IJBPAS, November, 2025, 14(11): 5929-5939

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

EVALUATION OF HYDROALCOHOLIC EXTRACT OF LEAVES OF *PAEDERIA FOETIDA* FOR WOUND HEALING ACTIVITY

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Received 15th July 2024; Revised 20th Sept. 2024; Accepted 1st Nov. 2024; Available online 1st Nov. 2025

https://doi.org/10.31032/IJBPAS/2025/14.11.9559

ABSTRACT

The purpose of this study is to screen the wound healing properties of a hydro-alcoholic extract of *Paederia foetida* leaves. *Paederia foetida* is widely used to treat varieties of skin diseases in the Ayurvedic medicine system, as well as it is also used as folk medicine in wound management. Besides, this been proved scientifically for its anti-microbial, anti-oxidant, and anti-inflammatory activity. So, it can be assumed that *Paederia foetida* may show potent wound healing activity as the three most important related activities - anti-microbial, anti-oxidant, and anti-inflammatory activity- has already been proved. But still there is no scientific data available on wound healing activity. So, we have attempted to investigate this activity.

The hydroalcoholic *Paederia foetida* leaves extract was obtained by percolation method. Two doses of *Paederia foetida* (2.5% and 5%) in suitable gel formulation was prepared with the help of HPMC as a gel base to apply topically. Evaluation of the wound healing activity was done by "Excision and Incision wound" models. In the excision wound model, rats treated with *Paederia foetida* leaves extract showed a significant improvement of the epithelialization time and 50%wound contraction. As well as, the breaking strength of rats treated with *Paederia foetida* leaves extract increased significantly in an incision wound model as compared to the control group.

Paederia foetida leaves extract gel formulations showed likely similar activities as compared to synthetic standard/marketed povidone-iodine as well as herbal standard *Aloe vera* gel formulation. It can be settled that *Paederia foetida* leaves extract (2.5 % and 5% gel preparation) has potent wound healing activity.

Keywords: *Paederia foetida,* Phytochemicals, epithelialization time, Breaking Strength, Wound healing, Excision wound model, Incision wound model

INTRODUCTION

There is an eternal bond between plant and man. Our society is grateful for food, fodder, fuel, and other purposes to the plant **[1]**. In the pharmaceutical technology ayurvedic formulation has become a worldwide topic in the recent times. This herbal formulation is beneficial medical and economic. The popular usage of herbs has raised severe concerns about their quality, safety, and efficacy throughout the world. In primary health care herbal plants shows an important role. The lack of evidence and quality inspection has created the barrier between the herbal medicine and its acceptability. So, the attempt to standardize the plant material that will be used as medicine becomes incredibly crucial **[2]**. *Paederia foetida* (Rubiaceae) is an indigenous plant locally known as Gandhavadulia (English name "skunkvine") **[3]**. It is found in India, Japan and SEA. It contains a bitter flavor and a foul odour. However, it prefers sunny flood plains and bottomlands. It can also be growing in tree gaps and other disturbed regions **[4]**. This plant has been used to treat coughs, rheumatoid arthritis, Hepatic diseases, diabetes, asthma, dysentery, constipation, flatulency, pneumonia, stomachache, itches, typhoid, wounds, discomfort, diarrhea, cancer, body ache, toothache, bone fractures etc. **[5]**.

Healing of wound is the earliest medical problem. It is not only about wound closure, but the quality of scar and restoration of functional competence is also important. Healing, the mechanism of survival maintains normal anatomical function and structure.

Mechanism of non-healing wounds is not simple and it is an expensive program. Scientists are looking to develop new medicines from the elements of nature turning to Ayurveda, India's traditional medical system. Ayurveda considers some herbal, mineral and veterinary medicines for their properties to heal wound. Many drugs of these kinds originate from plant. Though many plants have gone through scientific tests for their activity of healing wound in various

pharmacological models and patients, most of their possibilities remain unexplored. However, in several incidents, Chemical ingredients which are active have been identified. Some Ayurvedic medicinal plants named *Aloe vera, Bengal fig tree, Glycyrrhiza glabra, Cynodon dactylone, Simplelocus racemosa, Curcuma longa, Rubia cordifolia, Ficus racemosa, Berberis aristata, , Centella asiatica Eupfolia, Pterocarpus santalinus* has been shown wound curing activity in experimental wound model **[6]**.

P. foetida is regularly used to heal the wound in folk medicine. But still there is no scientific data is available, though *P. foetida* exerts anti-inflammatory, anti-oxidant and anti-microbial activity. These three activities scientifically indicate the chances of *P.foetida* to exert wound healing activity. Here is an attempt to reveal the wound healing action of hydro-alcoholic extract of *P. foetida* leaves scientifically.

MATERIALS & METHOD:

Experimental Animal:

Albino wistar rats around 200-250 gm weight and rabbits around 1.5 kg weight were used for the study. The animals were purchased from M/S Saha Enterprise (authorized animal breeder). They had also provided the commercial food pallets and tap water *ad libitum*. The animals were kept hygienically in separate polypropylene cage and all experiments were conducted between 10 am to 6 pm. The CPCSEA approved N.S.C.B.I.P. (Netaji Subhas Chandra Bose Institute of Pharmacy) animal house (approval no: 1502/PO/a/11/CPCSEA) was utilised to house the rats and rabbits. Standard laboratory conditions were followed, including a room temperature of 22±2°C and a 12-hour light/12-hour dark cycle.

Drugs and chemicals:

Ethanol (Dr. S.C. Deb's Dilution), Povidone iodine ointment (Betadine 10% Ointment, Win-Medicare Pvt Ltd), Ketamine (Ciron Drugs & Pharmaceuticals Pvt Ltd), Distilled water, Hydroxypropyl methylcellulose (Loba Chemie Pvt Ltd), Methylene blue, *Aloe vera* gel (Himalaya), Xylazine (Indian Immunologicals).

Collection of sample:

Fresh tender leaves were collected from the local area of Krishnanagar, West Bengal, India and washed with clean and fresh water for removing the dust particles followed by shade drying. Dried leaves were subjected for extraction.

Preparation of the extract: [7]

The extraction progression of *Paederia foetida* leaves were done with 70% ethanol by using cold percolation technique for uninterrupted 48 hours. The extract has been

collected and kept for evaporation under vacuum evaporator to get the constant weight. After that the *Paederia foetida* leaves extract was collected and stored under refrigeration at 4° C.

Preliminary phytochemical investigation of the extract: [7]

The *Paederia foetida* leaves hydro alcoholic extract was exposed to phytochemical analysis of several phytoconstituents such as Carbohydrates, Alkaloids, Flavonoids, Glycosides, Steroids, Phenolic acids, Saponins, and Proteins.

Gel preparation and Dose selection:

The ability of several herbal medications to cure wounds has been discovered in a range of topical formulations, such as gels, ointments, and creams. The selection of vehicles is biassed in favour of gel. This is advantageous because the aqueous composition of the gel should mix with the aqueous exudates from the wound more quickly and effectively. The phytochemical extract used in the different tests includes organic, hydroalcoholic and aqueous components. The gel was the best option because it would be challenging to seperate out the extract's lipophilic component from lipophilic ointments or lotions. The reduced retention and improved drug flow anticipated from a polymeric gel-based vehicle. For this reason, we decided to use hydroxypropyl methylcellulose (HPMC) as the gel foundation.

There is a topical HPMC gel formulation ready. *Paederia foetida* (2.5%) in HPMC (7.5%) is utilized as a low dose and *Paederia foetida* (5%) in HPMC (7.5%) as a high dose when applied topically in an excision, incision wound model. Models with excision wounds underwent treatment, 10 days of treatment were given to models with incision wounds, and until the scar completely slid off the wound.

Wound Healing Models:

Wound healing activity was evaluated through two models viz. excision wound model as well as incision wound model.

Excision Wound Model:

A 200–250 grams male albino wistar rats were taken. Three groups of six animals each were formed out of the animals. Animals were rendered unconscious both before and during the procedure by anaesthetized xylazine (13 mg/kg) and ketamine (87 mg/kg ip.). Excision wounds were produced on the rats. The fur on either side of the animals in the lumber section was cleaned with an electric clipper, and a 500mm2 circular stainless-steel stencil ($500mm^2$) was used to mark the anticipated location of the wound that would be created on the animals' backs using methylene blue. A full thickness excision wound of 500 mm^2 and

0.2 cm depth was formed along the marks using surgical scissors and toothed forceps.

Group I: Control group: animals of this group were not received any treatment, only 7.5% HPMC gel was provided two times a day.

Group II: Standard group: animals of this group were received povidone-iodine ointment USP 10%w/w (Betadine Ointment 10%) two times a day.

Group III: Test group: animals of this group were received *Paederia foetida* 2.5% in 7.5% HPMC gel till complete epithelialization, two times a day.

Group IV: Test group: animals of this group were received *Paederia foetida* 5% in 7.5% HPMC gel till complete epithelialization, two times a day.

By using cellophane paper and a permanent marker to trace the wound at days 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22 following wounding, the contraction of the wound was determined. The injured areas were identified and measured on a millimeter-scale graph paper. It was determined and documented how many days were needed for the escher to fall without any raw wounds left after the period of epithelialization **[8] [9]**.

Incision Wound Model:

The same as in the excision wound model, three groups of male wistar albino rats weighing 200–250 grams were formed. As in the previous model, rats were anaesthetized both before to and throughout the creation of the wound. An electric clipper was used to shave the animals' dorsal fur. According to Ehrlich and Hunt, a straight paravertebral incision of 6 cm was made on the back's skin and subcutaneous muscle. After complete hemostasis, the wound was closed with interrupted sutures placed at equal intervals of approximately 1 cm. Animals were given their planned drug every day (from the 0th to the 9th post-wounding day), on the 10th post-wounding day, the wound breaking strength test was conducted utilizing a continuous, constant water flow approach.

3mm away from the edge of the incision, Allis forceps were firmly placed on both flanks of the wound. The forceps were attached to a fixed metal rod on one side and a lightweight plastic container was used to tether the forceps to a thread that crossed a pulley on the other. The container, which was attached to a continuous water flow method (100 drips per minute), continued to hang. To avoid more tissue damage, the addition of weights was stopped as soon as the incision started to gap and the weight was lifted. The weights caused gapping was noted **[10] [11]**.

Skin Irritation Study [12]

Data from test methods specified in 16 CFR 1500.41 and/or NAS Publication 1138, as well

as toxicity categories described in 16 CFR 1500.3, were used to create ratings that corresponded to the following definitions.

There were two separate, roughly 500 mm2 dorsal shaving sites on the rabbit's skin. The first region functioned as a control for the vehicle application, and the rabbit was kept in a rabbit holder. A 5% solution of *Paederia foetida* gel was applied to the second region. After a 4 hour period, the skin was assessed and a score was determined by comparing it to the control.

Statistical Analysis:

Mean±S.E.M is the expression method of all the result. One-way Analysis of Variance (ANOVA) (control vs. treatment) followed by Dunnett's test is used to differentiate the experimental groups. The differences between experimental groups were statistically significant, when $P<0.05$.

RESULTS AND DISCUSSION:

Extract preparation:

The *Paederia foetida* leaves were subjected to cold percolation extraction by using 70% ethanol for consecutive 48 hours and 6.6 % yield was obtained.

Preliminary phytochemical investigation:

The hydroalcoholic extract of *Paederia foetida* leaves were imperiled for phytochemical investigation and the following observations were found **(Table 1)**.

Excision Wound Model

Evaluation of hydroalcoholic *Paederia foetida* leaves extract for wound healing activity was designed to evacuate the healing potential of *Paederia foetida* leaves in excision and incision wound model. 70% ethanol was used to extract the leaves, and 7.5% HPMC was used to make the gel.

Before beginning the experiment, the animal was procured from a CPCSEA-approved breeder and placed in quarantine at the NSCBIP animal house for a period of 14 days. The 5 pre-planned treatment groups served as the basis for the creation of the excision and incision wound models. The first group received the HPMC gel without any active components and was left untreated. In the current study, two groups standard I and standard II were retained as an exception. Animals in the Standard I group received Povidone Iodine treatment.

Antimicrobial, yet it is biassed to contrast the herbal formulation with a synthetic standard in this case. This starts to include the second standard, which is herbal and has been observed to have the ability to cure wounds. By keeping this logic in mind *Aloe vera* has been incorporated as a herbal standard (Standard II).

Both 2.5% and 5% gel of *Paederia foetida* showed a considerable decrease in duration of

epithelialization while comparing with the untreated control. Simultaneously, 50% wound contraction has also demonstrated outstanding results for both groups. 50% wound contraction is a crucial metric that may be used to evaluate the rate of healing and the quality of epithelialization. A quicker pace of healing may indicate that the injured cells are proliferating more quickly. The effects are somewhat similar to both synthetic drugs and traditional herbal remedies **(Table 2, Figure 1, 2)**.

Incision Wound Model

In an incision wound model, *Paederia foetida* has demonstrated a noteworthy influence on wound healing. When compared to the untreated control group, all groups that received two different doses of *Paederia foetida*, *Aloe vera*, and povidone iodine showed a noteworthy increase in breaking strength. This suggests that the two formulations of *Paederia foetida* have promoted collagenation in a way that is comparable to the effects of povidone iodine and possibly even superior to standard herbal *Aloe vera*.

The continuous water fall approach is utilised in the incision wound model to assess the collagen fiber's breaking strength. The drug's evident antioxidant qualities were used to demonstrate the collagen fiber's advancement by dictating the superoxide load in the wounded area **(Table 3, Figure 3)**.

Skin irritation test:

250 mg of hydro alcoholic extract of *Paederia foetida* was gel formulated by using HPMC and applied to the dorsal skin of the rabbit in the lumber section and observed for 4 hours, and found no irritation or colour changes in the open skin. From the findings mentioned it can be concluded that *Paederia foetida* does not produce any irritation in the skin or it can be stated as nonirritant /safe for topical application **(Table 4)**.

Table 1: Results of Preliminary Phytochemical investigation

Sl. No.	Phytochemicals	Test	Result
1	Flavonoids	Ferric Chloride Test	Positive
2	Proteins and Amino Acid Test	Biuret Test	Positive
3	Alkaloids	Dragendroff's Test	Positive
4	Saponins	Froth Formation Test	Positive
5	Steroids	Salkowski Test	Positive
6	Tannins	Lead Acetate Test	Positive
7	Phenolic compounds	Litmus Test	Positive
8	Carbohydrates	Barfoed's Test	Positive
9	Terpenoids	Salkowski Test	Positive

Table 2: Effect of *Paederia foetida* on period of epithelialization and 50%wound contraction in excision wound model

Treatment	Period of epithelialization (days)	50% Wound contraction (days)
Control (7.5% HPMC gel)	20.332±0.421	8.412±0.176
Aloe vera Gel	15.503±0.341***	6.452±0.364***
Povidone Iodine	14.661±0.494***	6.105±0.123***
Paederia foetida (2.5%) in 7.5% HPMC gel	17.372 ± 0.434***	7.015 ± 0.167***
Paederia foetida (5%) in 7.5% HPMC gel	16.341 ± 0.382***	6.817 ± 0.233***

All values are mean±SEM, n=6, ** p<0.01, *** p<0.001 vs. control

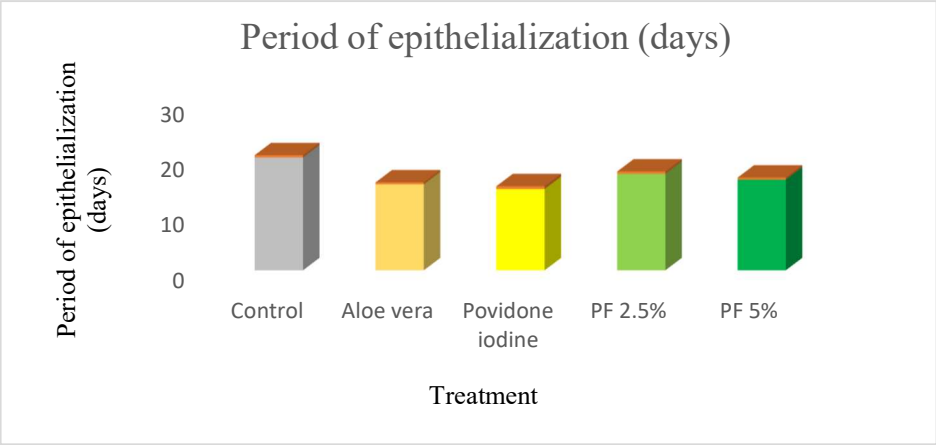

Figure 1: Effect of *Paederia foetida*. on period of epithelialization
All values are mean± SEM, n=6, ** p<0.01, *** p<0.001 vs. control

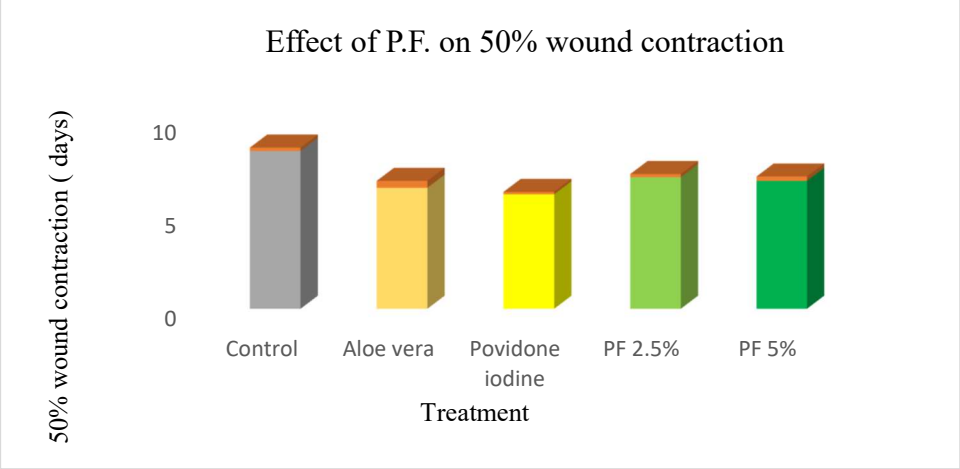

Figure 2: Effect of *Paederia foetida*. on 50%wound contraction in excision wound model
All values are mean ± SEM, n=6, ** p<0.01, *** p<0.001 vs. control

Table 3: Effect of *Paederia foetida* on breaking strength in incision wound model

Treatment	Breaking strength
Control (7.5% HPMC gel)	277.33±4.81
Aloe vera Gel	393.54±5.65***
Povidone Iodine	426.78±6.95***
Paederia foetida (2.5%) in 7.5% HPMC gel	351.75 ± 6.16***
Paederia foetida (5%) in 7.5% HPMC gel	381.66 ± 7.62***

All values are mean ±SEM, n=6, *** p<0.001 vs. control

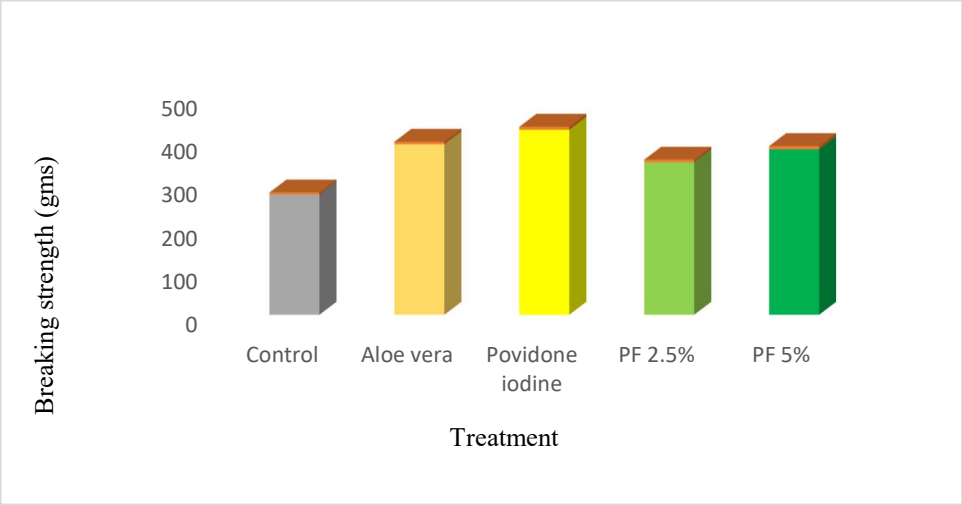

Figure 3: Effect of *Paederia foetida* on breaking strength in incision wound model
All values are mean ± SEM, n=6, *** p<0.001 vs. control

Table 4: Effect of *Paederia foetida* on skin irritation study

Group	Sign	Score
Control	**–**	
***Paederia foetida* (5%)**	**No noticeable inflammation and redness**	**0**

General outcome:

Through this current study, we have learned that *Paederia foetida* has shown the existence of tannin, steroids, alkaloids, protein, and carbohydrates in chemical tests, all of which may be linked to the organism's healing properties. A portion of these chemical components are in charge of showing the ability to repair wounds.

Alkaloids having a nitrogen atom in their structure typically have antioxidant, antibacterial, and anti-inflammatory properties **[13]**. By blocking phospholipase A2, which is essential for the synthesis of inflammatory chemicals, steroids have anti-inflammatory properties **[14]**. Tannins are known for their antioxidant properties, and the medication used to demonstrate these properties is also known to exhibit varying degrees of wound healing action. Protein is regarded as our body's building block.

Proteins are made up of amino acids. Amino acids can increase the rate the healing process by accelerating cell division. Additionally, amino acids support eschar's maturation. Flavonoids boost the endogenous antioxidants that prevent eicosanoid production. As a result, the inflammatory metabolites are reduced and exhibit strong anti-inflammatory effects **[15]**.

Paederia foeitida has been shown comprise effect of anti-inflammatory, antimicrobial and antioxidant properties by scientific research. Its alkaloids may be the cause of its

antioxidant properties. Sterol, tannin, and alkaloids may be the cause of its anti-inflammatory properties. The most potent component of a herb that promotes wound healing is called tannin.

To put it briefly, *Paederia foetida* is a miraculous herb with a variety of pharmacological benefits. While some of them are well-known, the plant's capacity to heal wounds has not been made public. Nonetheless, it is evident from all of the previously mentioned information that *Paederia foetida* has demonstrated a strong ability to heal wounds, which may be linked to the presence of its chemical constituents, which include tannin, alkaloids, steroids, and protein. These characteristics also distinguish *Paederia foetida* as a special plant.

CONCLUSION:

In this project hydro-alcoholic *Paederia foeitida* leaves extract has been evaluated for wound healing action by using two different models namely excision and incision wound model. This model has two distinct standard Povidone iodine and *Aloe vera*. *Paederia foeitida* shown impressive wound healing action in both models by accelerating the rate of collagen synthesis and epithelialization. *Paederia foeitida* has proven a healing capability that is on par with povidone iodine and to some extent superior than traditional herbal remedy *Aloe vera*. Its active ingredients, such as tannin, phenols, steroids, and alkaloids, may be the cause of these effects. These compounds have antioxidant, antibacterial, and anti-inflammatory properties. It is clear that the drug employed to generate these three actions has therapeutic qualities. This drug's strong healing capability could offer promise for the clinical therapy of wounds.

ACKNOWLEDGEMENTS:

We sincerely thank Dr. Arnab Samanta, the principal of the Netaji Subhas Chandra Bose Institute of Pharmacy. For his cooperation and providing of all required resources. We also want to express our gratitude to our family and friends for their time, patience, and support.

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