ANTI-ALLERGIC POTENTIAL OF ETHANOLIC EXTRACT OF *CORIANDRUM SATIVUM* LEAVES IN CONJUNCTIVITIS: AN EXPERIMENTAL STUDY IN RATS

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ABSTRACT

The *in vitro* antioxidant activity of the ethanolic extract of *Coriandrum sativum* (*C. sativum*) leaves was performed by DPPH scavenging and ferrous chelating methods. To induce allergic conjunctivitis, an intraperitoneal injection of 0.6 mL saline containing alum (2 mg), egg albumin (1 mg) and 10^{10} cells inactivated *Bordetella pertussis* was administered on the first day. On the fifth day, a booster dose was given subcutaneously, consisting of egg albumin (0.5 mg) injected at 10 sites on the back of rats. From the 14th to the 42nd day, rats were orally administered ethanolic extract of *C. sativum* eaves (EECS) in doses of 100 mg kg^{-1}, 200 mg kg^{-1}, and 400 mg kg^{-1}, depending on their respective groups. The standard group received 10 mg kg^{-1} cetirizine hydrochloride orally. 1 h after dosing, local sensitization was performed by applying 5 µL of egg albumin into both eyes using a micropipette. It was noted how frequently eye-scratching behaviours occurred over a five-minute period following the sensitization. Allergic symptoms, including conjunctival redness and swelling, were evaluated at five and twenty minutes, respectively. After 24 h of 14th and 42nd day treatment, one animal from each group was euthanised. The conjunctiva was excised, and 4-µm-thick sections were stained to assess eosinophil infiltration. Results showed that the ethanolic extract of *C. sativum* leaves produced *in vitro* antioxidant properties by DPPH scavenging and metal chelating activity against iron, with IC_{50} values of 200 µg mL^{-1} and 2000 µg mL^{-1}, respectively. The extract considerably reduced eosinophils infiltrating the conjunctival tissues ($p<0.01$) and significantly lowered allergy symptoms and eye scratching behaviours ($p<0.001$). Therefore, we conclude that the ethanolic extract of *C. sativum* leaves produced a significant anti-allergic conjunctivitis activity.

Keywords: *Coriandrum sativum,* eye scratching behaviour, allergic symptom, histopathology, anti-allergic conjunctivitis.

INTRODUCTION

Ocular allergies are among the most common disorders affecting the eyes in clinical settings. This allergy has no clear origin, and researchers presume that a number of factors, such as early exposure, pets, urban air pollution, and genetics, may be involved[1]. Conjunctivitis, commonly referred to as pink eye, is a conjunctival irritation[2]. Conjunctivitis can have a variety of causes, including bacterial, viral and allergic[3,4].

Allergy conjunctivitis symptoms include burning red eyes and yellow pus that discharges from the eyes, which makes them sticky and causes the eyelids to stick as you sleep[5]. The main objectives of treating allergic conjunctivitis are to lessen the symptoms of itching,

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redness, tearing, swelling, and other related issues of the conjunctiva or eyelids[6]. A variety of medications, including antihistamines, mast cell stabilisers, dual-action anti-allergic drugs, NSAIDs, corticosteroids, anti-leukotrienes, and anti-IgE, are used to treat allergic conjunctivitis[7].

India is home to the glabrous, branching plant known as *Coriandrum sativum*, which is a member of the Umbelliferae family. The crop becomes mature in two to three months. The plant's name, coriander, comes from its distinctively pungent and offensive smell. It is indigenous to Egypt, Morocco, Russia, Hungary, Holland and India[8].

Traditionally, coriander has been used to treat hay fever, amoebic dysentery, rashes, burns, sore throats, coughs, headaches, urticaria, allergies, urethritis, cystitis, and nose bleeding[9]. It is also used to treat headaches, burning sensations, localised pain and swelling, vertigo, stomatitis, conjunctivitis, memory loss, coughing, digestive issues and diuretics[10].

Studies on different parts of the coriander plant have shown a variety of pharmacological activities such as antibacterial activity[11], antioxidant and anticancer activity[12], hypoglycaemic activity[13], antifungal activity[14], antihemolytic activity[15], diuretic activity[16], treatment of migraine[17], cholesterol-lowering property[18], hepatoprotective activity[19], anthelmintic activity[20], sedative hypnotic and anxiolytic activity[21], anti-mutagenic activity[22], antiulcer activity[23], cardioprotective activity[24] and reversal of memory[25].

Based on literature analysis, no study has been found on the effect of coriander leaves on conjunctivitis. Therefore, we planned for the evaluation of its effects.

MATERIALS AND METHODS

Identification, collection and authentication of plant material

With reference number 2016/SOS/BOT/23, the plant was taxonomically recognised and authenticated as *C. sativum* by the Botany department of IFTM University, Moradabad, Uttar Pradesh, India. The collected leaves were ground into a coarse powder after being dried for 15 days at room temperature in the shade.

Extraction of plant material

After being dried and sieved over a 20-mesh screen, the plant powder was extracted using a series of solvents. The powder was first extracted using petroleum ether (40-60 °C) to defatify and decolorise the plant material, and the plant material to be employed was extracted using ethanol for the final extraction. After removing the solvent under low pressure to create a semisolid mass, the ethanolic extract of *C. sativum* (EECS) was vacuum-dried to produce solid residues. An airtight container was used to store the dried extracts before the time of use.

Preliminary phytochemical screening

Several chemical tests were performed on the plant's ethanolic extract to identify the phytoconstituents, including alkaloids, proteins, amino acids, carbohydrates, glycosides, tannins, flavonoids, steroids[26,27].

Drugs and chemicals

Egg albumin (S.D. Fine-Chem Limited, Mumbai), aluminium hydroxide (Central Drug House (P) Limited, New Delhi), *Bordetella pertussis* inactive microorganism suspension (Sigma-Aldrich Company LLC), cetirizine hydrochloride (GlaxoSmithKline Pharmaceuticals Limited, Baddi), sterile water (Nirlife Healthcare Private Limited, Mumbai) and carboxy-methyl cellulose (S.D. Fine-Chem Limited, Mumbai) were provided by IFTM University, Moradabad.

In vitro antioxidant activity

DPPH scavenging method

The free radical DPPH (1, 1-diphenyl 2-picrylhydrazyl) is frequently employed to examine the plant extract's initial capacity to scavenge radicals[28]. A common chemical used to assess antioxidant activity is DPPH. In order to neutralise DPPH's free radical nature, an antioxidant either donates an electron or a hydrogen atom to it[29]. DPPH scavenging is associated with lipid peroxidation inhibition[30]. An extract solution was made in 95% methanol with varying concentrations (50 µg mL^{-1}, 100 µg mL^{-1}, 150 µg mL^{-1}, 200 µg mL^{-1}, and 250 µg mL^{-1}). The DPPH solution (0.5 mM) was prepared in 95% methanol. To start the reaction, 0.2 mL of the extract solution was added to 2 mL of DPPH solution and allowed to complete the reaction for 30 minutes. Then, at 517 nm, the absorbance was measured and correlated with the ascorbic acid reference. The activity percentage was calculated using the following formula[31].

$$\% \text{ inhibition} = \frac{A_0 - A_1}{A_0} \times 100$$

where A_0 represents the control's absorbance (blank, extract-free) and A_1 represents the extract's or standard's absorbance.

Metal (ferrous ion) chelating activity

Because iron is necessary for breathing, oxygen transport, and the action of certain enzymes, it is vital for life. As a reactive metal, it causes oxidative alterations in lipids, proteins and other biological constituents[32]. The extract's capacity to chelate metals was assessed using the chelates of ferrozine with ferrous ion, which interact together to generate a crimson complex that absorbs light at 562 nm[33]. This process is inhibited when other chelating agents are present. These substances function as secondary antioxidants by forming a σ bond with a metal by stabilising the metal ion's oxidised form and lowering the complex's redox potency[34].

A solution of extract in water was prepared at different concentrations, namely 1000, 2000, 3000, 4000 and 5000 µg mL^{-1}. The reaction was initiated by adding 0.2 mL of ferrozine (5 mM) after 0.1 mL of extract solution and 0.5 mL of the ferrous chloride (0.2 mM) solution had been mixed. After mixing the solution, the mixture was allowed to complete the reaction for 10 min at room temperature, then the absorbance was measured at 562 nm and compared to the absorbance of EDTA[35].

Experimental animals

Wister albino rats weighing 140-150 g of both sexes were used. The rats were procured from the IFTM University animal house in Moradabad. The rats were fed with water and regular laboratory feed and water. With resolution no. 2016/837ac/MPh/09, the Institutional Animal Ethics Committee of IFTM University in Moradabad authorised the experimental protocol. Every procedure that involved the animals was carried out in compliance with the Animal Care and Use Committee's recommendations.

Table I: Grading method used for determining the severity of conjunctivitis

Score	Symptoms	
	Hyperaemia	Edema
0	No symptom	No symptom
1	Mild hyperaemia in one eye	Mild edema in one eye
2	Mild hyperaemia in both eyes	Mild edema in both eyes
3	Serious hyperaemia in one eye, while mild hyperaemia in another eye	Serious edema in one eye, while mild edema in another eye
4	Serious hyperaemia in both eyes	Serious edema in both eyes

Acute oral toxicity study

Using albino Wistar rats, acute oral toxicity experiments for ethanolic extracts of *C. sativum* were carried out in accordance with OECD guideline no. 423. The test medication was given to the animals orally in a single dose of 2000 mg kg^{-1} after fasting overnight and weighed. The animals were continuously monitored for the next 4 h following the test drug delivery to look for any clinical symptoms, behavioural changes, or fatality. The animal's weight was once again measured 6 h after the test was administered, and over the next fourteen days, a thorough clinical examination was conducted once daily[36].

EVALUATION OF ANTI-ALLERGIC CONJUNCTIVITIS ACTIVITY OF EECS

Grouping of the rats

Five sets of five rats each were created to assess the anti-allergic conjunctivitis effect of EECS. Group I received the CMC solution (vehicle) and served as the control group. The second group, designated as the standard group, received 10 mg kg^{-1} of cetirizine hydrochloride treatment. EECS treatments of 100 mg kg^{-1}, 200 mg kg^{-1}, and 400 mg kg^{-1} were administered to Groups III, IV, and V, respectively.

Sensitization of rats

To induce allergic conjunctivitis, an intraperitoneal injection containing alum (2 mg), egg albumin (1 mg) and 10^{10} cells inactivated *B. pertussis* was administered on the first day. On the fifth day, a booster dose was given subcutaneously, consisting of egg albumin (0.5 mg) injected at ten sites on the back. Then, from days 14 to 42, local sensitization was carried out with administration of egg albumin at 10 mg mL^{-1} in physiological saline using a micropipette, administering 5 µL to each eye.

Treatment of sensitized rats

From day 14 to day 42, the actively sensitized rats received their respective treatments 1 h before the local sensitization to assess the anti-allergic conjunctivitis activity. Rats in the control group received 1 mL of 1% CMC solution per day, rats in the standard group received 10 mg kg^{-1} of cetirizine hydrochloride, and rats in the test groups received the extract at doses of 100, 200, and 400 mg kg^{-1}; all dosages were administered orally.

Assessment of eye-scratching behaviours and symptoms of allergies

The number of eye scratching behaviours, such as an unbroken cluster of fast forelimb movements focused on

the ocular surface, was recorded for 5 minutes following topical antigen challenge, while allergic symptoms, such as conjunctival hyperaemia and edema, were noted at 5 and 20 minutes respectively, utilizing the rating methods given in Table I[37].

Histological assessment

24 h after treatment, on days 14 and 42, one animal from all groups was sacrificed by intraperitoneal injection of ketamine (50 mg kg^{-1}), decapitated and the eye was removed surgically. Conjunctivas were excised, placed in 10% neutral buffered formalin for two days and preserved. Following paraffin fixation, a 4-µm-thick conjunctival piece was stained to ascertain the number of eosinophils present[38].

RESULTS

Preliminary phytochemical screening

We perform the various chemical tests for identification of type of chemical compounds present in the extract and we found that the following compounds are present: carbohydrates, tannins, phenolic compounds, flavonoids, proteins, amino acids and triterpenoids. The chemical test for alkaloids and saponins was found to be negative.

In vitro antioxidant activity

DPPH scavenging method

The results indicated that the extract was found to be less effective during the DPPH scavenging study performed for the extract, and it showed that EECS has a dosage-dependent DPPH scavenging property. Graphical representation of data shows that the IC_{50} value ascribed to EECS was attained at 200 µg mL^{-1} (Fig. 1).

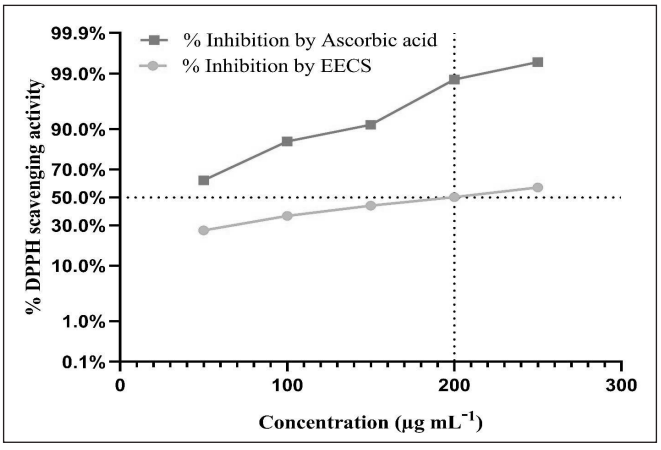

Fig. 1: Evaluation of DPPH scratching activity of EECS

Metal (ferrous ion) chelating activity

In the metal chelating activity of the extract, it was observed that the ethanolic extract of *C. sativum* has dose-dependent metal chelating activity against iron, with an IC_{50} value at 2000 µg mL^{-1}. By decreasing metal-catalysed oxidative processes against iron, which can produce dangerous free radicals through redox cycling, the ethanolic extract proved its ability to function as an antioxidant activity (Fig. 2).

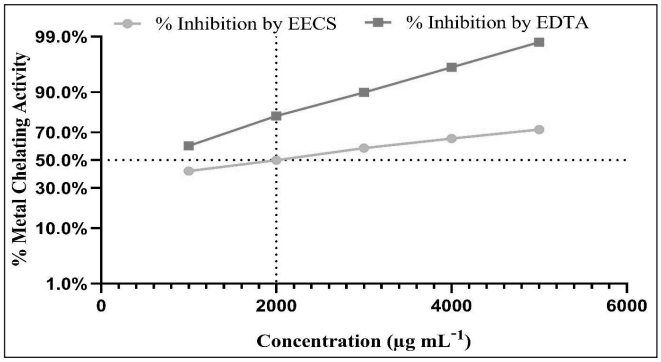

Fig. 2: Evaluation of metal chelating activity of EECS

Acute oral toxicity study

In the acute oral toxicity test, all test animals were found to be only lightly sedated during the first 1 h post administration and normal and active after 2 h. All the animals survived 14 days after administration of the ethanolic extract of *C. sativum* (EECS), whereas no additional signs of toxicity were seen during the whole observation period of 14 days.

Anti-allergic conjunctivitis activity

Evaluation of eye scratching behaviours

After the challenge with the antigen, scratching behaviours in the eye were significantly different. As soon as the antigen was applied topically, eye scratching behaviours were noted for upto five minutes. Repeated topical application of antigen upto day 18 considerably increased the frequency of eye scratching behaviour instances; however, from days 19 to 42, the treatment group's eye scratching behaviours were significantly lowered when compared to the control group (Fig. 3).

Evaluation of allergic symptoms

Following an antigen challenge, a remarkable alteration in allergy symptoms was reported. Frequent topical administration of antigen significantly increased the incidence of allergic symptoms, which were then maintained and decreased during local sensitization from 20th day of the study in the treatment groups, and

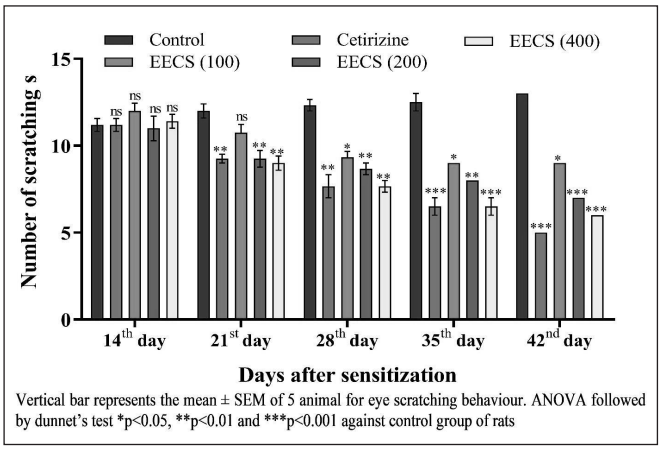

Fig. 3: Evaluation of eye scratching behaviours

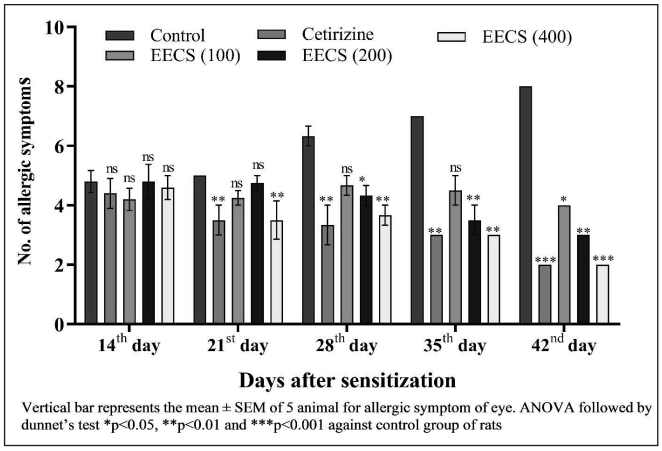

Fig. 4: Evaluation of allergic symptoms of the eye

the effectiveness of extract was seen to be in a dose dependent manner (Fig. 4).

Histopathological assessment

Histopathological photomicrographs of the rat's conjunctiva exposed to antigens, reveal the quantity of eosinophils in their conjunctival mucosa. In the control group, the number of conjunctival eosinophils rises between days 14 and 42. The number of conjunctival eosinophils was found to be decreased in the groups treated with EECS in comparison to the control group, and the effect was found to be dose dependent (Figs. 5,6).

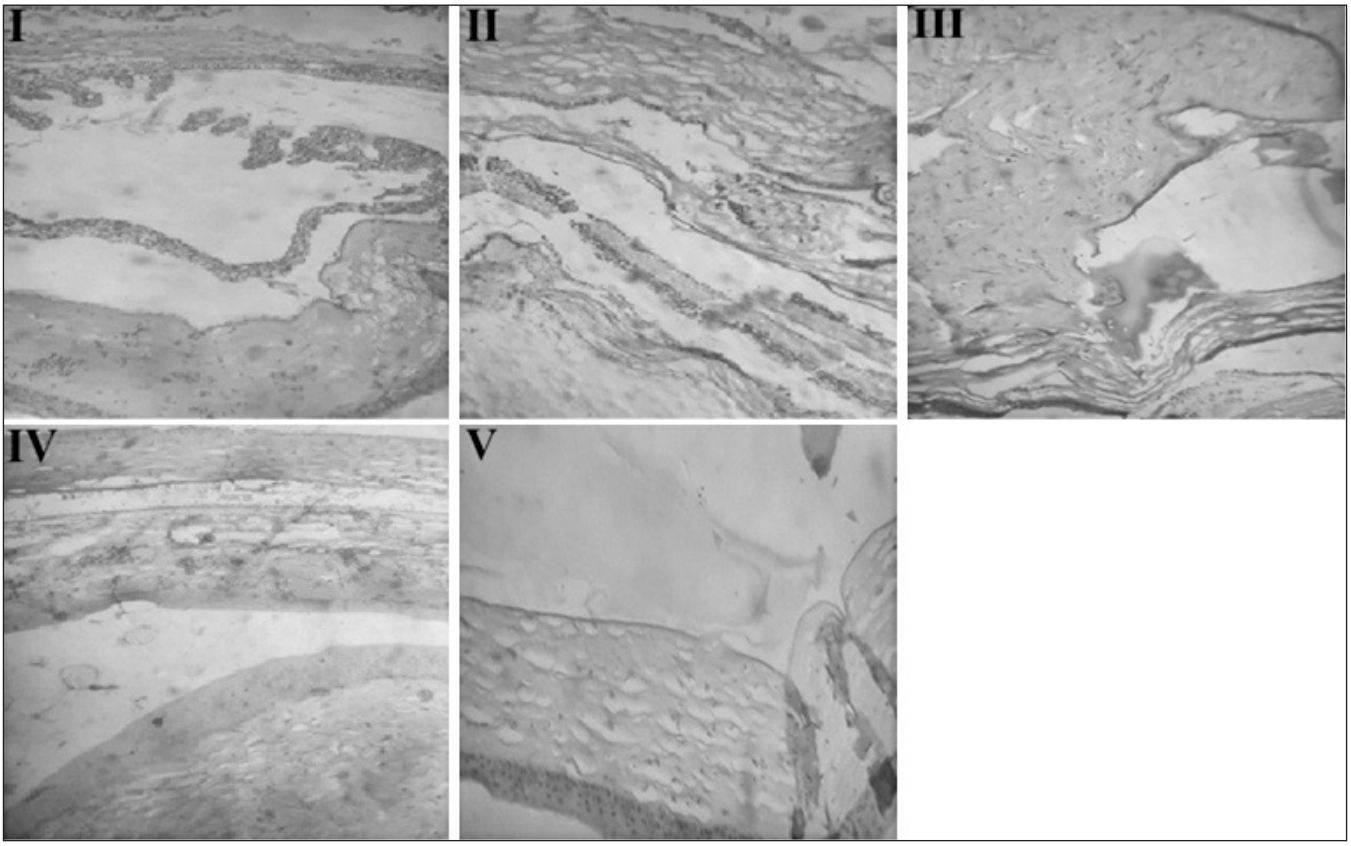

Fig. 5: Histopathological examination of the conjunctiva on the 14th day. (I) section of eye treated with 1% CMC, (II) section of eye treated with cetirizine hydrochloride (10 mg kg^{-1}), (III) section of eye treated with EECS (100 mg kg^{-1}), (IV) section of eye treated with EECS (200 mg kg^{-1}), and (V) section of eyeball treated with EECS (400 mg kg^{-1})

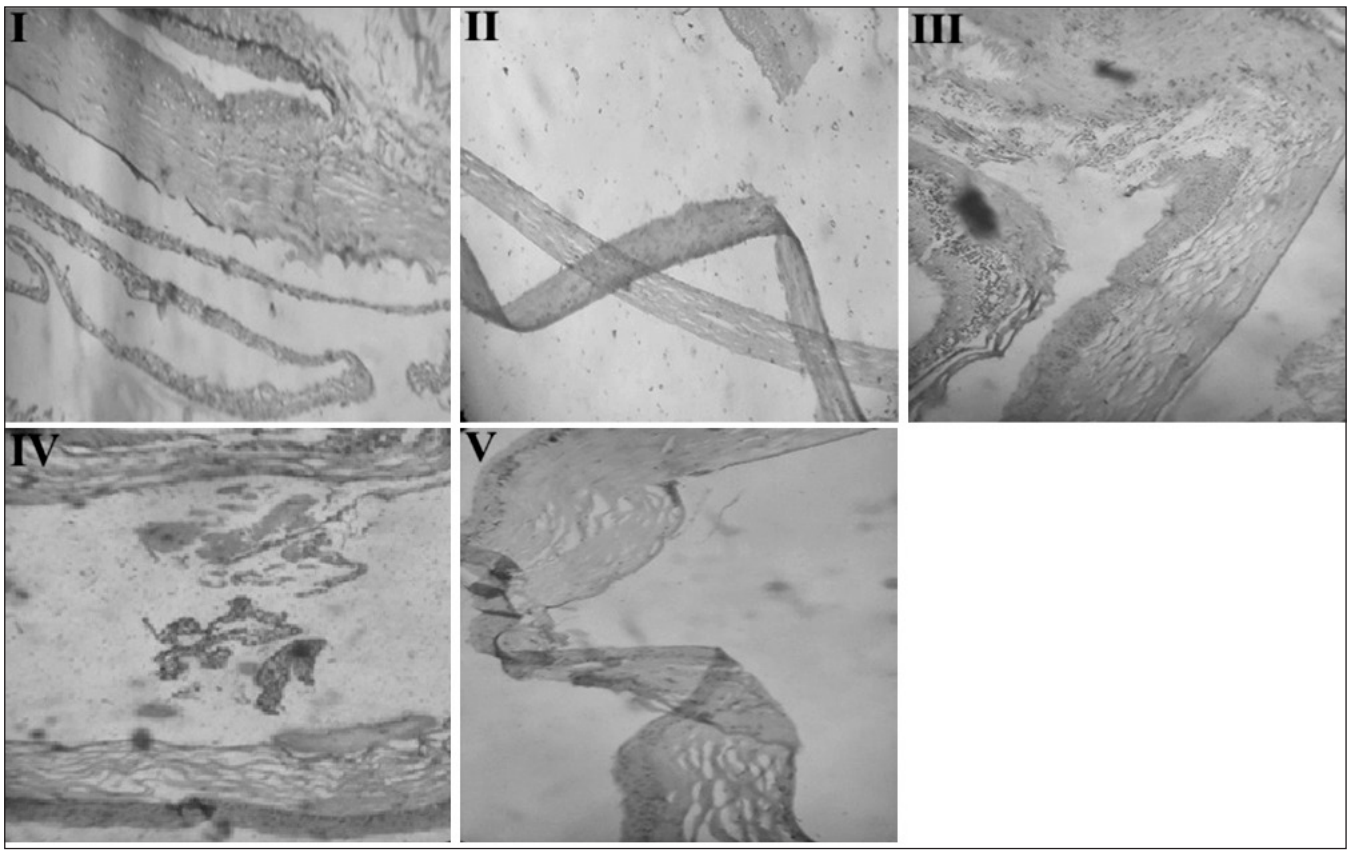

Fig. 5: Histopathological examination of the conjunctiva on the 42nd day. (I) section of eye treated with 1% CMC, (II) section of eye treated with cetirizine hydrochloride (10 mg kg^{-1}), (III) section of eye treated with EECS (100 mg kg^{-1}), (IV) section of eye treated with EECS (200 mg kg^{-1}), and (V) section of eyeball treated with EECS (400 mg kg^{-1})

DISCUSSION

Due to the growing trend of substituting natural antioxidants and antimicrobials for synthetic ones, the antioxidant capabilities of numerous plant extracts have attracted significant attention in the medical and food industries[39,40]. The results of our *in vitro* antioxidant analysis of *C. sativum* ethanolic extract (EECS) demonstrated that EECS has dose-dependent antioxidant activity by DPPH scavenging and metal chelating activity against iron, with IC_{50} values at 200 µg mL^{-1} and 2000 µg mL^{-1}, respectively.

Acute toxicity studies are necessary to explain the likely clinical symptoms elicited by the test chemicals under investigation, as well as to determine the additional range of dosages in animal experiments[41]. Rats fed with ethanolic extract of *C. sativum* (EECS) showed no signs of morbidity or mortality over the 14-day observation period during an acute toxicity investigation carried out in compliance with OECD guideline no. 423. Additionally, our results demonstrated that the ethanolic extract of *C. sativum* (EECS) had an LD_{50} larger than 2000 mg kg^{-1} and that there were no adverse effects up to 2000 mg kg^{-1}.

Based on the findings of the previous investigation, sensitized rats exhibited noticeable eye scratching behaviours following repeated topical application of antigen[42,43]. Antigen-presensitized guinea pigs and sensitized mice have also been shown to exhibit eye-scratching behaviours and topical antigen administration, respectively[37]. However, compared to rats, guinea pigs and mice showed fewer instances of eye scratching behaviours[44,45].

Rats with ovalbumen-induced allergic conjunctivitis have been utilised in preclinical research to test the efficacy of anti-allergic drugs[46,47]. It has been identified as the best model for allergic conjunctivitis caused by both IgE and non-IgE[6,48]. The extract's effectiveness in reducing the unpleasant symptoms linked to the underlying pathology of allergic conjunctivitis is supported by the clinical scores attained for the extract-treated group[49,50]. The treatment with EECS gives a relevant decline in allergen-specific immunoglobulins. This indicates that the ethanolic extract of *C. sativum* may have an immunosuppressive effect[51].

EECS was reported to considerably decrease experimental allergic conjunctivitis produced by antigen in rats at dosages of 100, 200, and 400 mg kg^{-1}, respectively. In allergic conjunctivitis, the extract's anti-allergic properties are thought to be antihistaminic and mast cell stabilisation. As a standard medication, cetirizine reduced the ocular scratching behaviours in rats that were sensitized by allergen. Cetirizine has been shown to exhibit H1 antagonistic action[52,53]. It is commonly known that the conjunctiva contains mast cells and that conjunctivitis causes eosinophils to get into the conjunctiva. Since histamine is present in both mast cells and eosinophils, cetirizine demonstrates a strong affinity for IgE receptors expressed on their surface as well as H1 antagonist action[54,55]. As our study demonstrated, H1 antagonists nearly stopped the antigen-induced eye scratching behaviours. Thus, we believe that eye itches brought on by antigen-antibody reactions might be caused by histamine generated by mast cells and eosinophils. Additionally, we discovered in this study that EECS significantly decreased the number of eosinophils in the conjunctival tissues.

CONCLUSION

During ethanolic extract of *C. sativum* acute oral toxicity study, no animal death was observed up to 2000 mg kg^{-1} doses of extract, indicating their practically nontoxic in nature. *In vitro* antioxidant study of the extract exhibited dose-dependent antioxidant activities by DPPH scavenging and metal chelating activity against iron, with IC_{50} values at 200 µg mL^{-1} and 2000 µg mL^{-1}, respectively. The extract significantly decreased allergic symptoms, eye scratching behaviour and eosinophils in the conjunctival tissues and its effect was found to be dose dependent. Therefore, we conclude that the ethanolic extract of *C. sativum* leaves (EECS) shows a strong anti-conjunctivitis effect against allergic conjunctivitis.

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