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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

OPEN ACCESS Pakistan Journal of Biological Sciences

ISSN 1028-8880
DOI: 10.3923/pjbs.2025.660.667

Research Article
Formulation and Evaluation of *Marchantia paleacea* Gel for Treating Second-Degree Burn Wounds in Rats

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Abstract

Background and Objective: Second-degree burns can cause significant tissue damage, pain and infection risk, necessitating prompt and effective treatment strategies. Natural therapeutic agents with antioxidant and anti-inflammatory properties are gaining attention for burn management. *Marchantia paleacea*, a liverwort species, is known for such properties. This study aimed to formulate and evaluate *M. paleacea* gel for its wound healing potential in second-degree burns. **Materials and Methods:** A gel was prepared using ethanol extracts of *M. paleacea* at concentrations of 5, 10 and 15%, with Hydroxypropyl Methylcellulose (HPMC) as the base. The formulations were evaluated for pH, viscosity, spreadability, homogeneity, stability and skin irritation. A 14-day *in vivo* study was conducted on rats with second-degree burn wounds to assess healing. Statistical analysis included ANOVA and *post hoc* comparisons, with significance level set at $p<0.05$. **Results:** All gel formulations showed good physical stability, pH values between 5.04 and 5.30, viscosity ranging from 2459.7 to 2991.5 cps and no irritation in volunteers. The 15% *M. paleacea* gel demonstrated the most significant wound healing effect, reducing wound size to 0.12 cm^2, increasing epithelial thickness to 387.67 µm and enhancing collagen deposition to 18.60 on day 14 ($p<0.05$). **Conclusion:** *Marchantia paleacea* gel, particularly at 15% concentration, exhibited significant burn healing effects, likely due to its strong antioxidant and anti-inflammatory properties. This formulation holds promise as a natural topical agent for second-degree burn treatment. Further clinical studies are recommended to validate its efficacy.

Key words: Antioxidant, burn healing, *Marchantia paleacea*, topical gel, wound regeneration

Citation: Siregar, E.S., N. Pasaribu, S. Hutahaean, P.C. Situmorang and M.R. Hasibuan, 2025. Formulation and evaluation of *Marchantia paleacea* gel for treating second-degree burn wounds in rats. Pak. J. Biol. Sci., 28: 660-667.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Burns are a common form of thermal injury and can be caused by various heat sources, including direct exposure to fire, hot liquid spills, electrical currents and exposure to hazardous chemicals[1]. Second-degree burns are of particular concern because they involve deeper damage, not only to the epidermal layer, but also to the underlying dermis. This tissue damage causes severe pain, swelling (edema) and an increased risk of secondary infection due to disruption of the skin's protective layer and exposure to microorganisms from the outside environment[2]. The healing process of second-degree burns is complex and involves several interrelated biological mechanisms, ranging from the initial inflammatory phase as the body's response to injury, followed by the cell proliferation phase where new tissue begins to form, to the remodeling phase aimed at strengthening the newly formed tissue to approach normal skin structure and function[3]. Given the complexity of the wound healing process, there is a need for therapeutic agents that not only effectively accelerate the healing process but also have anti-inflammatory properties to control excessive inflammatory responses, antibacterial activity to prevent secondary infections and regenerative effects to support the formation of healthy new tissues.

Marchantia is a genus of the division of liverworts (Marchantiophyta). *Marchantia* has about 40 species distributed worldwide, 15 of which are found in Indonesia and 7 species in North Sumatra, one of which is *M. paleacea* Bertol. *Marchantia* species are generally found growing wild on the edge of slightly open to open forests or near settlements, on soil substrates as well as rocks. *Marchantia* is easily recognized by its thallus shaped, there are pores and gemmae cup on the dorsal surface of the thallus[4-6].

Marchantia paleacea is one of the species of liverworts that have long been used empirically in various regions such as China, ancient Greece, North America and Indonesia. Some of the properties possessed by this plant are to treat burns, open wounds, venomous snake bites, hepatotoxicity and anti-inflammatory[7]. Various studies have revealed various pharmacological activities possessed by *M. paleacea*. In one study, methanol extract of *M. paleacea* was found to have high antioxidant activity with an LC_{50} of 25.25 µg/mL when tested with 1.1-diphenyl-2-picrylhydrazyl (DPPH)[7]. Ethanol extract of *M. paleacea* is known to have significant antibacterial activity against *Staphylococcus aureus*, *Salmonella typhimurium* and *Pseudomonas aeruginosa*[8]. The plant is also known to exhibit immunostimulatory activity by increasing specific and non-specific immune responses, increasing phagocytosis index and spleen organ index and increasing IL-2 cytokine levels and delayed-type hypersensitivity response (DTH)[9].

The active compounds possessed by *M. paleacea* include macrocyclic bis (bibenzyls) and triterpenes. These compounds have various pharmacological activities, including as antifungal, antimicrobial, anti-inflammatory, antioxidant, anticancer and muscle relaxant. Some benzyls isolated from *M. paleacea* have significant cytotoxic activity against some cancer cells, such as MCF-7 and A549. Other active compounds obtained from *M. paleacea* such as marchantin A, B, D and E; paleatin B, perrottetin F and plagiochin E are also known to have antimicrobial, antifungal and cytotoxic activities[10]. Overall, *M. paleacea* has great potential as a source of active compounds with various beneficial biological activities.

The formulation of herbal ingredients for topical use aims to improve the bioavailability and stability often found in conventional herbal preparations[11]. Topical drug delivery has several advantages in various diseases, such as not passing through the gastrointestinal tract, thus avoiding gastrointestinal irritation and metabolic processes in the liver and can directly reach the lesion, thereby reducing unnecessary side effects[12]. One form of preparation for topical use is gel preparations. Gel preparations have several advantages over other dosage forms. Some of these advantages include patient comfort, easy application and enhancement of the therapeutic effect of herbal medicines[13]. With these various advantages, herbal-based gels have great potential to become the main solution in modern medicine. Therefore, the development of a gel formulation based on *M. paleacea* extract is a promising approach for burn healing. This study aimed to formulate a topical gel using *Marchantia paleacea* ethanol extract at concentrations of 5, 10 and 15% and to evaluate its physicochemical properties and therapeutic effectiveness in promoting the healing of second-degree burn wounds in rats.

MATERIALS AND METHODS

Study area and duration: This study was conducted at the Bukit Barisan Grand Forest Park, located in Bandar Baru Village, Sibolangit District, North Sumatra, Indonesia. The research was carried out from September to December, 2023.

Sample preparation and extraction: *Marchantia paleacea* samples (Fig. 1) were collected in a fresh state, cleaned of all impurities attached to it with running water until it is clean. Next, the sample is dried at room temperature until dry (about 7 days). The dried sample is pulverized using an electric

Fig. 1: Morphology of *M. paleacea* (personal documentation)

Table 1: Gel formulation of *Marchantia paleacea* ethanol extract with HPMC gel base in 200 g

Material	F1	F2	F3
Marchantia paleacea extract	10 g	20 g	30 g
HPMC	10 g	10 g	10 g
Propylene glycol	30 g	30 g	30 g
Methyl paraben	0.4 g	0.4 g	0.4 g
Aquadest	149.6 mL	139.6 mL	129.6 mL

F1: Gel formulation containing 5% *M. paleacea* ethanol extract, F2: Gel formulation containing 10% *M. paleacea* ethanol extract, and F3: Gel formulation containing 15% *M. paleacea* ethanol extract

blender until smooth. Extraction was performed using the maceration method. Samples that have been taken in the form of fine flour powder are taken up to 1 kg, extracted with 5 L of 70% ethanol for 3×24 hrs and shaken with a shaker. The solution is then filtered with Whatman 42. The filtrate obtained is centrifuged at a speed of 4000 rpm, the supernatant is concentrated with Rotavapor at a temperature of 40°C with a pressure of 13.5 kg/cm^2.

Gel formulation: The gel formulation of *M. paleacea* was performed using HPMC (Hydroxypropyl Methyl Cellulose) as the gel base[14]. The HPMC is dissolved in a portion of methanol and stirred until a gel base is formed. Methyl paraben dissolved in propylene glycol is added and stirred until homogeneous and *M. paleacea* extract is added to the gel base, then stirred until homogeneous and added with Aquadest (Table 1). The finished gel preparation is stored in an airtight container.

Evaluation of gel

Organoleptic and homogeneity tests: Organoleptic testing is carried out by direct observation of the color, smell and shape of the gel preparation[15]. The homogeneity test is carried out by applying the gel to a piece of transparent glass and then observing the presence or absence of insoluble particles or coarse grains[16].

pH test: The pH of gel preparations is measured using a universal pH stick. The pH test was performed by weighing 1.0 g of gel preparation, adding 10 mL of Aquadest, stirring until well mixed, measuring the pH and recording the results[17].

Spreadability test: A total of 0.5 g of gel preparation is placed on a glass with a size of 10×10 cm and covered again with the same glass. An additional 125 g of weight is then added and left for 1 min and the diameter is measured[18].

Viscosity test: Viscosity measurement using a Rheosys viscometer. A total of 15 mL of gel base is placed in a cylinder container, then the viscosity is measured with a viscometer equipped with spindles (25 mm *Concentric cylinders*) at a speed of 10 rpm[19].

Skin irritation test: The skin irritation test was carried out using an open patch test by applying the preparation to the

forearm and observing the reaction that occurs[20]. A positive irritation reaction is characterized by the appearance of redness, itching or swelling on the treated skin[21].

Stability test: The stability of the gel preparation was tested by storing the gel preparation in frozen conditions at -4°C for 24 hrs and at a high temperature, i.e., 40°C for 24 hrs; this treatment was calculated as 1 cycle. The stability test is performed for 6 cycles[22]. Stability testing of *M. paleacea* gel preparations includes organoleptic, homogeneity, pH, spreadability and viscosity tests[23].

Experimental design: The animals used in this study were approved by the Animal Research Ethics Committee of FMIPA, University of North Sumatra, No. 0686/KEPH-FMIPA/2024. A total of 25 white rats used in the experiment were acclimatized for 1 week to adapt to the new environment. The rats were given standard chow and water ad libitum. Then the rats were divided into 5 groups, namely the positive control group, the negative control group and the treatment group. The positive control group received bioplacenton® burn gel, (PT Kalbe Farma, Indonesia). The negative control group received no treatment and the F1, F2 and F3 treatment groups received *M. paleacea* ethanol extract in gel preparations with concentrations of 5, 10 and 15%, respectively. Second-degree burns were created by shaving the hair on the back of the rat and disinfected with 70% alcohol. The rats were then anesthetized with ketamine and xylazine injected intraperitoneally and allowed to recover until they were unconscious. A box-shaped iron (2×2 cm) was prepared, heated under a Bunsen flame for 1 minute and then applied to the skin of the rat's back until a second-degree burn developed. Burns on the backs of injured rats are treated according to the predetermined grouping of experimental animals. Burns are treated up to once a day from day 1 to 14. Burns are treated openly until healing, which is indicated by closure of the burn[24]. Wound healing in rats was observed visually for 14 consecutive days and the area of the wound was measured with a caliper on days 3, 7 and 14. After 14 days, the rats were sacrificed for observation of skin tissue by the paraffin method and staining with hematoxylin-eosin dye. Measurements of epithelial tissue thickness and collagen amount were performed microscopically using a light microscope (Olympus CX 43) at 5 fields of view in each group replicate.

Data analysis: The results of the microscopic observation were analyzed using statistical tests, beginning with the normality test and the homogeneity test (using the test of homogeneity of variance), followed by a One-way (ANOVA) test and the Duncan's test to detect significant differences at $p<0.05$ between treatment groups.

RESULTS AND DISCUSSION

Gel preparation evaluation test: The results of organoleptic and homogeneity tests (Table 2) show that the gel preparation of *M. paleacea* ethanol extract for 6 cycles (12 days of storage) at low temperature (-4°C) and high temperature (40°C) has a stable and consistent scent, color, shape and homogeneity. The F1, F2 and F3 gels have a distinctive odor, which is the odor of *M. paleacea* extract, but F3 has a sharper odor than F1 and F2. When observing the gel color, it was found that the F1 gel has a light brown color, the F2 gel is brown and the F3 gel is dark brown, which is more intense. This is due to the increase in the concentration given; the higher the concentration, the more intense the color obtained[25]. Observing the gel shape, all three formulations have the same gel-like shape. The results of the homogeneity test carried out on the preparation show that the gels F1, F2 and F3 have a homogeneous and stable arrangement in gel form, as evidenced by the absence of coarse particles or lumps in the preparation.

The pH test results of the gel preparation (Table 2) showed that after 6 cycles (12 days of storage), the gel preparation F1 had a pH of 5.30, the gel preparation F2 had a pH of 5.18 and the gel preparation F3 had a pH of 5.04. In the pH test results, gel preparations with a higher concentration have a lower pH compared to gel preparations with a lower concentration, but the pH obtained is still within the normal skin pH range.

The results of the spreadability test (Table 2) for 6 cycles (12 days of storage) carried out on F1, F2 and F3 gel preparations using a load of 125 g obtained results of 4.3, 4.6 and 4.8 cm, respectively. Gel preparations with *M. paleacea* extract concentration, the higher the concentration, disperse more when the same load is applied to each gel preparation. The spreadability test of gel preparations is carried out to ensure the even distribution of the gel to be used topically[26].

The results of the viscosity test (Table 2) for 6 cycles (12 days of storage) performed on the gel preparations F1, F2 and F3 showed that the highest to lowest viscosity of the gel preparations were F1, F2 and F3 with values of 2991.5, 2617.4 and 2459.7 cps, respectively.

The results of the test of the gel preparation applied to the forearm of 9 volunteers were carried out to see the irritation reaction when applied to the skin. The results of the

Table 2: Results of the evaluation test of *M. paleacea* gel preparation

Formula	Scent	Color	Shape	Homogeneous	Ph	Spread ability (cm)	Viscosity (cPs)	Irritation
F1	Moss scent	Light brown	Gel	Homogeneous	5.30	4.3	2991.5	No erythema, no itching and no edema
F2	Moss scent	Brown	Gel	Homogeneous	5.18	4.6	2617.4	No erythema, no itching and no edema
F3	Moss scent	Dark brown	Gel	Homogeneous	5.04	4.8	2459.7	No erythema, no itching and no edema

F1: Gel formulation containing 5% *M. paleacea* ethanol extract, F2: Gel formulation containing 10% *M. paleacea* ethanol extract, and F3: Gel formulation containing 15% *M. paleacea* ethanol extract

Table 3: Size of the wound

	Wound size area (cm)		
Group	Day 3	Day 7	Day 14
C (-)	1.76	1.198	0.54
C (+)	1.46	1.126	0.10
F1	1.49	1.128	0.24
F2	1.23	0.832	0.23
F3	1.13	0.580	0.12

C(-): Negative control; C(+): Positive control (Bioplacenton), F1: Gel formulation containing 5% *M. paleacea* ethanol extract, F2: Gel formulation containing 10% *M. paleacea* ethanol extract, and F3: Gel formulation containing 15% *M. paleacea* ethanol extract

irritation test (Table 2) showed that gel preparations F1, F2 and F3 did not cause any erythema, itching or edema on the forearms of 9 volunteers.

The result of the stability test of the gel formulation containing *M. paleacea* ethanol extract, conducted over 6 cycles (12 days of storage) under alternating low (-4°C) and high (40°C) temperatures, showed that the gel remained stable with respect to scent, color, shape, homogeneity, pH, dispersion, and viscosity.

Burn healing

Wound observation: The results of the measurements of burn area (Table 3) on days 3, 7 and 14 showed a significant decrease in burn area in all groups. The negative control group (C-) showed the slowest healing, with a wound area of 0.54 cm^2 on day 14. The positive control group (C+) with Bioplacenton showed the fastest healing, with a wound area of 0.10 cm^2 on day 14, indicating high efficacy in accelerating tissue regeneration. In the F1, F2 and F3 groups, it was found that the increase in concentration was found to be directly proportional to the acceleration of wound healing. The formula with a concentration of 5% (F1) showed a better improvement than the negative control, with a wound area of 0.24 cm^2 on day 14. The formula with a concentration of 10% (F2) showed higher efficacy, with the wound area reduced to 0.23 cm^2 by day 14. Meanwhile, the formula with a concentration of 15% (F3) showed the best results among the *M. paleacea* gel formulation group, with a wound area of 0.12 cm^2.

Epithelial tissue thickness and amount of collagen: The results of the analysis of skin epithelial tissue thickness (Table 4) showed that the difference in epithelial tissue thickness between F1, F2 and F3 groups and the negative control (C-) group was significantly different. The highest epithelial tissue thickness was obtained by the F3 group with a value of 387.67 µm and the lowest was obtained by the negative control (C-) group, which was 155.15 µm. The thickness of the epithelial tissue in each group is shown in Fig. 2(a-e).

The results of collagen count analysis (Table 4) showed a significant difference in the amount of collagen between the F2 and F3 groups and the negative control (C-) group. The highest amount of collagen was obtained in the F3 group with 18.60 and the lowest was obtained in the negative control group with 14.40.

The formulation of herbal gels containing *M. paleacea* moss extract is carried out with the aim of producing stable and effective preparations. The formulation process is focused on blending key components such as *M. paleacea* ethanol extract, HPMC and other additives that support the stability and effectiveness of the preparation. The gel preparation evaluation test aims to ensure the quality of the gel preparation. Organoleptical tests and homogeneity tests are performed to assess the physical characteristics of gel preparations, such as color, scent and consistency of gels and are used to ensure an even distribution of active ingredients in the preparations[27]. *Marchantia paleacea* gel preparations have a stable and consistent scent, color, shape and homogeneity. Gel preparations that have good homogeneity are characterized by the absence of clumps, coarse particles or separate phases in gel preparations[28]. The pH test is important to ensure the pH compatibility of the gel with human skin, thereby reducing the risk of irritation and discomfort when using. The pH test results of *M. paleacea* gel preparations are in the range of 5.04-5.30, which is in accordance with the

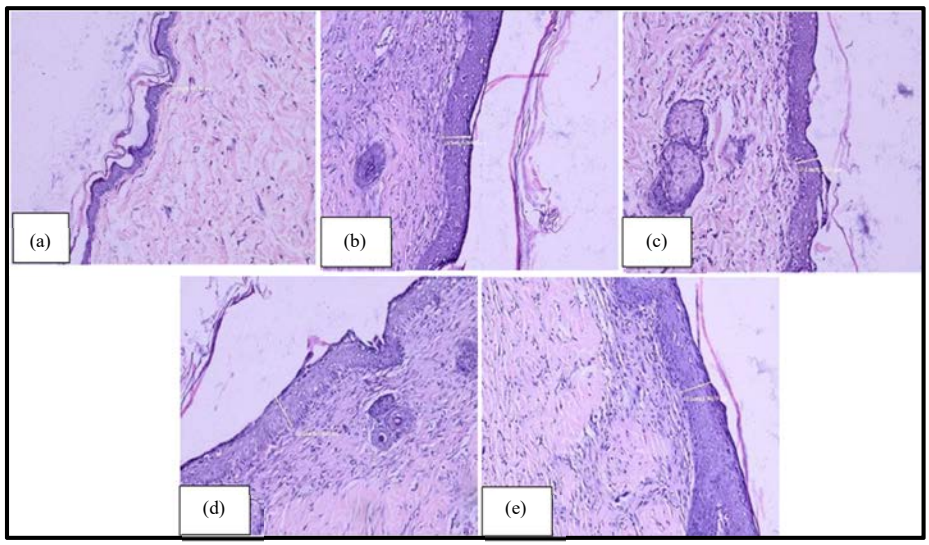

Fig. 2(a-e): Thickness of rat epithelial tissue. (a) C(-): Negative control, (b) C(+): Positive control (Bioplacenton®), (c) F1: Gel formulation containing 5% *M. paleacea* ethanol extract, F2: Gel formulation containing 10% *M. paleacea* ethanol extract, and F3: Gel formulation containing 15% *M. paleacea* ethanol extract
Histology of skin epithelial tissue using hematoxylin-eosin staining at 200x microscopic magnification

Table 4: Epithelial tissue thickness and collagen amount

Group	Epithelial thickness (μm)	Collagen
C (-)	155.15±22.54	14.40±0.50
C (+)	293.51±40.75	15.60±0.50
F1	348.43±74.42*	15.00±0.54
F2	355.51±68.74*	17.00±0.37*
F3	387.67±55.18*	18.60±0.50*

C (-): Negative control, C (+): Positive control (Bioplacenton), F1: Gel formula of *M. paleacea* ethanol extract with a concentration of 5%, F2: Gel formula of *M. paleacea* ethanol extract with a concentration of 10%, F3: *Marchantia paleacea* ethanol extract gel formula with a concentration of 15%, all values are Mean+SEM, n = 6 and *Significant at $p<0.05$ vs control

physiological pH of human skin, which is 4-6[29]. Gel spread refers to how wide an area can be covered when the gel is applied to the affected skin or surface. Spreadability testing on gel formulations is important because it affects ease of application and user comfort[30]. In addition, the bioavailability efficiency of the gel formulation is greatly influenced by the spreadability value, as better spreadability ensures a more even application and can improve the absorption as well as effectiveness of the active ingredient. The spread of *M. paleacea* gel preparations range from 4.3 to 4.6 cm with a weight of 125 g. The spread of this gel indicates that the gel has a good spread[31]. Viscosity tests play an important role in determining the spreadability of a gel preparation, so the viscosity must be characterized to ensure that the gel has the optimal spreadability to be applied[32]. *Marchantia paleacea* gel preparations have a viscosity of 2991.5, 2617.4 and 2459.7 cPs, where these values are in a good viscosity range of gel preparations, which is 2000-50,000 cPs[33]. In addition, irritation tests are performed to evaluate the safety of using the preparation on the skin, ensuring there are no adverse reactions such as redness or itching[34].

The results of each of these evaluations provide an overview of the physical, chemical and safety stability of the herbal gels formulated. Visual evaluation of wound size and burn measurement with a caliper showed that the group treated with *M. paleacea* gel preparation experienced a much faster acceleration of burn healing when compared to the negative control group. This is supported by histological observations, which show that epithelial thickness and collagen count in the F1, F2 and F3 groups were higher than in the control group, especially in *M. paleacea* gel with a concentration of 15%. Epithelial thickness and collagen content are two critical parameters used to assess the wound healing process. Epithelial thickness reflects the degree of re-epithelialization, which refers to the regeneration of epithelial cells that cover the wound and protect the underlying tissue from infection and dehydration[35,36].

CONCLUSION

Marchantia paleacea gel demonstrated favorable physical stability and notable wound healing potential in second-degree burns. Among the tested concentrations, the 15% formulation showed the greatest efficacy by accelerating wound closure, enhancing epithelial regeneration and improving collagen deposition. These findings suggest that *M. paleacea* gel is a promising natural topical treatment for burn injuries, warranting further clinical investigation to establish its therapeutic potential in humans.

SIGNIFICANCE STATEMENT

This study discovered the therapeutic potential of *Marchantia paleacea* gel in accelerating second-degree burn healing, which can be beneficial for developing safe, effective and natural alternatives to synthetic burn treatments. By demonstrating its antioxidant and anti-inflammatory activities, the study highlights the ability of *M. paleacea* gel to enhance wound closure, epithelial regeneration and collagen deposition. These findings provide valuable insights into the application of liverwort species in modern wound management, an area that has received limited scientific exploration. This study will help researchers to uncover the critical areas of natural product-based burn therapeutics that many researchers were not able to explore. Thus, a new theory on bioactive compounds in liverworts for wound healing may be arrived at.

ACKNOWLEDGMENT

The authors are grateful to the Rector of Universitas Sumatera Utara, who granted study funding through TALENTA 2023 with contract number 205/UN5.2.3.1/PPM/KP-TALENTA/R/2023 on 29 August, 2023. Furthermore, the authors are grateful to the teamwork on the field.

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