



# EVALUATION OF HERBAL OINTMENT CONTAINING ETHANOLIC EXTRACT OF STEM BARK OF *Berberis aristata* DC. FOR ITS ANTIPSORIATIC AND ANTIINFLAMMATORY POTENTIALITY

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## ABSTRACT

**Objective:** *Berberis aristata* DC. is traditionally used medicinal plant and having a wide therapeutic effect for the treatment of different kinds of illnesses. The aim of this present research work was to evaluate the anti-psoriatic activity and anti-inflammatory activity of plant *Berberis aristata* DC. (stem bark).

**Methods:** Screening for phytochemicals was performed to investigate the inclusion of plant-based components in *Berberis aristata* DC. (stem bark). To evaluate the anti-psoriatic activity of *Berberis aristata* DC (stem bark) on Swiss albino mice tail model was used.

Then Evaluation parameters (redness, erythema and scales) were observed and histopathological examination was performed to observe the symptoms and changes in epidermal thickness of mice skin. Safety profile of *Berberis aristata* DC. was confirmed by acute dermal toxicity test by following OECD



guideline 402. For anti-inflammatory activity of *Berberis aristata* DC. (stem bark) on Wistar rats histamine induced paw edema model was used. Three hours after an intraplantar injection of histamine, the number of neutrophils in tissue samples from the paws was counted.

**Results:** In present study findings, the phytochemicals were found to be alkaloids, flavonoids, coumarins, glycosides, polyphenols, saponins and tannins. BAEE ointments 0.5% and 1% w/w were more significant towards anti-psoriatic activity. The dose of 400mg/kg was more potent towards anti-inflammatory activity.

**Conclusion:** From the observed findings it was concluded that BAEE has therapeutic efficacy for the management and treatment of psoriasis and inflammatory activity.

**Keywords:** Phytochemical, inflammation, OECD, psoriatic, *Berberis aristata* DC. epidermal thickness, Munro micro abscess, spleen index, acute dermal toxicity.

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## INTRODUCTION

Chronic inflammation causes psoriasis, immune-mediated rashes are a symptom of a skin condition, scales, red patches, and itching. The inflammatory processes mentioned here could be linked to the progression of morbidity and comorbid conditions, both of which can seriously harm a patient's health [1]. The skin becomes rigid in psoriasis due to an increase in cholesterol levels and a decrease in ceramides levels, resulting in a decrease in skin water content. This poses a significant challenge in terms of getting the drug to the target tissue via a topical route [2]. The inflammatory response is the body's reaction to a harmful stimulus. Numerous toxic compounds have the potential to cause it to occur (eg, infections, antibodies, or physical injuries). The inflammatory response of the host is crucial for halting and ending the infectious process, but it is also in charge of producing illness signs and symptoms. Complement, kinin, and coagulation pathways are among the complex host responses involved. Inability to kill or contain the microbe usually leads to more damage as inflammation and infection progress [3]. Daruharidra, Daru Haldi, Indian barberry, Tree turmeric, and Chitra are all names for *Berberis aristata* DC. It's a spiny, hard, yellowish herb from the *Berberidaceae* family. This plant is primarily grown in the sub-Himalayan region, the Nilgiri hills of southern India, and hilly Nepalese areas between 2000 and 3500 meters [4]. Due to its medicinal value, it is considered the most important herbal plant in the Ayurvedic, Siddha, and Unani medicinal systems [5]. The plant roots are considered the official source of the drug [6]. The plant has historically been utilized to treat wound healing, skin diseases, rheumatism, snakebite, menorrhagia, jaundice, and eye problems as a tonic, demulcent, diaphoretic, diuretic, and alternative [7,8]. The present paper the research work was planned to performed phytopharmacological evaluation of *Berberis aristata* DC. (stem bark) BAEE for anti-inflammatory and anti-inflammatory activity.

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**Figure 1: PHOTOGRAPH OF STEM, LEAVES AND FLOWERS OF *BERBERIS ARISTATA* DC.**

## **MATERIAL AND METHODS**

### **Collection of plant materials:**

The whole part of *Berberis aristata* DC. was collected in December 2020, from Dr. Yashwant Singh Parmar University of Horticulture & Forestry, University in Nauni, Himachal Pradesh, India. Plant was authenticated and identified by Dr. K. C. Bhatt, senior scientist, National Bureau of Plant Genetic Resources, Pusa Campus, New Delhi-110012 and specimen voucher no. (Ref No. NHCP/NBPGR/2021/4 dated 08.02.2021).

### **Preparation of plant extract (*Berberis aristata* DC.):**

The dried stem bark of the plant *Berberis aristata* DC. was procured and 100g bark pieces from the shade-dried were extracted to a coarsely ground powder. Use ethanol and water as solvents, the soxhlet method was used for hydroethanolic extraction. The obtained extract was purified using millipore filtration assembly and rotating vacuum evaporator-based concentration while under vacuum, and the extract then kept in desiccators at 4°C until use. The therapeutic yield of ethanol extract of *Berberis aristata* DC. in terms of percentage

yield on dry weight basis was noted. Then extract was taken for further preliminary phytochemical studies[9].

### **Phytochemical screening**

To identify the different phytochemicals present in ethanolic extract of *Berberis aristata* DC. (stem bark) BAEE, the preliminary phytochemical analysis was performed using accepted techniques [10].

### **Formulation of BAEE ointment**

In order to treat mild to moderate skin diseases, topical therapy is the gold standard. So, Using oleaginous phase and extract consisting of wool fat, hard paraffin, yellow soft paraffin, and cetosteryl alcohol, and an aqueous phase consisting of glycerin and water in accordance with the formula showed in Table 1, herbal ointment containing BAEE, There were prepared at 0.5 and 1.0 percent w/w by taking 400 mg/kg of BAEE and 200 mg/kg, respectively. Paraffin that is firm, cetosteryl alcohol, and wool fat were heated at 70 °C to create oleaginous base. The BAEE extract, mixture of glycerin and water boiled at 70 °C to create the aqueous phase. The aqueous phase was

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gradually added while continuously stirring the oleaginous phase once it reached 70 °C, then allowed to cool [11].

**Table 1 - Formulation of ointment**

Ingredients	Quantity for 0.5% w/w	Quantity for 1.0% w/w
Yellow soft paraffin	27 g	27 g
Hard Paraffin	27 g	27 g
Wool Fat	22 g	22g
Cetosteryl alcohol	11g	11 g
Water	5 ml	5 ml
Glycerin	11 ml	11 ml
Ethanollic extract	0.5 percent	1.0 percent

### Evaluation of ointment

Physical characteristics like the ointment's color, pH, viscosity, spreadability, and washability were assessed according to protocol [12].

### Acute dermal toxicity study

The acute dermal toxicity was assessed in accordance with OECD guidelines (402) for the formulation of the herbal ointment. Swiss albino mice were split into two groups, each of which had six mice. 24 h before the experiment, the hairs was removed from the 10% of dorsal surface of animal's body. On the shaved area, topical application 0.5 and 1 percent (w/w), formulated ointment was made. Both groups' treated animals underwent 14 days observation period to check for redness, erythema, and changes in fur, sleep patterns, behavioral patterns, and mortality [13].

### Experimental Animals

Swiss albino mice, 4 months old weight about 25-30gm (either sex) were used in this investigation, which was previously authorized by the Institutional Animal Ethical Committee (IAEC) with approval number **PROTOCOL NO. IAEC/NIET/2020/01/24**. The animals were obtained from the Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida, Uttar Pradesh, and they were kept under 12 h light and 12 h dark cycles at controlled environmental conditions where the temperature of the room was

maintained at 25 ± 2 °C and the relative humidity at 55-65%. All of the animals had unrestricted access to regular laboratory food and water. All of the tests were carried out in strict accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) ethical principles and guidelines.

### Mouse Tail Model for Anti-Psoriatic Study

Four groups of six animals each were formed. There were six Swiss albino mice in each group weighing 25-30 gm. For induction of psoriasis hairs on the animal's dorsal region (2cmX 2cm) were removed using depilatory cream (Reckitt Benckiser, Inc., UK). Each test animal (n = 6) received 0.1 ml of the prepared complete Freud's adjuvant (CFA) and formaldehyde mixture (1:10 ratio) were applied topically over the shaved area for 7 days. Group II was treated with standard drug clobetasol propionate ointment 0.5mg/g, topically while those animals in group I was served as control which was treated with distilled water 2. Groups III and IV were treated with BAEE 0.5% and 1% w/w ointment, topically. For comparison, mice in group I were treated with distilled water and fed as usual. All groups received treatment over the course of 21 days. Animals that had been given psoriasis were tracked for the presence of psoriatic lesions seven days a week. An objective scoring system was created based on



the clinical severity index and psoriasis area index. On a scale from 0 to 4, redness, erythema, and scales were independently scored: None, slight, moderate, marked, very marked, and four other options. The PSI (psoriasis severity index) was calculated as the sum of the redness, erythema, and scaling scores (scale 0–12). At the conclusion of the study, ketamine over dose was used to anaesthetize the animals. Skin samples were then collected, preserved in glass vials with a 10 percent formalin solution, and subjected to histological analysis. Mice skin samples were cut into longitudinal sections using a microtome, which were then stained with Hematoxylin (H) and Eosin (E) dye [14].

Following psoriasis induction, animals received treatment with the ointment once daily for three weeks. Every week, the antipsoriatic effect of the ointment was assessed based on the severity of psoriatic lesions, which showed a decrease in psoriatic symptoms [15].

#### **Experimental Animals for Anti-Inflammatory Activity**

Healthy Wistar albino rats weighing 210-230 gm (either sex) were used in this investigation, which was authorized by the Institutional Animal Ethical Committee (IAEC) with approval number **PROTOCOL NO. IAEC/NIET/2020/01/24**. The animals were obtained from the Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida, Uttar Pradesh, and they were kept under 12 h light and 12 h dark cycles at controlled environmental conditions where the temperature of the room was maintained at  $25 \pm 2$  °C and the relative humidity at 55-65%. All of the animals had unrestricted access to regular laboratory food and water. All of the tests were carried out in strict accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) ethical principles and guidelines.

#### **Histamine Induced Paw Edema Model**

There were six Wistar rats in each group weighing 210-230 gm. For induction of inflammation 0.1% histamine was given by intraplantar injection to rats of every group. Group II was treated with standard drug chlorpheniramine 2.5mg/kg, i.p. while those in groups I served as a control treated with distilled water. Groups III and IV were treated with test BAEE 200mg/kg and 400mg/kg, i.p. respectively and group V was treated with combination of BAEE 200mg/kg + chlorpheniramine 2.5mg/kg, i.p. For comparison, mice in Group I were, treated with distilled water and were fed and watered as usual. BAEE and chlorpheniramine was administered 30 and 20 minutes before intraplantar administration of histamine respectively.

#### **Induction of Paw Edema**

Each rat was subcutaneously injected with 100 microliter histamine (0.1%) in the ventral surface of the right hind paw with a 29-gauge injection needle and then returned to its cage to induce paw edema [16]. The severity of paw edema was determined by using a fine caliper to measure dorsal-plantar paw thickness 1 hour before and 1, 2, and 3 hours after histamine injection [17]. The increase in paw thickness (mm) after histamine injection compared to the pre-injection value for each animal was used to measure edema [18].

#### **Histopathological Evaluation**

The animals were euthanized by decapitation 3 hours after completing the experiment, and their paw tissues were collected for histopathological examination. The samples were fixed in 10% buffer formal saline and processed for paraffin embedding as usual. To assess acute inflammation, 4-5 m thick sections of each sample were cut and stained with hematoxylin and eosin. Neutrophils were counted in a 0.25 mm<sup>2</sup> microscopic field from 10 different areas of the sections using a special morphometric lens, and mean values were calculated. The total number of neutrophils was



calculated as the average of the counts from six animals in each group [17, 18].

## Result and Discussion

### Therapeutic yield

The yield of the BAEE by using soxhlet extraction was found to be on dry basis 9.2% w/w

### Preliminary Phytochemical Screening

The extract of BAEE was found to be intense presence of alkaloids, coumarins, flavonoids, glycosides, polyphenols, saponins, tanins, and terpenoids, according to the qualitative phytochemical examination

(Table. 2).

Phytochemical test	<i>Berberis aristata</i> DC. test results	Color or precipitate formed
Alkaloids	+++	White precipitate was observed
Coumarins	++	Yellow color was observed
Flavonoids	+	Yellow color present showed presence of flavonoids
Glycoside	+	Reddish-brown color was observed
Polyphenols	+	A blue, green, red or purple color was a positive test for polyphenols
Proteins	-	Absence of violet or pink color
Saponins	+	formation of stable foam was observed
Amino acids	-	Purple color was not observed
Tanins	+	Dark blue or green black color was observed
Fatty Acids	-	filter paper's appearance was not transparent
Terpenoids	+	Reddish brown coloration of the interface indicated terpenoids was present

**Table: 2 Phytochemical test results of *Berberis aristata* DC. (BAEE)**

Keywords: (+) Minute presence, (++) Moderate presence, (+++) Maximum presence, Absence.

### Formulation of Herbal Ointment

According to the chemicals in Table 3, simple ointments comprising 0.5 and 1.0 percent (w/w) ethanol extract of *Berberis aristata* stem bark were formulated.

**Table 3 - Formulation of ointment**

**Table 1 - Formulation of ointment**

Ingredients	Quantity for 0.5% w/w	Quantity for 1.0% w/w
Yellow soft paraffin	27 g	27 g
Hard Paraffin	27 g	27 g
Wool Fat	22 g	22g
Cetosteryl alcohol	11g	11 g



Water	5 ml	5 ml
Glycerin	11 ml	11 ml
Ethanol extract	0.5 percent	1.0 percent

### Analysis of Prepared Herbal Ointments

The physicochemical parameters of the produced ointments comprising of BAEE were assessed. The ointment's pH was within the range that is typical for human skin (6.8–1). After being administered to the animal skin for a week, the produced ointments did not caused any skin irritation, including erythema and

edema. The produced ointments' spread-ability was determined and found to be in the range of 6.5 to 6.6, indicating that they were simple to apply to the skin and that the active component would be released for a localized impact. In general, all ointment formulations satisfied the requirements for application-acceptable consistency showed in Table 4.

**Table: 4 Physical Analysis of the Finished Ointment**

Physico-Chemical Parameters	Observation (0.5% w/w)	Observation (0.1% w/w)
Color	Yellow	Brown
Odour	Characteristic	Characteristic
pH	6.5	6.6
Consistency	Smooth	Smooth
Spreadability	6.7	6.8
Washability	Good	Good
Non irritancy	Non irritant	Non irritant

### Evaluation of Antipsoriatic Activity

Silvery scales, erythema, and redness were noticed on the exposed area on the seventh day after induction, and the severity gradually worsened. The cumulative PSI score was considerably higher on day 7 of psoriatic induction (\*P<0.05). (Table 51). When compared to normal animal skin, the mouse skin with psoriasis that was induced by the topical application of CFA and formaldehyde

displayed a number of pro-inflammatory symptoms, including redness, erythema, scales, elongation of rete ridges, the presence of Munro's micro abscess, dilation of the capillary loop, increased epidermal thickness, keratinocyte proliferation, and absence of the granular. All of these mouse phenotypic and histological traits mimic psoriatic lesions in human plaque psoriasis.

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**Table: 5 Examination of redness, erythema and scales in complete Freud's adjuvant and formaldehyde treated mice**

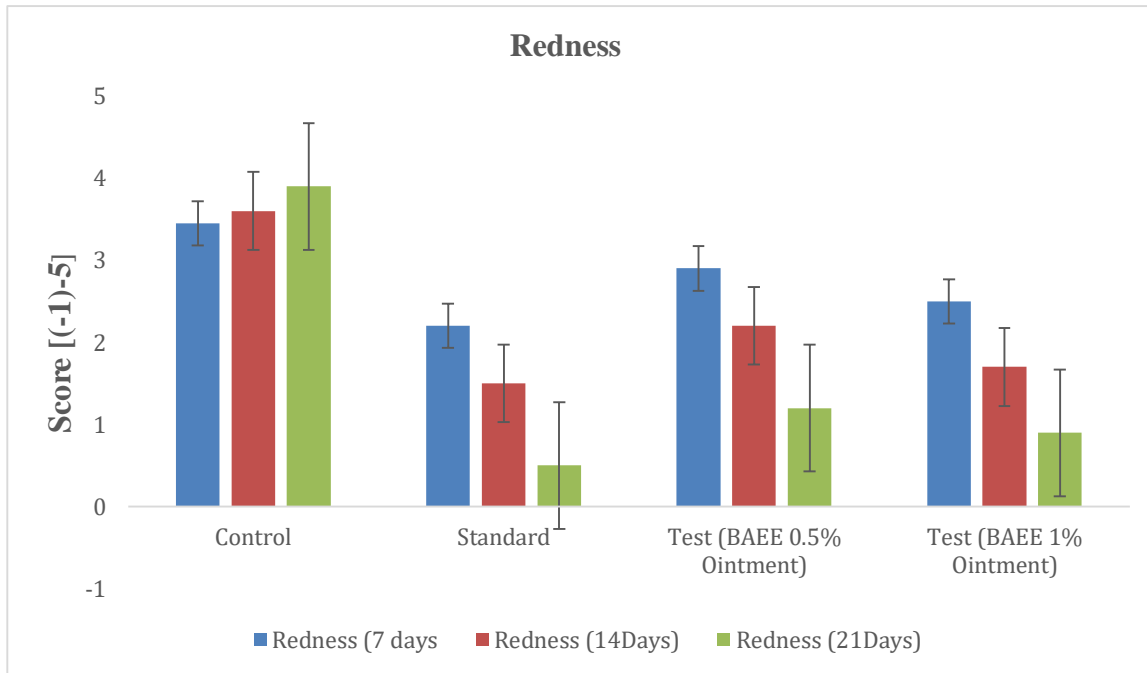
Day	Redness	Erythema	Scales	Cumulative score (PSI)
1	1.04±0.05	-	-	1.04±0.05
2	1.45±0.08**	0.44±0.08	-	1.89±0.16*
3	1.75±0.08**	1.02±0.10	-	2.77±0.18*
4	2.04±0.08	1.65±0.06	0.85±0.08	4.54±0.22
5	2.49±0.05	2.24±0.07	1.78±0.09	6.51±0.21
6	2.86±0.05	2.54±0.04*	2.44±0.12	7.84±0.21
7	3.45±0.06	3.31±0.05	2.65±0.08**	9.41±0.19*



**Effect of test formulations on completely freund's adjuvant- and formaldehyde-induced psoriasis in mouse skin through histopathological examination**

The severity of the psoriatic lesions was determined by visual and histological tests after ointments containing 0.5 and 1.0 percent (w/w) BAEE were applied once daily for three weeks to animals with psoriasis. The severity of the psoriatic lesions was steadily increased in the control animal group (Group I) during the

course of the trial, and the cumulative PSI score was significantly higher on day 21 compared to the other groups. The therapeutic effect of a standard clobetasol propionate ointment 0.5mg/g was confirmed in the standard group of animals (Group II) by the topical application of the standard medicine, which decreased the severity of psoriatic lesions and cumulative score progressively (\*\*P<0.01) from day 7 to day 21.



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**Figure: 2 Effect of herbal ointment containing ethanol extract of *Berberis aristata* DC. (BAEE) on the Redness**



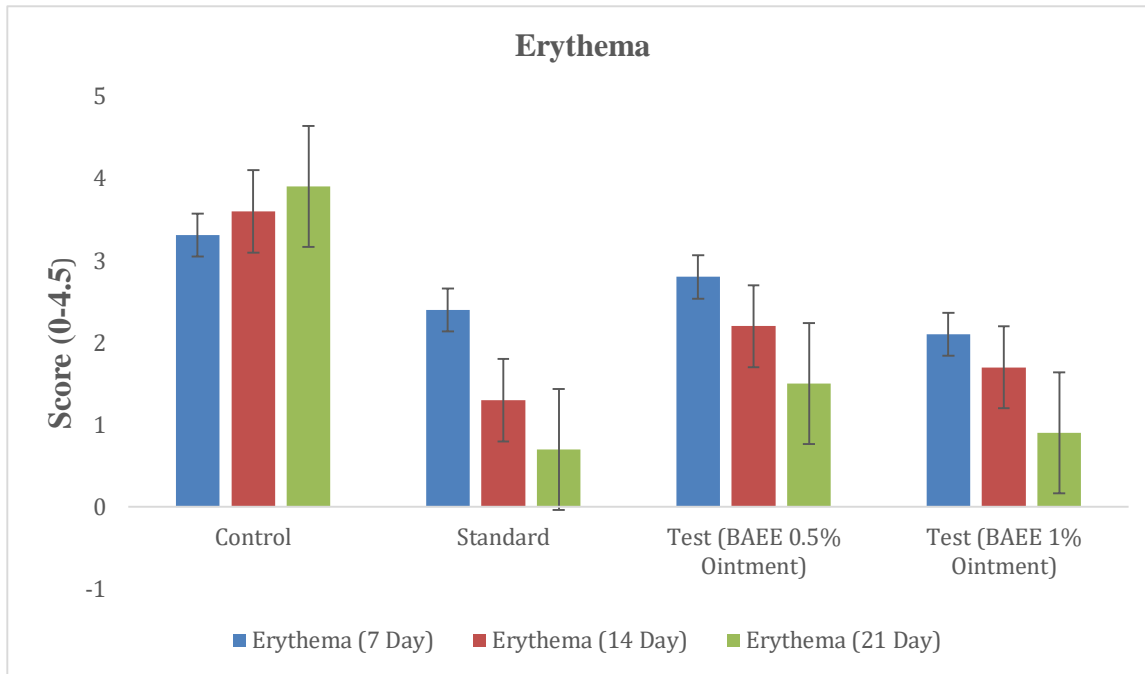


Figure: 3 Effect of herbal ointment containing ethanol extract of *Berberis aristata* DC. (BAEE) on the Erythema

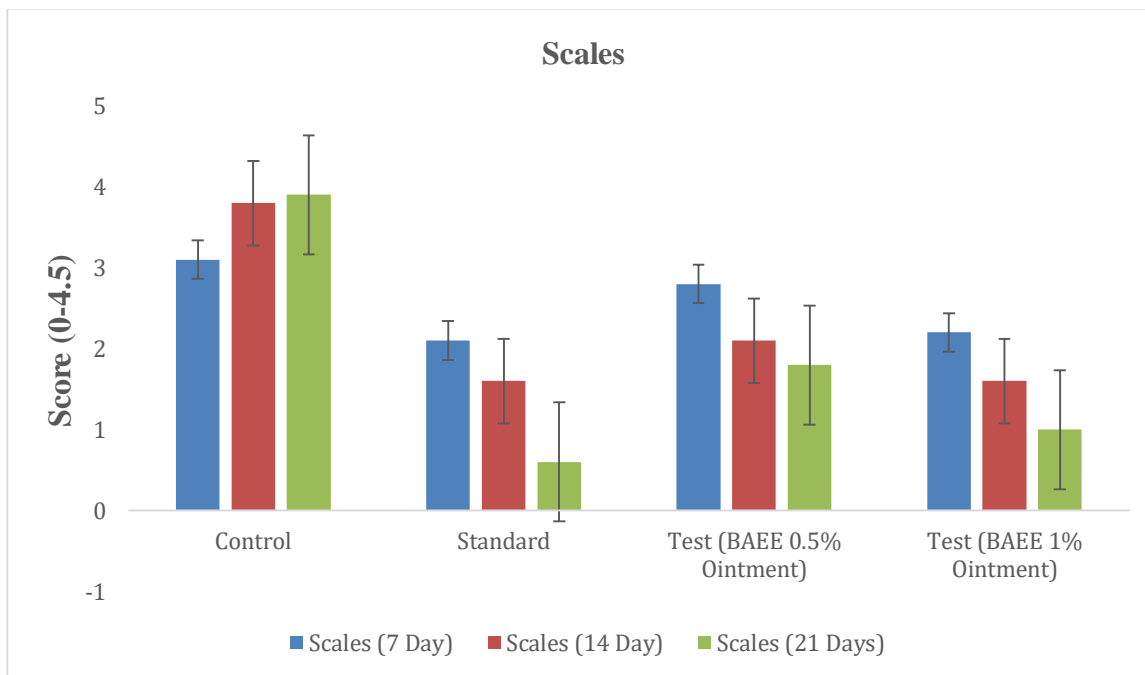
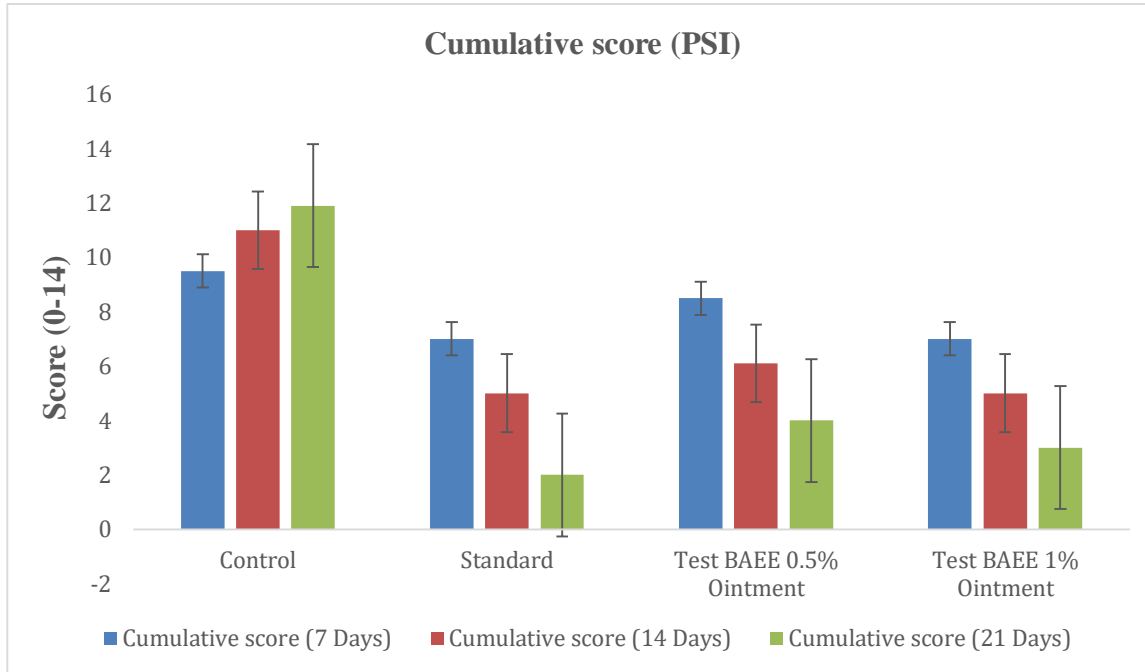


Figure: 4 Effect of herbal ointment containing ethanol extract of *Berberis aristata* DC. (BAEE) on the Scales



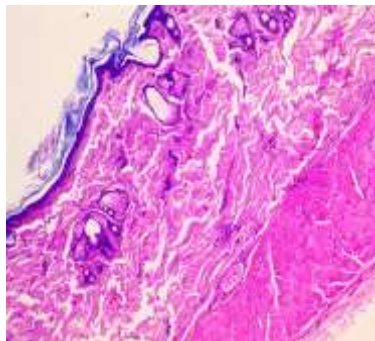


**Figure: 5 Effect of herbal ointment containing ethanol extract of *Berberis aristata* DC. (BAEE) on the Cumulative score (PSI)**

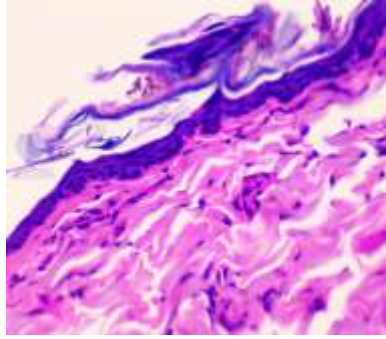
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The values are represented by the mean and standard error of six measurements taken simultaneously. One-way ANOVA and the Tukey Kramer multiple comparison test were used to analyze the data. When compared to the control, the values are \* $P < 0.05$  and \*\* $P < 0.01$ .

#### 5.4.1 Histopathology of Mice Tail

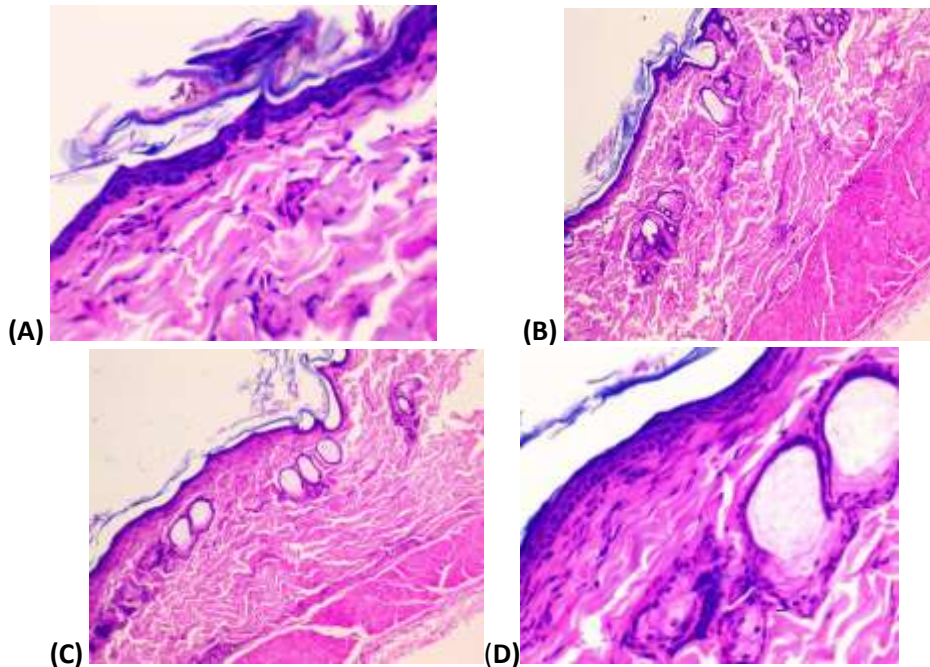


**Figure: 6 (a) Normal mice skin**



**Figure: 6 (b) CFA and formaldehyde induced in mice skin**

**Figure: 6 (a)** Section of normal mice skin. Normal epidermal thickness, absence of granulocytes infiltration, hyper proliferation of keratinocytes cells, the absence of Munro's micro abscess with no capillary loop dilatation, granular cell layer (para keratosis) were observed through histological examination. **Figure: 6 (b)** Section of CFA and formaldehyde induced psoriasis mice skin. epidermal thickness increased, hyper proliferation of keratinocytes with granulocyte infiltration, Munro micro abscess, capillary loop dilatation, elongation of rete ridges are present, and absence of the granular cell layer (para keratosis) were observed through histological examination in CFA- and formaldehyde-treated mice skin are present.



**Figure: 7 Histological screening of mice skin of each group (A) Control mice skin, (B) Psoriasis induced treated with Clobetasol propionate. (C) Psoriasis induced treated with BAEE 0.5%w/w ointment, (D) Psoriasis induced treated with BAEE 1%w/w ointment.**

### Histological studies

After histological examination the observed epidermal thickness of mice skin was found to be increased (figure.7). Granulocyte infiltration, hyperproliferation of keratinocyte cell and collection of neutrophils presence was indicate

the high induction of psoriasis in group I animal (figure 7A) in comparison to group II (figure 7B), group III (figure 7C) and group IV (figure 7D) animals. Table 3 depicted the reports of all Groups histological examination findings.

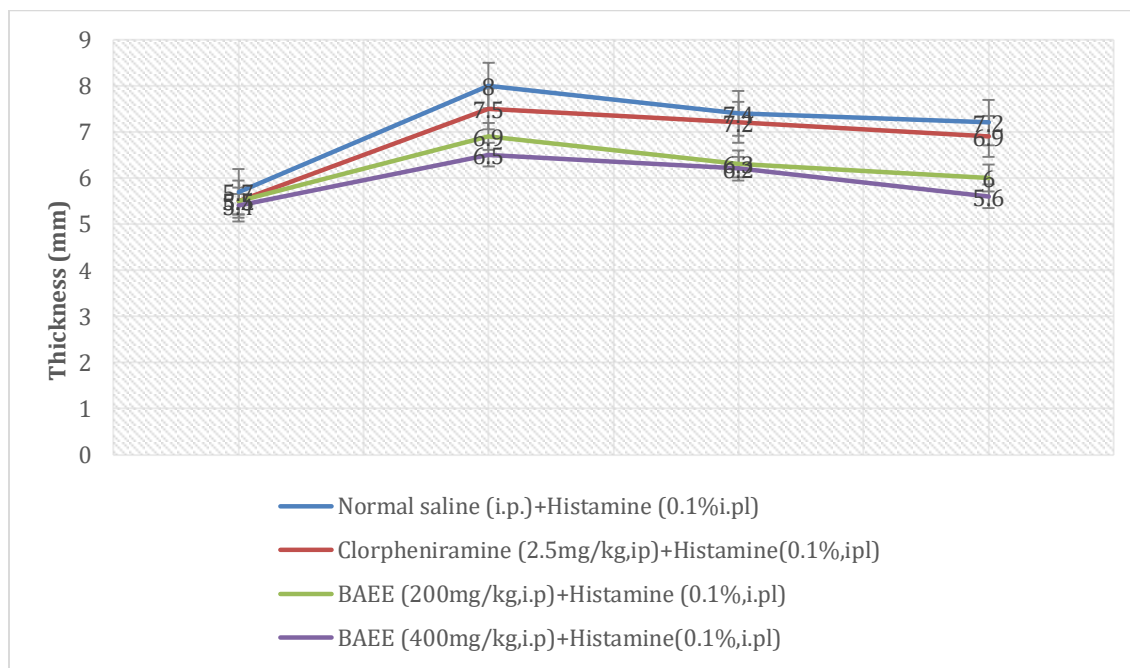
**Table: 6 Histological examination report**

Group	Group details	Hematoxylin and Eosin (H&E) dye-stained skin sample report
1	Normal mice treated with water	Dermis layer was normal in skin.
2	Psoriasis induced mice treated with Clobetasol propionate ointment 0.5mg/g, topically	Epidermal thickness was decreased in comparison to group I and group III and reduction in all features (epidermal thickness and proliferation of keratinocytes cell) in skin
3	Psoriasis induced mice treated with BAEE 0.5% w/w Ointment, topically	Epidermal thickness was decreased, reduction in granulocytes infiltration and hyper proliferation of keratinocytes cell was observed.
4	Psoriasis induced mice treated with w/w 0.5% Ointment, topically	Epidermal thickness decreased, reduction in granulocytes infiltration and hyper proliferation of keratinocytes cell, reduction in all feature in skin was found.

**Evaluation of Anti-inflammatory Activity:**

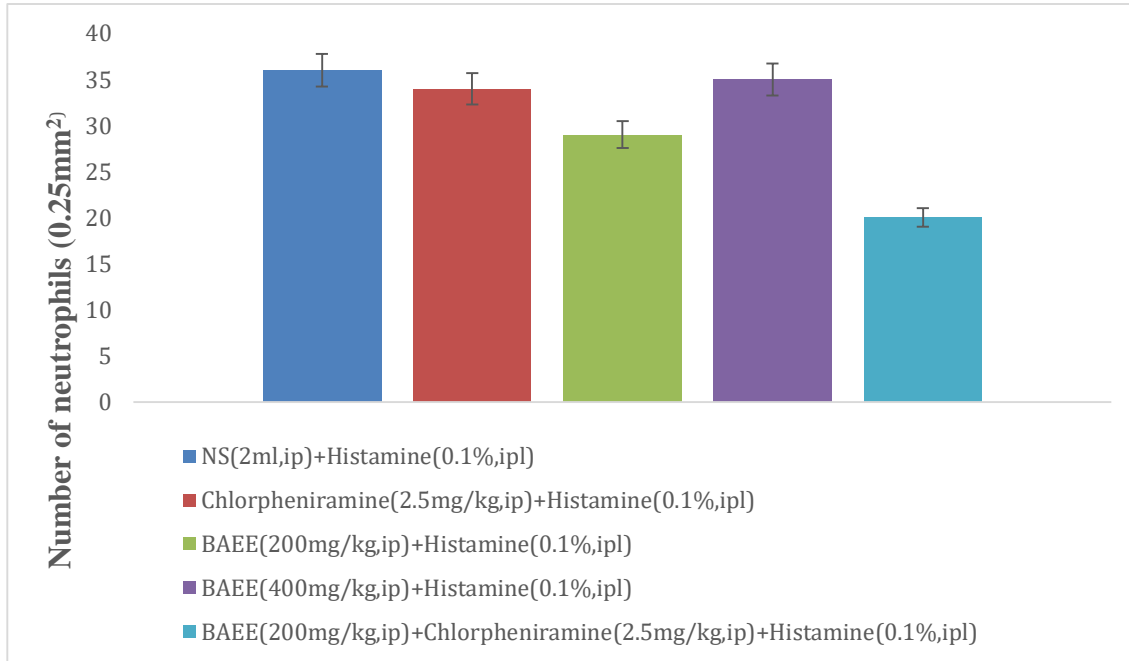
Histamine administered intra-plantarily induced a local edema, the rate of which peaked 1 h after injection and then gradually decreased until the experiment's end. BAEE injections intra-peritoneally at doses of 200 and 400 mg/kg, significantly reduced histamine-induced paw thickness at 1, 2, and 3 hours. (3, 80) = 23.636,  $p < 0.05$ ).

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**Figure: 8 Effect of BAEE on the thickness of the rats' paws after intraplantar histamine injection. The mean and SEM of all values are used (n = 6). Factorial ANOVA and Duncan's tests were used to compare statistics between the groups. \* $p < 0.05$  versus 1 h prior to histamine injection; \* $p < 0.05$  versus normal saline + histamine group. ip: intraperitoneal, ipl: intraplantar.**

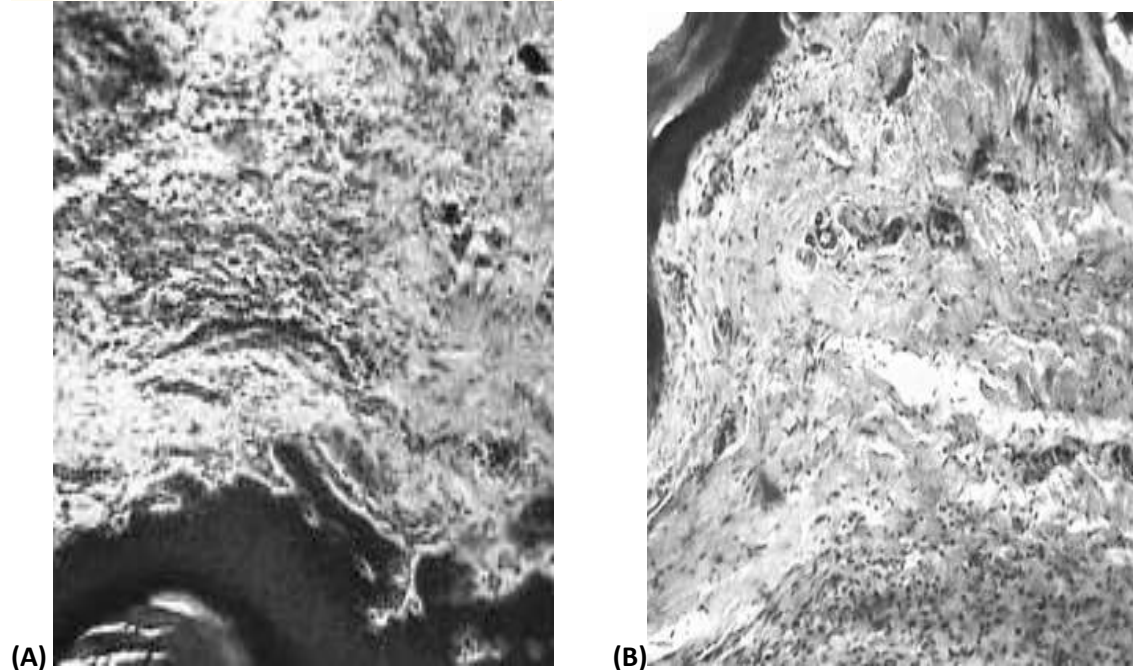


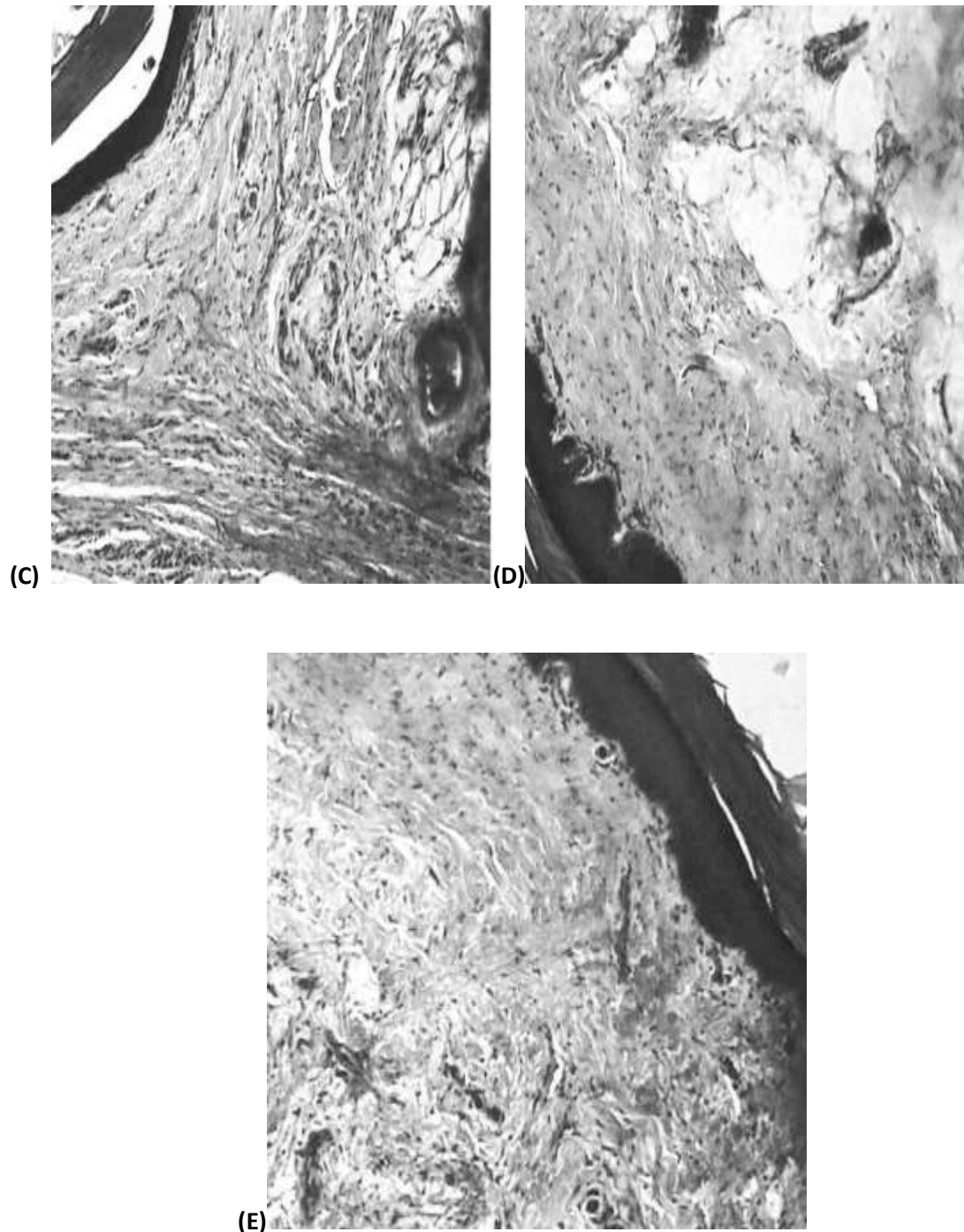


**Figure: 9** Effects of individual and combined BAEE and chlorpheniramine treatments on the quantity of neutrophils in rat paw tissues. The data are all mean SEM (n=6). One-way ANOVA and Duncan's tests were used to compare the statistical differences between the groups. \*p<0.05 versus normal saline + histamine group, +p<0.05 versus chlorpheniramine (2.5 mg/kg) + histamine group, and \*p<0.05 versus BAEE (200 mg/kg) + histamine group. NS: Normal saline, ip: intraperitoneal, ipl: intraplantar.

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**Histopathology of histamine induced rat paw**





**Figure: 10** Effect of separate and combined treatments with BAEE and chlorpheniramine on neutrophil infiltration induced by Histamine in rat paw tissues. Animals were treated with (A) Normal saline + Histamine, (B) Chlorpheniramine (2.5mg/kg) + Histamine, (C) BAEE (200mg/kg) + Histamine, (D) BAEE (400mg/kg) + Histamine, (E) BAEE (100mg/kg) + Chlorpheniramine (2.5mg/kg) + Histamine. Extensive neutrophils are seen in A, B AND C. Moderate neutrophils infiltration was seen in D and E

**Conclusion:** The ethanol extract of *Berberis aristata* DC. stem bark (BAEE) was evaluated for anti-psoriatic and anti-inflammatory activity. The present study was concluded that both of the BAEE test formulations (0.5% and 1% ointments, topically) reduced mean PSI as well as the signs of psoriasis in mice and in anti-inflammatory activity local paw edema caused by histamine was prevented by BAEE (200mg/kg and 400mg/kg, intraperitoneally). So it might be concluded that the BAEE is mainly acting via suppressing the acute inflammatory mediators and inflammation which also plays an important role in the progression of psoriasis.

The histopathological findings also supported the CFA induced mouse tail model for anti-psoriatic activity by epidermal thickness decreased reduction in granulocytes infiltration and hyper proliferation of keratinocytes cells. Hence, the present research work concluded that the plant *Berberis aristata* DC. stem bark possesses strong anti-psoriatic and anti-inflammatory activity which is in agreement with its traditional use.

### Acknowledgement

### Conflict of interest

No conflict of interest

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