzyme solution. 1 ml of the enzyme solution was incubated at 37 °C for 4 h with 0.1 µg/ml L-histidine. The enzyme reaction was terminated using HClO₄. The histamine formed is measured fluorimetrically (Ridzwan et al., 1990). Balb/c mice were used to determine the locomotor activity test of Catechin, cetirizine and the combination using determination of locomotor activity by photoactometer. Overnight fasted mice were administered drug and post an hour, animal was placed in the photoactometer and number of 'cut offs' were recorded for 30 min (Rakh and Chaudhari, 2010). Statistical analysis results are represented as mean $\pm$ S.E.M. Statistical analysis was performed using Graph pad prism 5 statistical software. Statistical differences between the means of various groups were evaluated using one way analysis of variance (ANOVA) followed by turkey's test. Data were considered statistically significant at $P < 0.05$.

3. Results

3.1. Effect of treatment on clinical scoring for physical characteristics

Ovalbumin challenge showed significant increase in clinical score in disease control group as compared to normal control group, while treatment with catechin, cetirizine and combination of catechin and cetirizine showed significant ($P < 0.05$) reduction in clinical score compared to disease control group of animals. The combination has produced effect comparable to cetirizine 10 mg/kg (Fig. 1, Table 2).

3.2. Effect of treatment on vascular permeability

A significant increase in vascular permeability in disease control group was observed proceeding ovalbumin challenge as compared to normal control group, while the disease treated with catechin,

Table 1
Clinical scoring method for physical characteristics.

Feature	Characteristic	Clinical scoring
Conjunctiva redness	Normal	0
	Pink	1
	Red	2
	Dark red	3
Eyelid edema	No edema	0
	Lower lid edema	1
	Upper & lower lid edema	2
	Swollen, everted eye lids	3
	Swelling of both lids and side of face	4
Discharge	No discharge	0
	Glazed, glassy appearance	1
	Moist lids and surrounding hair	2
	Moist lids and surrounding hair, thicker mucous like	3

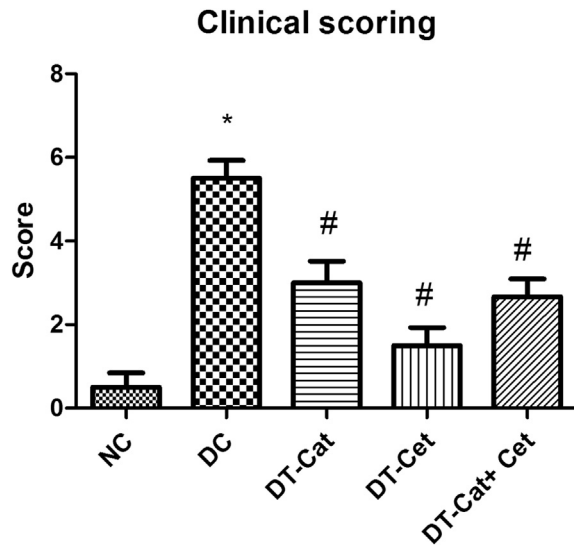


Fig. 1. Effect of treatment on clinical scoring for physical characteristics. * Significantly different from normal control ($p < 0.05$), # significantly different from disease control ($p < 0.05$), each group consists of 6 animals. Values are expressed as Mean $\pm$ SEM, NC–Normal control, DC–Disease control, DT-Cat – Disease treated with catechin (100 mg/kg/day), DT-Cet – Disease treated with cetirizine (10 mg/kg, p.o), DT-Cat + Cet – Disease treated with combination of catechin & cetirizine (50 mg/kg/day, p.o & 5 mg/kg, p.o).

cetirizine and combination of catechin and cetirizine showed significantly ($P < 0.05$) decreased vascular permeability compared to disease control group of animals. The effect produced by the combination is similar to cetirizine at the dose of 10 mg/kg (Fig. 2).

3.3. Effect of treatment on mast cell and blood histamine content

Ovalbumin challenge with 100 μ g/kg intraperitoneal for 14 days showed significant ($P < 0.05$) increase in Histamine concentration in mast cells and blood as compared to normal control group, while the disease treated with catechin and combination of catechin and cetirizine showed significantly decreased histamine concentration compared to disease control group of animals. Cetirizine treated group does not produce decrease in histamine levels in mast cells and blood. The combination group however shows similar efficacy as Catechin at the dose of 100 mg/kg (Fig. 3, Fig. 4).

3.4. Effect of treatment on histidine decarboxylase enzyme activity

A significant ($P < 0.05$) increase in histidine decarboxylase enzyme activity was observed in disease control group as compared to normal control group, while the disease treated with catechin and combination of catechin and cetirizine showed significantly decreased enzyme activity compared to disease control group of animals. Cetirizine treated group did not show any decrease in histidine decarboxylase enzyme activity. (Fig. 5).

Table 2

Effect of treatment on vascular permeability.

Parameters	NC	DC	DT-CAT	DT-CET	DT-CAT + CET
Clinical scoring of conjunctiva	0.5 $\pm$ 0.341	5.5 $\pm$ 0.428*	3.0 $\pm$ 0.516#	1.5 $\pm$ 0.428#	2.667 $\pm$ 0.421#
Histamine release from mast cells (ng/ml)	36.06 $\pm$ 9.183	135.8 $\pm$ 2.602*	94.05 $\pm$ 4.333#	103.1 $\pm$ 6.551#	100.7 $\pm$ 14.66#
Histamine release in blood (ng/ml)	4.186 $\pm$ 2.831	70.26 $\pm$ 11.56*	36.06 $\pm$ 3.797#	62.19 $\pm$ 10.46#	38.87 $\pm$ 10.15#
Histidine Decarboxylase assay	25.12 $\pm$ 4.726	94.12 $\pm$ 7.591*	59.99 $\pm$ 8.752#	85.05 $\pm$ 3.741#	57.41 $\pm$ 9.170#
Vascular permeability (ng/ml)	161.7 $\pm$ 8.809	768.9 $\pm$ 107.7*	404.4 $\pm$ 23.14#	276.1 $\pm$ 14.49#	402.2 $\pm$ 28.68#

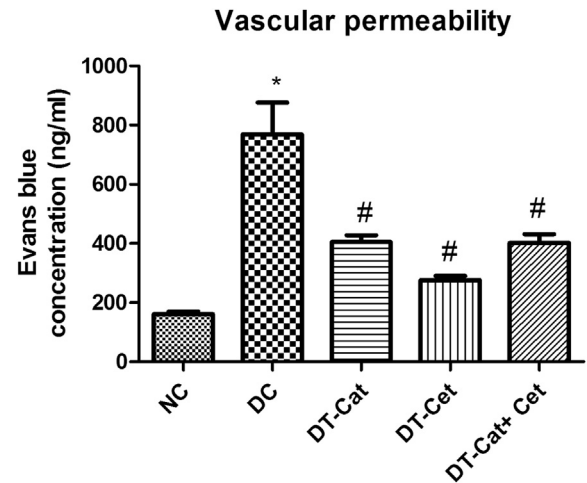


Fig. 2. Effect of treatment on vascular permeability. *Significantly different from normal control ($p < 0.05$), # significantly different from disease control ($p < 0.05$), each group consists of 6 animals. Values are expressed as Mean $\pm$ SEM, NC–Normal control, DC–Disease control, DT-Cat – Disease treated with catechin (100 mg/kg/day), DT-Cet – Disease treated with cetirizine (10 mg/kg, p.o), DT-Cat + Cet – Disease treated with combination of catechin & cetirizine (50 mg/kg/day, p.o & 5 mg/kg, p.o).

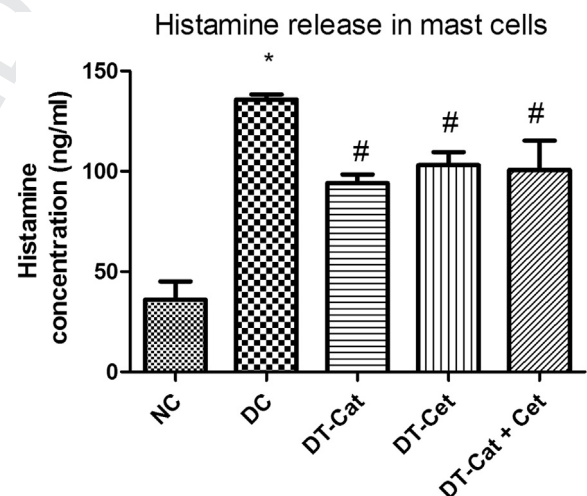


Fig. 3. Effect of treatment on mast cell histamine content. *Significantly different from normal control ($p < 0.05$), # significantly different from disease control ($p < 0.05$), each group consists of 6 animals. Values are expressed as Mean $\pm$ SEM, NC–Normal control, DC–Disease control, DT-Cat – Disease treated with catechin (100 mg/kg/day), DT-Cet – Disease treated with cetirizine (10 mg/kg, p.o), DT-Cat + Cet – Disease treated with combination of catechin & cetirizine (50 mg/kg/day, p.o & 5 mg/kg, p.o).

3.5. Effect of catechin, cetirizine & combination of catechin and cetirizine on histopathology of conjunctiva

Histological findings demonstrated by toluidine blue staining showed the presence of numerous mast cells and neutrophils

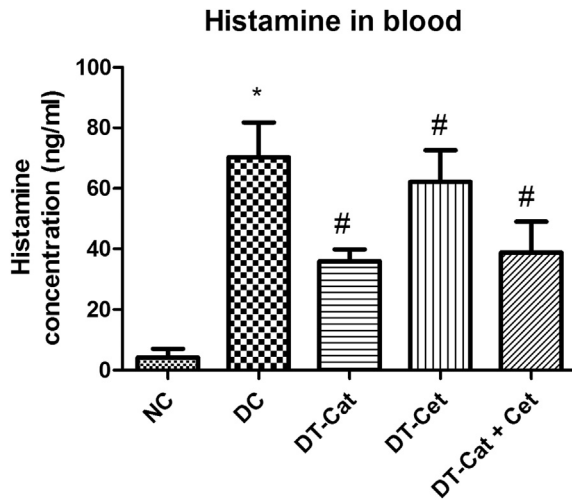


Fig. 4. Effect of treatment on blood histamine content. *Significantly different from normal control ($p < 0.05$), # significantly different from disease control ($p < 0.05$), each group consists of 6 animals. Values are expressed as Mean $\pm$ SEM, NC—Normal control, DC—Disease control, DT-Cat—Disease treated with catechin (100 mg/kg/day), DT-Cet—Disease treated with cetirizine (10 mg/kg, p.o), DT-Cat + Cet—Disease treated with combination of catechin & cetirizine (50 mg/kg/day, p.o & 5 mg/kg, p.o).

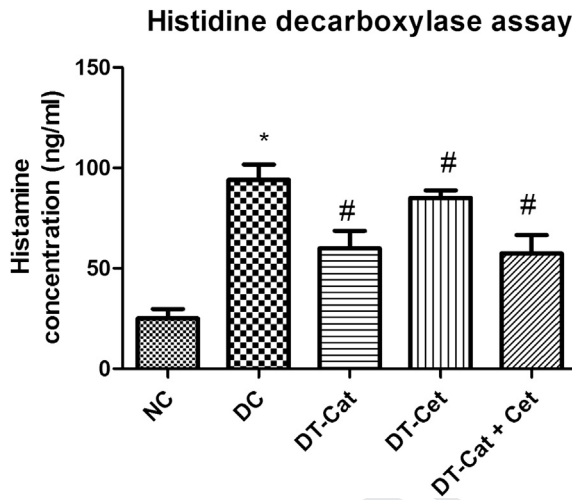


Fig. 5. Effect of treatment on histidine decarboxylase enzyme activity. *Significantly different from normal control ($p < 0.05$), # significantly different from disease control ($p < 0.05$), each group consists of 6 animals. Values are expressed as Mean $\pm$ SEM, NC—Normal control, DC—Disease control, DT-Cat—Disease treated with catechin (100 mg/kg/day), DT-Cet—Disease treated with cetirizine (10 mg/kg, p.o), DT-Cat + Cet—Disease treated with combination of catechin & cetirizine (50 mg/kg/day, p.o & 5 mg/kg, p.o).

infiltration in lamina propria and stroma of conjunctiva, and corneal ulceration. While, in the catechin treated groups infiltrating mast cells and neutrophils were mainly granulated and the number of degranulated mast cells was significantly lower as compared to untreated ones. Treatment with cetirizine did not show any significant change in histopathology of conjunctiva. While, the combination produced decrease in number of degranulated mast cells, infiltrated neutrophils and conjunctival ulcerations. (Fig. 6(a–j)).

3.6. Effect on locomotor activity

Catechin treatment did not show any significant ($P < 0.05$) change in the locomotor activity as compared to the normal control

animals. But, treatment with cetirizine and combination showed significant ($p < 0.05$) decrease in the locomotor activity as compared to the normal group of animals (Table 3).

4. Discussion

Histamine is one of the inflammatory mediators which produce various symptoms of allergy such as itching, sneezing, spasm of airways, tissue swelling, etc. Hence, targeting the enzyme would decrease the production of histamine and may produce anti-allergic activity [Hingorani et al., 1998; Bielory et al., 2012; Bonini et al., 1996; Kaminuma et al., 1998]. Cetirizine, H_1 histaminic blocker produces its action by blocking H_1 receptors hence reducing the allergic symptoms. Cetirizine has been an excellent drug in allergic conditions; however it has a short duration of action as well as sedative effects. Catechin has a slower onset of action but a longer duration of action and hasn't been reported to produce sedative effects. By the virtue of these properties, a combination of catechin and cetirizine may be beneficial in allergic conjunctivitis (Takada et al., 2000; Kamei et al., 1991, 1995a,b).

In present study it was observed that clinical scoring of disease control group is significantly increased as compared to normal control group when ovalbumin was instilled topically in eye. Histamine is well established as a classical itch-producing substance that can produce physical symptoms such as pruritis, redness, tear discharge, hyperemia and edema when applied locally (Davies and Greaves, 1981; Kamei and Minami, 2004). Administration of Ovalbumin to guinea pig provided strong evidence of allergic conjunctivitis by development of redness of the conjunctiva, eyelid edema, and tear discharge which leads to pathophysiological changes in conjunctival tissue by decreasing levels of histamine in serum. Treatment with catechin, cetirizine and the combination showed significant reduction in the physical score compared to disease control group. This effect may be due to the inhibition of histamine synthesis by catechin and blocking of histamine receptors by cetirizine which also leads to decreased histamine activity resulted in decreased clinical scoring.

In current study, animal model of allergic conjunctivitis showed significant increase in the histamine concentration in disease control group of animals as compared to the normal control group. After the allergen presentation along with the class II histocompatibility molecules, the Th 2 lymphocytes expand and secrete a series of cytokines, which in turn promote specific IgE synthesis (Maling et al., 1974).

These IgE molecules further bind to the membrane of the conjunctivae mast cells via specific high affinity receptors and immediate allergic reaction response is triggered. Histamine is released as a result of this response (Sanchez and Lopez, 2010). Histamine is released in both early and late phase of allergic reactions. In early phase, it is released from activated mast cells upon degranulation, while in late phase histamine release occurs due to mast cells and basophils (Ohbayashi and Manzouri, 2010; Hamid et al., 2003; Kamei and Minami, 2004). Treatment with catechin showed significant decrease in histamine concentration in blood and peritoneal fluid mast cells as compared to the disease control group while cetirizine group alone did not showed significant change in histamine level (Spilsbury, 2012). It has been reported that Catechin produces anti-ulcer activity by inhibition of release of histamine (Parmar et al., 1984). Furthermore, previous findings suggest that Catechin is having anti-allergic activity by acting on histamine synthesis pathway. Therefore, decrease in histamine levels in blood as well as mast cells may be due to its action on histamine synthesis pathway.

During the later phase of allergy response, release of chemotactic factors, cytokines and chemokines from activated mast cells

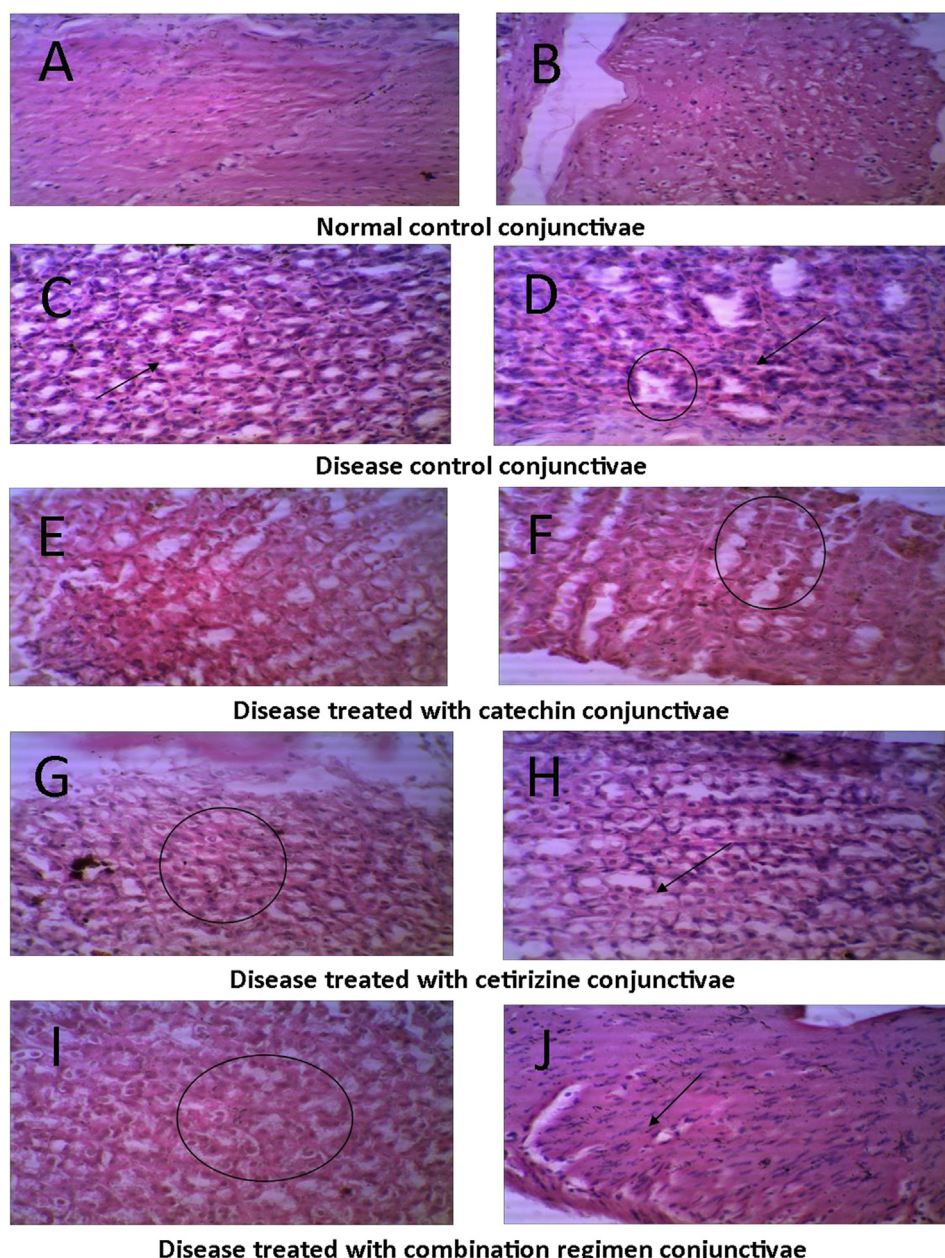


Fig. 6. Effect of catechin, cetirizine & combination of catechin and cetirizine on histopathology of conjunctiva. A & B – Shows normal epithelial cells. C & D – Excessive infiltration of inflammatory cells and ulceration marked. E & F – Less ulceration as compared to disease control. G & H – Comparatively less infiltration of inflammatory cells observed than disease control. I & J – Less or no ulceration seen in combination regimen.

Table 3

Effect of cetirizine on locomotor activity.

Photoactometer (Time)	NC	CAT	CET	CAT + CET
0 min	52.5 ± 1.25	51.5 ± 1.35	49 ± 0.36	48.66 ± 1.35*
30 min	52.83 ± 0.87	51.66 ± 1.14	44 ± 1.26*	44.66 ± 0.76*
60 min	51.5 ± 1.14	47.66 ± 1.02	41.33 ± 0.61*	43.66 ± 1.58*

induce the onset of the reaction which is characterised by vasodilatation as well as increases vascular permeability. Vascular permeability can be assessed by evans blue dye leakage in the conjunctiva which was measured by spectrophotometer. Results showed that there was significant increase in vascular permeability in the disease control group of animals as compared to the normal

control group. The pathological processes of an allergic reaction are thought to be mediated by mast cells which releases histamine, a crucial mediator of hypersensitivity reactions and expression of adhesion molecules, chemokines, which influence the recruitment, trafficking and activation of inflammatory cells [Ingram and Kraft, 2012; Barsumian et al., 1981]. Different studies in murine models

of allergen challenge have shown that histamine is an important chemical mediator which increases vascular permeability striking resemblance to human allergic conjunctivitis (Hamid et al., 2003). The catechin, cetirizine and combination treated groups showed significant decrease in vascular permeability. Catechin produces decrease in synthesis of histamine which leads to decrease in histamine levels hence there is a decrease in vasodilatation which eventually decreases the vascular permeability. Cetirizine blocks H₁ histaminic receptors preventing vasodilatation leading to decreased vascular permeability. The combination treated group shows decreased vascular permeability by the action of two different mechanisms; decrease in histamine level by catechin as well as H₁ receptor blockade by cetirizine.

In present investigation, we found an increased histidine decarboxylase enzyme activity in stomach tissues of disease induced guinea pigs as compared to normal control animals. Histidine decarboxylase enzyme seems to have a highly restrictive and hydrophobic catalytic site. It only binds to histidine or imidazole containing analogs such as α -fluoromethyl histidine, histidine methyl ester, and natural polyphenols such as catechins by inducing a similar conformation change of the enzyme bound substances (Hayashi et al., 1993; Olmo et al., 2002; Rodri-guez-Caso et al., 2003). High concentrations of histidine decarboxylase have already been found in the patients with allergic disease. Recently, experimental model has also revealed increased activity of histidine decarboxylase. Treatment with catechin abrogated this augmented activity of histidine decarboxylase. Catechin has shown effectiveness in allergic disorders in several studies carried out (Polidori, 2003). Catechin also significantly reduced gastric tissue histamine levels as effectively as cimetidine in reducing gastric acid secretion (Parmar et al., 1984). Furthermore, it has shown to have histidine decarboxylase inhibitory activity in in vitro study. Catechin being an enzyme inhibitor of histidine decarboxylase enzyme, it acts upon the synthetic pathway of conversion of the amino acid L-histidine to histamine.

Neutrophils release proteolytic enzymes, cytotoxic proteins and oxygen radicals which further cause corneal damage. The corneal fibroblasts stimulated by neutrophils take part in collagen degradation leading to corneal ulceration. Hence, the infiltration of neutrophils plays a major role in the pathogenesis of disruption of corneal epithelium (Bonini et al., 1996). Histopathology studies of the conjunctivae were performed and it showed significant increase in the infiltration of mast cell in lamina propria and stroma of conjunctiva along with ulceration, infiltration of neutrophils and edema. This can be due to decrease in corneal epithelial and basement-membrane damage caused by major basic and cationic proteins, neurotoxin, peroxidase, and collagenase released by neutrophils. Degranulation of mast cells releases preformed heparin, histamine, and neutral proteases and increases the allergic inflammatory process (Abelson and Schaefer, 1993; Bacon et al., 1993). The catechin treatment showed improvement in the ulceration, infiltration of neutrophils and edema. This protective effect may be due to inhibition of release of histamine which increases allergic inflammatory process (Nicolaou et al., 2010). In present study, the normal control conjunctiva was used as the control to compare the differences between the normal and the diseased groups. It was observed that the disease control group showed excessive infiltration of inflammatory cells such as neutrophils and eosinophils as compared to the normal control. In comparison to the disease control, the disease treated with catechin, cetirizine and the combination regimen showed relatively less or no ulceration and infiltration of inflammatory cells indicating that the combination regimen is protective against physical damage to the conjunctivae during allergic conjunctivitis.

Several antihistaminic drugs produce CNS side effects such as

sedation which is mediated by muscarinic receptors in central nervous system (Garaczi et al., 2004; Snowman and Synder, 1990). Moreover, Catechin and cetirizine both cross the blood brain barrier hence locomotor activity of Catechin, cetirizine and the combination was carried out. The treatment with cetirizine as well as the combination produced decrease in locomotor activity as compared to normal group of animals. This may be due to sedative effect of cetirizine. But, the combination group produced less decrease in locomotor activity as compared to cetirizine group which indicates that combination is safer than cetirizine alone with minimal or reduced CNS side effect.

5. Conclusion

Histidine decarboxylase inhibitors as well as anti-histamines have been used in several allergy disorders. The combination of Catechin and cetirizine showed statistically significant effectiveness in the management of allergic conjunctivitis when compared with the standard disease control and Catechin and cetirizine alone groups. The foregoing analysis upon the experimental work performed and results obtained suggest that catechin has significant anti allergic activity in allergic conjunctivitis. The combination of catechin and cetirizine also has significant anti-allergic activity in allergic conjunctivitis with similar efficacy by improving allergic symptoms, inhibiting histamine release from mast cells as well as basophils, reduced histidine decarboxylase enzyme activity, decrease in vascular permeability and less or no side effects. This type of cocktails will not only decrease the side effects of currently marketed drugs but also would enhance their clinical efficacy.

Conflicts of interest

The authors state that there are no conflicts of interest pertaining to this manuscript.

Uncited references

Junqueira et al., 2004, Lambert and Yang, 2003, Lebrech et al., 1999, Mainardi and Bielory, 2011, Menon et al., 1999.

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