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EVALUATION OF METHANOLIC EXTRACT OF *PHYLLANTHUS EMBLICA* FRUIT GEL AGAINST PHTHALIC ANHYDRIDE INDUCED CONTACT DERMATITIS MODEL ON *Balb/c* MICE

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ABSTRACT

Objective: The current study aims to investigate the anti-inflammatory and antioxidant effects of the methanolic fruit extract gel of Phyllanthus emblica on Phthalic anhydride-induced contact dermatitis in Balb/c mice. **Methods:** The experimental protocol involved dividing Balb/c mice into six groups: a control group, a contact dermatitis model group, a 0.02% clobetasol propionate group, and groups treated with low-dose and high-dose methanolic fruit extract of Phyllanthus emblica. Contact dermatitis was induced by applying 5% Phthalic anhydride to the mice. Various parameters were assessed to evaluate the efficacy of the treatments, including body weight, feed and water consumption, scratching frequency, histopathological examination, and immunohistochemical staining. **Results and Conclusion:** The results indicated that the methanolic extract of Phyllanthus emblica (at 2.5% w/v and 5% w/v) showed a decrease in inflammation and redness compared to the contact dermatitis model group. Histopathological analysis and immunohistochemical staining confirmed reduced inflammation and the presence of antioxidant activity in the treated groups. The study concludes that the methanolic fruit extract of Phyllanthus emblica has anti-inflammatory and antioxidant activities, making it a promising therapeutic strategy for the treatment of contact dermatitis. Further investigation and development of this Phyllanthus fruit extract gel are warranted.

KEYWORDS: Contact dermatitis, Phthalic Anhydride, Phyllanthus emblica, Clobestaol Propionate.

INTRODUCTION

The skin serves as the primary barrier between the body and the external environment, playing a crucial role in host defense mechanisms. As the largest and most exposed organ, the skin is constantly facing a myriad of environmental challenges, ranging from physical, chemical, and biological insults. Maintaining the delicate balance of skin defense systems is of utmost importance, as any imbalance or inappropriate immune responses can lead to the development of severe skin inflammatory conditions, such as atopic dermatitis and contact dermatitis.[1]

According to the European Society of Contact Dermatitis, contact dermatitis is defined as an eczematous, localized inflammatory reaction of the skin. This condition is typically caused by direct and repeated exposure to harmful substances or irritants in the environment. The manifestation of contact dermatitis can occur anywhere on the body, depending on the site of contact with the offending agent. Contact dermatitis is further classified into two distinct subtypes: irritant contact dermatitis and allergic contact dermatitis.[2]

Irritant contact dermatitis is a non-immunologic form of the condition, wherein the skin is damaged directly by the offending agent without any prior sensitization of the immune system. In contrast, allergic contact dermatitis is characterized as a type IV delayed hypersensitivity reaction, which requires previous sensitization of the individual to the specific allergen. This means that the person must have been exposed to the allergen before experiencing the characteristic inflammatory response upon subsequent encounters.[3]

Phyllanthus emblica, commonly known as Amla, Indian gooseberry, or Emblica myrobalans, is a medium-sized deciduous tree belonging to the family Euphorbiaceae. This plant has been extensively used in traditional and folk medicine systems in India for centuries.[4] 86 In the Ayurvedic tradition, Phyllanthus emblica is revered as a potent rejuvenator and immunomodulator, capable of stalling degenerative processes, promoting longevity, and

enhancing various physiological functions. It is believed to be effective in improving digestion, treating constipation, reducing fever and cough, alleviating asthma, strengthening the cardiovascular system, benefiting eye health, stimulating hair growth, invigorating the body, and even enhancing intellectual capacities.[5]

The current study aims to investigate the anti-inflammatory and antioxidant effects of the methanolic fruit extract of Phyllanthus emblica on phthalic anhydride-induced contact dermatitis in BALB/c mice. This research endeavor seeks to elucidate the potential therapeutic applications of this traditional medicinal plant in the management of skin inflammatory disorders, particularly contact dermatitis.

MATERIALS AND METHODS

EXTRACTION OF MEPE

The fruits of *Phyllanthus emblica* were collected from the local market of Vadapalani, Chennai, Tamil Nadu. The fruit was identified and authenticated by SIDDHA CENTRAL RESEARCH INSTITUTE Anna Govt. Hospital Campus, Arumbakkam, Chennai – 600106. Reference no: **686.18122309.** The collected *Phyllanthus emblica* fruit were dried, powdered, weighed and extracted with methanol: water(90:10) in soxhlet's apparatus. 300g powder of *Phyllanthus emblica* extracted with 1000ml of methanolic solvent using a Soxhlet apparatus at 50°C for 72h. The extract is filtered and Vacuum – dried. The dried residue of the extract was cooled in a desiccator for 30 min and then accurately weighed for analysis.[6]

PERCENTAGE YIELD

$$\text{Percentage yield (\%W/W)} = \frac{\text{Weight of extract after extraction (gm)}}{\text{Weight of dry powder before extraction (gm)}}$$

PRELIMINARY PHYTOCHEMICAL ANALYSIS[7]

The methanolic extract of Phyllanthus emblica fruit was subjected in a different test tube to preliminary phytochemical screening for the presence or absence of phytoconstituents.

PREPARATION OF *Phyllanthus emblica* FRUIT EXTRACT GEL:

Making a gel base

The base is made by dispersing Hydroxy propyl methyl cellulose with 60 ml of distilled water, pouring the distilled water gradually and increasing the volume with the remaining 60 ml of distilled water the homogenized.

Gel Making

Phyllanthus emblica fruit extract gel with a concentration of 2.5% and 5% is made by dispersing HPMC (Hydroxy Propyl Methyl Cellulose) with 60 ml of distilled water, which has been added with sodium benzoate, stirring until homogeneous, adding the remaining 650 ml distilled water.

EVALUATION OF GEL

The prepared gel is evaluated for stability, consistency, color, form, PH and Spredability.

EXPERIMENTAL ANIMALS

The *Balb/c* mice, aged 2 months weighing 25-30 g were used in this study. The inbreed animals were procured from the animal house of C.L. Baid Metha College of Pharmacy, Chennai-97. They were housed five per cage under standard laboratory conditions at room temperature at 22+2°C with a 12-hour light / dark cycle. The animals were acclimated to laboratory conditions for one week and provided with standard pellet chow and water ad libitum. Ethics committee clearance was obtained from IAEC (Institutional Animal Ethics Committee) of CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals).

IAEC APPROVAL NO: 08/321/PO/Re/S/01/CPCSEA/dated 24/11/23 valip upto 25/11/24.

ACUTE TOXICITY STUDY

Acute dermal toxicity studies will be conducted as per OECD guidelines 402. Three females Balb/c mice is taken and kept in their cages for atleast 5 days prior to dosing to allow for acclimization to the laboratory conditions. The test drug should be applied as uniformly as possible over the exposed area of dorsal skin (atleast 10% of the total body surface area). Test drug should be held in contact with the skin with a porous gauze dressing and non irritating tape throughout a 24-hour exposure period. The test site should be further covered in a suitable manner to retain the gauze dressing and test chemical and ensure that the animals cannot ingest the test chemical. During the 24-hour exposure period, animals may be caged individually in order to avoid oral ingestion of the test drug by other animals in the cage. At the end of the exposure period, residual test drug should be removed. Animals are observed immediately after dosing at least once during the first 30 minutes, periodically during the first 24 hours, with special attention given during the first 2 to 6 hours after the beginning of the exposure period, and daily thereafter, for a total of 14 days.

EXPERIMENTAL PROCEDURE

Balb/c mice were divided into five groups of six animals.

GROUPING

Group I – Control treated with Normal saline.
Group II - Contact dermatitis is induced by 5% Phthalic anhydride 3 times a week for 28 days.
Group III – Contact dermatitis was induced with 5% w/w Phthalic anhydride at the dorsal surface 3 times a week for 28 days. Followed by Clobetasol Propionate cream 0.05% w/w (Positive Standard) topically for 28 days at the dorsal surface,
Group IV – Contact Dermatitis was induced with 5% w/w Phthalic anhydride at the dorsal surface 3 times a week for 28 days. Followed by Methanolic extract of

Phyllanthus emblica fruit extract 2.5% (low dose of test drug) was applied topically at the dorsal surface.

Group V – *Contact Dermatitis was induced with 5% w/w Phthalic anhydride at the dorsal surface 3 times a week for 28 days. Followed by a methanolic extract of* Phyllanthus emblica *fruit extract 5% (high dose of test drug) was applied topically at the dorsal surface.*

PARAMETERS ASSESSED

BODY WEIGHT MEASUREMENT

The body weight of each animal in each group was determined at Day 0, 7,14,21 and 28th day.[8]

FEED AND WATER CONSUMPTION

Animals will be provided with sterilized, standard laboratory chow. They will have free access to clean drinking water and laboratory feed. From day 0, pre-weighed feed and pre-measured water was made available daily. Every next day, the remaining feed and water were measured and the volumes consumed on the previous day will be calculated. Regularly water feeding bottles were washed to maintain hygiene and prevent contamination.[8]

EVALUATION OF CLINICAL SKIN SEVERITY SCORES

The five signs of skin lesions were

1. Pruritus/ Itching
2. Erythema/ Hemorrhage
3. Edema
4. Excoriation/ Erosion
5. Scaling/Dryness.

The above-mentioned symptoms were graded as follows: 0 (no symptoms), 1 (mild), 2 (moderate), and 3 (severe).[9]

SCRATCH SCORE

Itching was evaluated by measuring the cumulative rubbing/scratching botus time during a 2-min observation period. Scratch score will be recorded weekly after every 30 min of drug administration.[9]

EXVIVO STUDY

I. SPLEEN TO BODY WEIGHT INDEX

The spleens are carefully removed after the sacrifice of the animal. Apart from visual examination, spleens were collected, and cleaned each spleen weight will be recorded in grams using a digital balance & weighed. The spleen weights were normalized with body weight to obtain organ index (spleen weight/bodyweight) and results were expressed in g/g. The measurements are expressed as mean.[8]

$$\textbf{Spleen To Body Weight Index} = \frac{\text{WEIGHT OF SPLEEN [g]}}{\text{WEIGHT OF ANIMAL (MICE)[g]}}$$

II. HISTOPATHOLOGICAL ANALYSIS

After the 28th day; Groups I, II, III, IV, and V were anesthetized and sacrificed. Dorsal skin regions from Groups I, II, III, IV, and V were collected and preserved in glass containers containing 10% formalin solution. Longitudinal sections of specimens (about 5 mm thickness) are prepared by Microtome and stained with Haematoxylin-eosin dye for Histopathological examination. The thickness of the cellular part of the epidermis will be determined using a calibrated ocular micrometer and all measurements will be adjusted for magnification optics.[10]

III. IMMUNOHISTOCHEMICAL STAINING

The skin tissue was fixed with Neutral Buffered Formalin (NBF) and washed with flowing water for O/N. Dehydration was carried out using ethanol, the cleaning response was studied using xylene, and the tissue was embedded in paraffin wax. Tissue blocks were sectioned into 5µm thickness. The sectioned tissues were stained with haematoxylin and eosin (H&E) to measure the degree of eosinophil tissue infiltration. To observe the infiltration of mast cells, the tissue was stained with toluidine blue. The tissues were washed twice with TBS and blocked with 10% normal serum in TBS for 30 min. The tissues were then incubated with $CD4^+$ antibodies at 4°c for 24h. the colour reaction of $CD4^+$ T cells was examined using a Polink 2 plus AP rabbit kit according to the manufacturer's instructions. The background was stained with haematoxylin. Stained tissue was observed by a light microscope at ×400 magnification.[11]

IV. ESTIMATION OF SUPEROXIDE DISMUTASE

The SOD levels from the ear tissue homogenate were estimated. The assay procedure is defined in brief, the reaction mixture contains 0.4ml of ear tissue homogenate, diethylenetriamine Penta acetic acid (1mM), 0.5ml of pyrogallol (0.2mM) in 50mM Tris buffer (pH 8.5). the reaction mixture incubated at room temperature (RT) for 1.5h. Finally, the absorbance will be taken at 420 nm.[12]

STATISTICAL ANALYSIS

Data were analyzed using One-way ANOVA (Dunnett's comparison test) expressed as Mean ± Standard Error of Mean (SEM). Statistical analyses were performed using Graph Pad Prism version 9.5.1, for Windows.

Comparison

Group Ⅰ vs Group Ⅱ, Group Ⅲ, Group Ⅳ and Group Ⅴ [considered as a]

Group Ⅱ vs Group Ⅲ, Group Ⅳ and Group Ⅴ [considered as b]

Group III vs Group IV and Group V [considered as c]

Differences between mean values of different groups were considered statistically significant at ($P<0.0001$) ****, ($P<0.001$) ***, ($P<0.01$) **, ($P<0.05$) *, ns- non-significant.

RESULTS

EXTRACTION YIELD

The percentage yield of Phyllanthus emblica extract gel was found to be 38.76%.

EVALUATION OF GEL

The gel was thick dark brown in colour in the form of hydrogel. The PH of hydrogel was found to be 6.5. The Spredability of hydrogel was found to be 7.

PHYTOCHEMICAL SCREENING

The result of preliminary phytochemical screening showed the presence of Tannins, Flavonoids, carbohydrates, Glycosides, Alkaloids, and Phenols.

ACUTE DERMAL TOXICITY STUDY

The acute dermal toxicity is performed according to 402 OECD guidelines. A repeated topical administration of a Phthalic anhydride was administered to 3 female mice and a observed for 14 days. There was no considerable change before and after the experiment and no signs of toxicity were observed.

Comparison

Group Ⅰ vs Group Ⅱ, Group Ⅲ, Group Ⅵ and Group Ⅴ [considered as a]

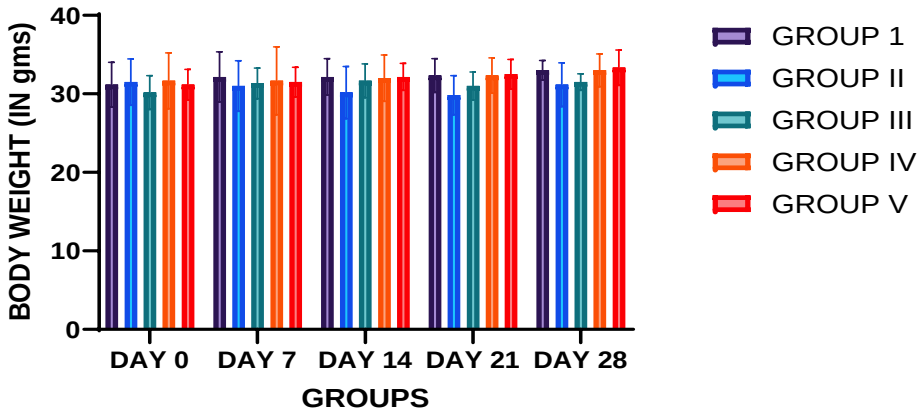
Group Ⅱ vs Group Ⅲ, Group Ⅵ and Group Ⅴ [considered as b]

Group III vs Group IV and Group V [considered as c]

Statistical significance test for comparison was done by one way ANOVA followed by Dunnet's 't' test, ns – non-significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

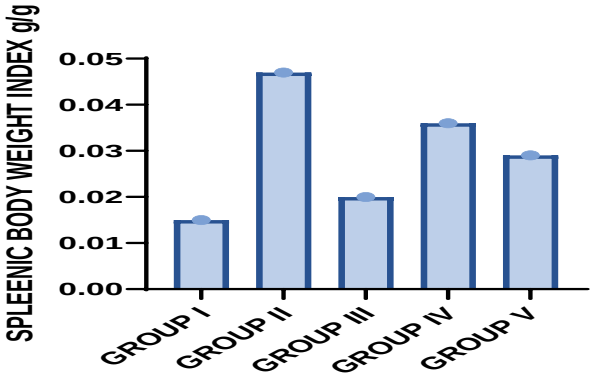
EFFECT OF MEPE GEL ON BODY WEIGHT ON PHTHALIC ANHYDRIDE 5% INDUCED CONTACT DERMATITIS IN Balb/c MICE ON DORSAL SURFACE

GROUPS TREATED	BODY WEIGHT				
	Day 0	Day 7	Day 14	Day 21	Day 28
Group Ⅰ	31±1.63	32.04±1.67	31.0±0.83	32.54±0.58	33.20±0.91
Group Ⅱ	31±1.80 a^{****}	31.0±1.44 a^{ns}	30.80±0.37 a^{****}	29.09±0.56 a^{****}	31.45±1.13 a^{****}
Group Ⅲ	30.20±0.96 a^{ns} b^{**}	31.80±0.58 a^{ns} b^{ns}	31.80±0.48 a^{ns} b^{ns}	31.58±0.56 a^{ns} b^{ns}	31.00±0.31 a^{ns} b^{****}
Group Ⅵ	31.0±1.94 a^{*} b^{ns} c^{ns}	31.40±1.67 a^{**} b^{*} c^{ns}	32.60±0.50 a^{*} b^{*} c^{*}	32.95±0.63 a^{*} b^{*} c^{*}	33.60±0.84 a^{**} b^{****} c^{*}
Group Ⅴ	31.80±0.48 a^{*} b^{ns} c^{ns}	31.40±1.81 a^{****} b^{****} c^{**}	32.0±0.63 a^{***} b^{****} c^{***}	32.45±0.85 a^{***} b^{****} c^{***}	38.00±0.54 a^{****} b^{****} c^{****}



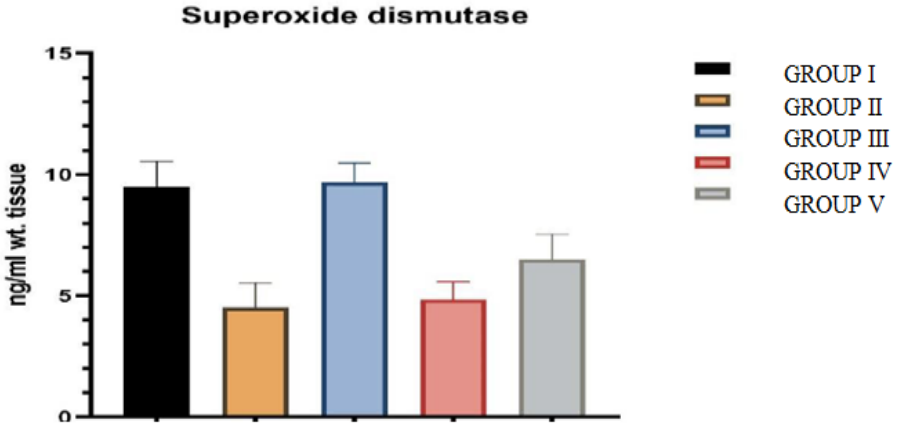
EFFECT OF MEPE GEL ON SPLEEN TO BODY WEIGHT INDEX ON PHTHALIC ANHYDRIDE 5% INDUCED CONTACT DERMATITIS IN Balb/c MICE ON DORSAL SURFACE

SNO	GROUPS	SPLEENIC WEIGHT INDEX g/g
1	GROUP I	0.015
2	GROUP II	0.047
3	GROUP III	0.020
4	GROUP IV	0.036
5	GROUP V	0.029

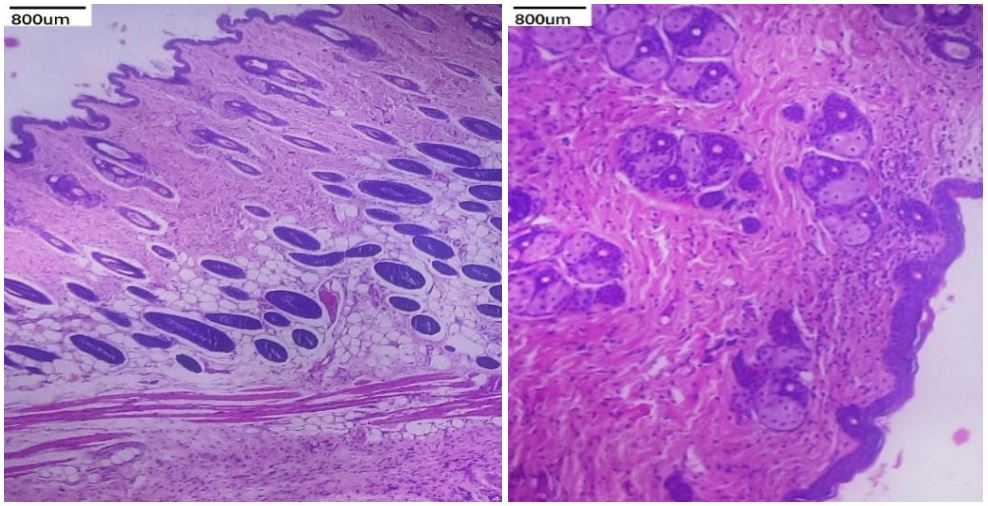


EFFECT OF MEPE GEL ON SUPEROXIDE DISMUTASE ON PHTHALIC ANHYDRIDE 5% INDUCED CONTACT DERMATITIS IN Balb/c MICE ON DORSAL SURFACE

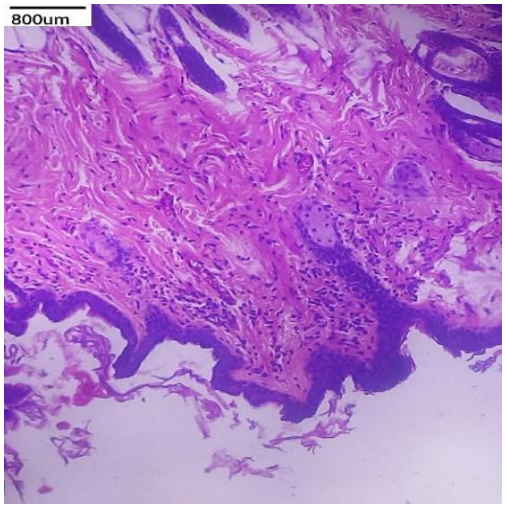
SNO	TREATMENT GROUPS	ng/mg protein
1	Group I	9 ±0.845ns
2	Group II	4.27±1.35ns
3	Group III	8.11±1.6ns
4	Group IV	7.5±1.15ns
5	Group V	9.99±1.85ns



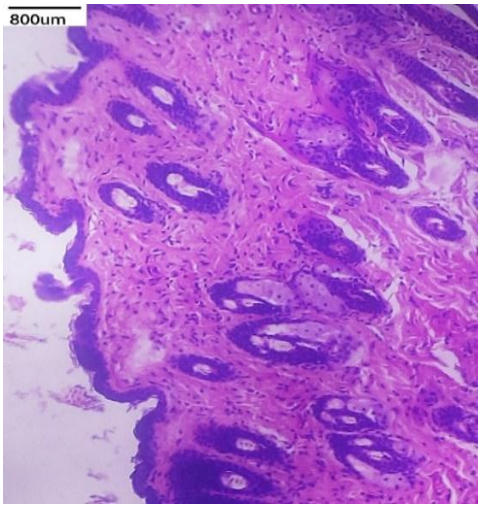
HISTOPATHOLOGICAL EXAMINATION OF PHTHALIC ANHYDRIDE 5% INDUCED CONTACT DERMATITIS IN Balb/c MICE



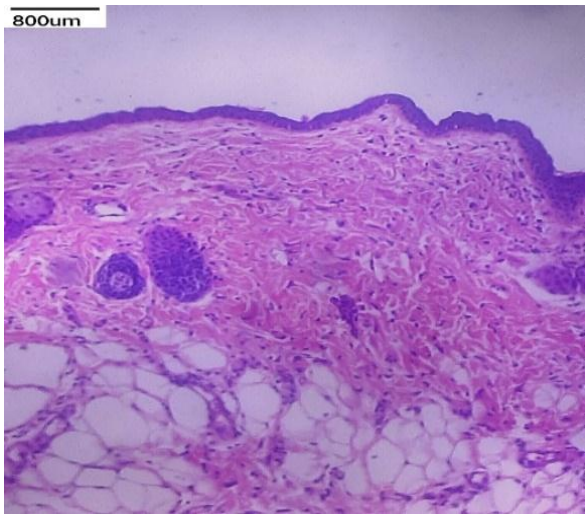
GROUP I **GROUP II**



GROUP III

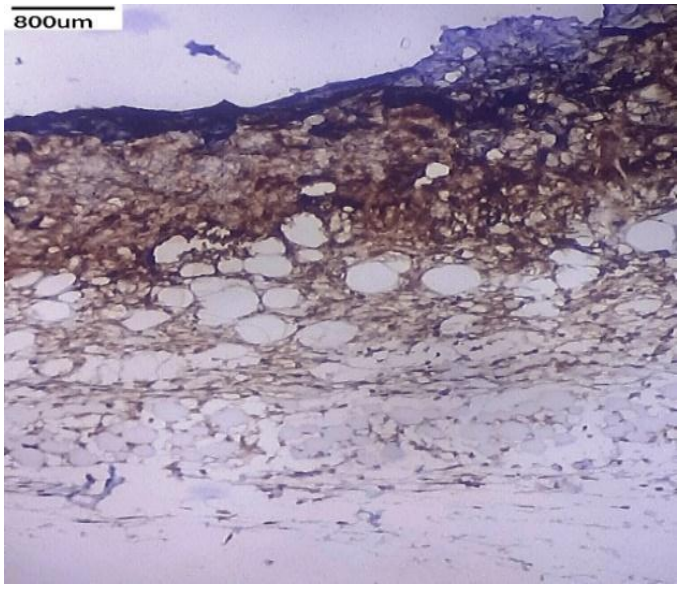


GROUP IV

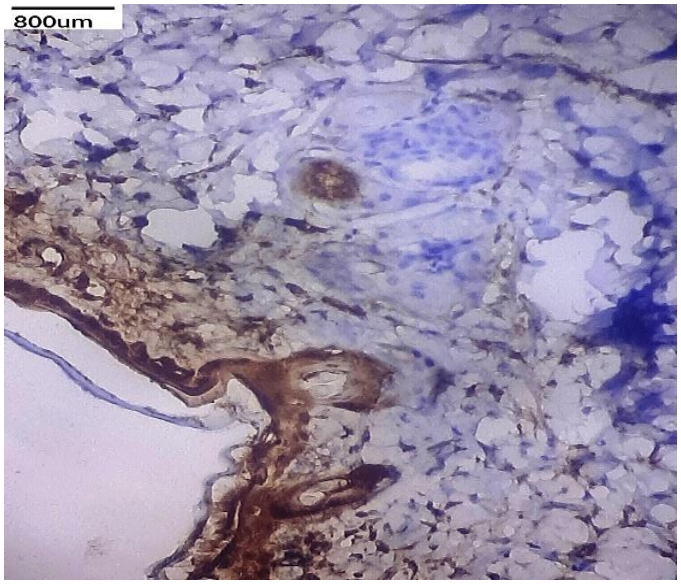


GROUP V

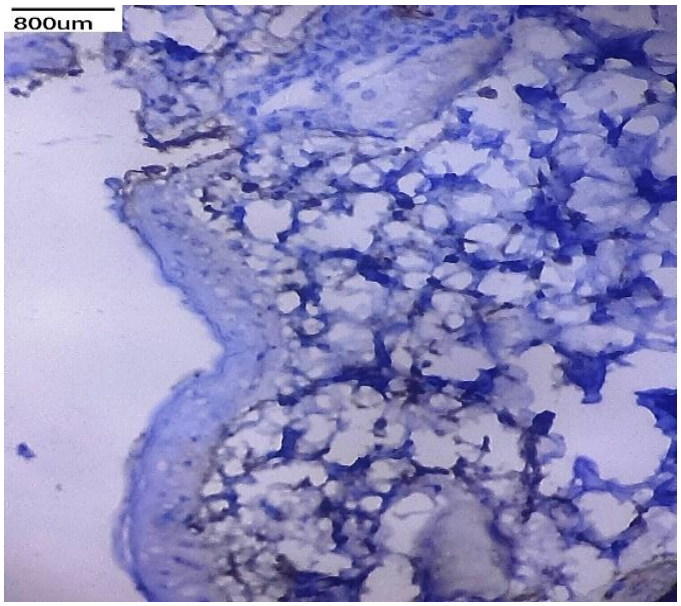
IMMUNOHISTOCHEMICAL STAINING OF PHTHALIC ANHYDRIDE 5% INDUCED CONTACT DERMATITIS IN Balb/c MICE.



GROUP II.



GROUP III.



GROUP V.

DISCUSSION

Contact dermatitis is a common inflammatory skin condition characterized by redness, swelling, itching, and sometimes blistering of the skin. It occurs when the skin comes into contact with an irritant or allergen, triggering an immune response and subsequent inflammation.

At the cellular level, contact dermatitis involves a complex series of immune responses. When the skin is exposed to an irritant or allergen, it activates specialized immune cells known as dendritic cells. These dendritic cells process and present the offending substance (the antigen) to another type of immune cell called T cells. The activation of T cells leads to their migration to the site of inflammation, where they release inflammatory mediators, such as cytokines. These cytokines cause vasodilation (widening of blood vessels), increased vascular permeability, and the recruitment of additional immune cells, including mast cells, to the affected area. Mast cells also contribute to the inflammatory response by releasing histamine and other inflammatory molecules, which further exacerbate the characteristic symptoms of contact dermatitis, such as redness, swelling, and itching.

Contact dermatitis can be caused by exposure to a wide range of substances, including chemicals, metals, plants, cosmetics, and certain medications. Irritant contact dermatitis occurs when the skin comes into direct contact with an irritating substance, leading to damage to the skin barrier and subsequent inflammation. Allergic contact dermatitis, on the other hand, occurs when the skin develops an allergic reaction to a specific allergen, usually after repeated exposure. Common allergens that can trigger allergic contact dermatitis include nickel, fragrances, preservatives, and latex.

The anti-inflammatory and antioxidant properties of MEPE (methanolic extract of Phyllanthus emblica fruit extract) are believed to contribute to its therapeutic effects in the treatment of contact dermatitis. MEPE is thought to act by scavenging free radicals, reducing oxidative stress, and inhibiting the release of inflammatory mediators, thereby attenuating the inflammatory response in the skin.

Furthermore, MEPE's immunomodulatory effects may play a crucial role in regulating the immune response associated with contact dermatitis. By modulating immune cell activity and cytokine production, MEPE helps restore immune homeostasis and alleviate inflammation in the skin.

The findings of this study suggest that MEPE holds promise as a natural remedy for the treatment of contact dermatitis induced by phthalic anhydride. Its potent anti-inflammatory, antioxidant, and immunomodulatory properties make it a valuable therapeutic agent for managing inflammatory skin conditions.

However, further research is needed to elucidate the underlying mechanisms of MEPE's action and optimize its formulation for clinical use. Additionally, clinical trials are warranted to evaluate the efficacy and safety of MEPE in human subjects with contact dermatitis. With continued investigation and development, MEPE may emerge as a promising alternative or adjunctive therapy for the management of contact dermatitis, offering patients a safe and effective treatment option with fewer side effects compared to conventional therapies.

The study's findings indicate that MEPE's multifaceted therapeutic properties, including its ability to scavenge free radicals, reduce oxidative stress, inhibit inflammatory mediator release, and modulate immune responses, make it a compelling candidate for the treatment of contact dermatitis. However, further research is necessary to fully understand the mechanisms of action and optimize the clinical application of MEPE for the management of this inflammatory skin condition. Ongoing investigation and clinical trials will be crucial in determining the true potential of MEPE as a safe and effective natural remedy for contact dermatitis.

While allopathic (conventional) medicine offers various treatment options for contact dermatitis, including topical corticosteroids, antihistamines, and immunomodulators, these approaches have certain limitations. Many allopathic medications provide symptomatic relief but do not address the underlying cause of contact dermatitis. Without addressing the root cause, symptoms may recur upon re-exposure to the offending substance. Some medications, such as topical corticosteroids, can have side effects with prolonged use, including skin thinning, discoloration, and increased susceptibility to infections. Allopathic treatments may not be effective for all individuals with contact dermatitis, especially in cases of severe or chronic inflammation. Additionally, some patients may experience resistance to certain medications over time. The cost of prescription medications for contact dermatitis treatment can also be a significant financial burden for patients, particularly for long-term management.

Phthalic anhydride is a potent irritant known to induce allergic contact dermatitis upon skin exposure. Its mechanism of action involves the activation of immune cells in the skin, leading to the release of inflammatory mediators and cytokines, resulting in skin inflammation and irritation.

The study also explored the safety profile of MEPE, a potential therapeutic compound, by evaluating its potential adverse effects and toxicity. Acute toxicity studies indicated that MEPE was well-tolerated and did not induce any significant adverse reactions in the animal models.

The experimental setup involved inducing contact dermatitis in animal models through the application of phthalic anhydride to the skin. The severity of dermatitis was assessed based on parameters such as erythema (redness), edema (swelling), and skin thickness. Animals were then treated with MEPE to evaluate its therapeutic efficacy.

The results from the study demonstrated a significant reduction in the severity of contact dermatitis following treatment with MEPE. Animals treated with MEPE exhibited decreased erythema, edema, and skin thickening compared to untreated controls. Histopathological analysis (examination of tissue samples) and immunohistochemical staining revealed a reduction in inflammatory cell infiltration and tissue damage in MEPE-treated animals, indicating the compound's potential as a therapeutic agent for contact dermatitis.

CONCLUSION

This study investigated the potential of methanolic extract of Phyllanthus emblica fruit (MEPE) in mitigating contact dermatitis induced by phthalic anhydride. The prepared topical formulation demonstrated good stability, pH, Spredability, and viscosity. Acute dermal toxicity testing showed no signs of toxicity. Through in vivo experimentation, the efficacy of Phyllanthus emblica fruit extract was evaluated using various parameters relevant to contact dermatitis. The results revealed that the application of MEPE gel significantly reduced the severity of contact dermatitis induced by phthalic anhydride. Parameters such as erythema, edema, and skin thickness were notably diminished in the MEPE-treated group compared to the control group. Specifically, the 5% w/w MEPE gel showed a significant result in reducing the inflammation. Histopathological and Immunohistochemical analysis further supported these findings, showing reduced

infiltration of inflammatory cells and preservation of skin architecture in the MEPE gel-treated group.

These results suggest that MEPE gel holds promise as a potential therapeutic agent for managing contact dermatitis induced by phthalic anhydride. Further studies are warranted to elucidate the underlying mechanisms of action and to optimize the formulation for clinical application.

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