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Evaluation of *In Vivo* Wound Healing Activity of Ethanolic Extract of *Bougainvillea glabra* Choisy Bracts on Diabetic Induced Albino Wistar Rats

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ABSTRACT

Background: Chronic non-healing ulcers are a significant complication of diabetes, largely due to impaired circulation and immune response. While conventional therapies are often costly and have side effects, *Bougainvillea glabra* Choisy bracts, rich in bioactive compounds such as flavonoids and polyphenols, present a promising herbal alternative for wound healing. **Aim of this study:** This study aimed to assess the wound-healing potential of ethanolic extracts of *Bougainvillea glabra* Choisy bracts (EEBGCB) in an excision wound model using diabetic induced Albino Wistar rats. **Methods:** Ethanolic extracts of *Bougainvillea glabra* Choisy bracts (EEBGCB) were formulated into 1% w/w and 5% w/w ointments and the formulations were characterized for physicochemical properties, and safety was confirmed through acute dermal toxicity studies. Wound-healing activity was assessed in streptozotocin-induced diabetic rats using parameters such as wound contraction, epithelialization period, hydroxyproline estimation, and histopathology. **Results:** The 5% w/w EEBGCB ointment exhibited significant wound-healing properties. Enhanced wound contraction, reduced epithelialization period, and increased hydroxyproline levels were observed and histopathological analysis revealed improved collagen deposition, vascularization, and reduced inflammation in 5%w/w EEBGCB Ointment treated group. **Conclusion:** *Bougainvillea glabra* Choisy bracts demonstrated strong wound-healing activity, likely due to their flavonoid and polyphenolic content. These findings suggest its potential as an effective and affordable option for diabetic wound care, warranting further studies to identify active compounds and underlying mechanisms.

Keywords: Chronic wound management, herbal formulation, Framycetin sulphate, wound contraction, epithelialization, hydroxyproline, collagen synthesis, tissue regeneration.

INTRODUCTION

Diabetic wounds, particularly chronic non-healing foot ulcers, are a significant complication of diabetes mellitus caused by impaired circulation, neuropathy, and reduced immune function. [1] Prolonged hyperglycemia damages blood vessels, reduces angiogenesis, and disrupts fibroblast proliferation and keratinocyte migration. This leads to excessive inflammation, increased risk of infections, and delayed healing. [2] In 2018, approximately 34.2 million Americans were diagnosed with diabetes, while 88 million were pre-diabetic, contributing to an annual healthcare cost of $237 billion. [3] Nearly 25% of individuals with diabetes develop wounds, especially in type-2 diabetes, with treatment costs forming a substantial portion of diabetes-related expenses. [4]

Current treatment options include antimicrobials, antibiotics, antiseptics, and topical agents like collagen and framycetin sulphate, which address infections and support tissue repair. However, these methods can be expensive and have side effects. [5] Medicinal plants offer a promising alternative due to their affordability and bioactive compounds, such as flavonoids, tannins, and saponins, which exhibit antioxidant, anti-inflammatory and antimicrobial properties. These natural products can effectively accelerate wound healing by targeting various phases of the process, making them a potential solution for managing chronic wounds. [6]

Bougainvillea glabra Choisy, an ornamental plant, contains Phytochemicals such as flavonoids, phenolic acids, tannins, and glycosides, which are known for their wound-healing properties. [7] Preliminary Phytochemical analysis of Ethanolic Extract of *Bougainvillea glabra* Choisy Bracts (EEBGCB) confirmed the presence of bioactive compounds with antioxidant and antimicrobial

activity. *In vitro* studies of EEBGCB further validated their potential, showing significant wound-healing efficacy, including proangiogenic properties. Based on these findings, further *in vivo* investigations of EEBGCB were conducted to evaluate its ability to enhance wound healing in diabetic models.

This study addresses the knowledge gap regarding the wound-healing potential of *B. glabra* Choisy bracts, focusing on their application for diabetic wound management. The findings suggest that it could serve as a cost-effective and accessible alternative to conventional treatments, particularly in resource-constrained settings. By leveraging the plant's natural bioactive properties, this research paves the way for developing novel herbal therapies to treat diabetic wounds effectively.

MATERIALS AND METHODS

PREPARATION OF HERBAL FORMULATION[8]

Ingredients for Ointment Base

- Wool fat (5 %w/w)
- Hard paraffin (5 %w/w)
- Cetostearyl alcohol (5 %w/w)
- White soft paraffin (85 %w/w)

Procedure

❖ Hard paraffin (5 gm) and Cetostearyl alcohol (5 gm) were taken in a china dish and it was kept it in a water bath at 70ºC.

❖ Then, Wool fat (5 gm) and White soft paraffin (85 gm) were added to the above mixture and stirr the mixture until all the ingredients were melted.

❖ It was decanted or strained if necessary, and mixed cold, packed in an appropriate container.

❖ 1 %w/w Ointment contains 0.5 gm of Ethanolic Extract of *Bougainvillea glabra* Choisy Bracts (EEBGCB) and 5 %w/w Ointment contains 2.5 gm of EEBGCB. Ointments were prepared by trituration method.

PHYSICOCHEMICAL CHARACTERIZATION OF FORMULATION[9]

❖ **Colour and Odour:** Colour and Odour were evaluated through visual examination to determine the physical appearance and sensory characteristics.

❖ **Consistency:** Consistency was assessed by rubbing a small amount of ointment between the thumb and forefinger to observe its texture and immediate skin feel.

❖ **p^H:** The p^H was determined using a pH meter calibrated with a standard buffer. Approximately 0.5 g of the ointment was dissolved in 50 mL of distilled water, allowed to stand for 2 hours, and then measured.

❖ **Centrifugation:** Stability was evaluated by centrifuging the formulation in a 10 mL graduated cylinder at 10,000 rpm for 10 minutes to simulate accelerated spoilage conditions.

❖ **Spreadability:** Spreadability was measured by placing 1 g of the ointment between two glass slides and applying a 50 g weight for 5 minutes to achieve uniform thickness. The time required to separate the slides was recorded, and spreadability was calculated using the formula:

$$S = M \times L / T$$

Where, S is spreadability,

M is the weight tied to the upper slide,

L is the slide length and

T is the time to separate the slides.

IN VIVO WOUND HEALING STUDIES

EXPERIMENTAL ANIMALS

This study was ethically approved by the Institutional Animal Ethics Committee, Madras Medical College, Chennai-03, and complied with the national guidelines of CPCSEA/IAEC approval no.1917/GO/ReBi/S/16/CPCSEA/20.09.2021 for the experimental protocol no.07/AEL/IAEC/MMC dated 14/08/2024. Healthy male Albino Wistar rats (150–200 g, aged 6–8 weeks) were procured and housed in a controlled environment (22 ± 2°C temperature, 55–65% relative humidity, 12:12 light/dark cycle) with free access to standard laboratory chow and drinking water. Seven days quarantine and acclimatization period were observed before the study.

ACUTE DERMAL TOXICITY

Acute dermal toxicity study was performed as per OECD guidelines 402. The dorsal trunk area of the rats was shaved, and 2000 mg/kg of EEBGCB ointment was applied under a porous gauze dressing. Observations for clinical signs and mortality were recorded at regular intervals for 14 days.

DIABETES INDUCTION AND WOUND CREATION

Diabetes was induced using Streptozotocin (60 mg/kg, i.p.), and blood glucose levels were measured on the third day. Animals with glucose levels >200 mg/dL were considered diabetic. [10] Excision wounds were created under ketamine anesthesia (30 mg/kg, i.p.) by excising a 2 cm diameter full-thickness skin section from the back of the rats using a circular ring template. [11]

EXPERIMENTAL DESIGN

30 Animals were divided into five groups as follows:

Group 1 (Normal Control): No treatment.

Group 2 (Disease Control): Simple ointment base applied topically.

Group 3 (Standard): 1% Framycetin sulphate ointment applied topically.

Group 4 (Test 1 Low dose): 1% EEBGCB ointment applied topically.

Group 5 (Test 2 High dose): 5% EEBGCB ointment applied topically.

All treatments were applied once daily for 14 days. On day 7 and 15, the rats were anaesthetized and the wound tissues were isolated for hydroxyproline estimation histopathological examinations.

EVALUATION PARAMETERS

1. Visual Assessment

Wounds were examined daily for signs of inflammation, secretion, redness, pus formation, pain, or bleeding. Observations were recorded and photographed. [12]

2. Wound Contraction

Wound contraction was measured at 2–4 day intervals by tracing wound margins on sterilized transparency sheets. The area was calculated using graph paper, and the percentage wound contraction was determined by

Wound contraction % = Wound diameter on day 0 - Wound diameter on day 28 / Wound diameter on day 0. [13]

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3. Period of Epithelialization

The time required for the eschar to fall off without raw tissue exposure was recorded as the epithelialization period. [14]

4. Hydroxyproline Estimation

Hydroxyproline, an indicator of collagen content, was estimated using a modified spectrophotometric method. 50 mg of wound tissue was hydrolyzed in 4 mL of 6N HCl in sealed glass tubes at 110°C for 22 hours. The hydrolysate was evaporated to dryness, and the residue was dissolved in distilled water to a final volume of 10 mL. 1 mL of the hydrolyzed sample was mixed with 1 mL of chloramine-T solution and incubated for 20 minutes at room temperature. 1 mL of perchloric acid was added, followed by 1 mL of p-dimethyl amino benzaldehyde reagent. Samples were incubated at 60°C for 20 minutes and cooled. The color intensity was measured at 557 nm using a spectrophotometer. Hydroxyproline concentration was determined from a standard curve prepared with known concentrations (20–200 µg/mL). [15]

5. Histopathological Examination

Histological analysis was conducted to assess the level of wound healing and tissue regeneration. 3–5 mm thick tissue samples, including wound margins, were excised and fixed in 10% formalin for 24–48 hours. Fixed tissues were embedded in paraffin, sectioned at 4–6 µm thickness, and stained using hematoxylin and eosin (H&E). Slides were examined for epithelial regeneration, fibroblast proliferation, neovascularization, and collagen deposition. [16]

STATISTICAL ANALYSIS

Data were analyzed using GraphPad Prism software version 10.2.2. Results were expressed as mean ± SEM, and statistical significance was assessed using one-way and two-way ANOVA, followed by Dunnett's multiple comparison test. P values ($P < 0.01$, $P < 0.001$, $P < 0.0001$) were considered statistically significant. [17]

RESULTS AND DISCUSSION

EVALUATION OF PREPARED HERBAL OINTMENT

The prepared 1% w/w and 5% w/w EEBGCB ointments were evaluated for parameters including colour, odour, consistency, p^H, accelerated spoilage, and spreadability. The results are summarized in Table-1 and Figures 1 to 3 depict the ointment base and prepared formulations.

Table-1 Physiochemical evaluation of EEBGCB Ointments

S NO.	PHYSIOCHEMICAL PARAMETERS	1%w/w EEBGCB OINTMENT	5%w/w EEBGCB OINTMENT
1	Colour Odour	Light Green Odourless	Dark Green Odourless
2	Consistency	Smooth, Little grittiness	Smooth Little grittiness
3	p^H	6.3	6.7
4	Accelerated spoilage (Centrifugation)	No phase separation	No phase separation
5	Spreadability	42 mm	58 mm

Fig.1 Ointment Base

Fig.2 1 %w/w EEBGCB Ointment

Fig.3 5 %w/w EEBGCB Ointment

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ACUTE DERMAL TOXICITY

The acute dermal toxicity study confirmed the safety of EEBGCB ointments. Animals treated with 2000 mg/kg exhibited normal behavioral and physiological responses, with no signs of toxicity, mortality or adverse effects over 14 days. Parameters such as alertness, motor coordination, reflex actions, and food and water consumption remained normal throughout. These findings suggest that the formulations are safe for topical application at the tested doses.

IN VIVO WOUND HEALING STUDIES

1. Visual Assessment

The wound sites were assessed for signs of inflammation, secretion, and redness. Both the standard and 1 %w/w and 5 %w/w EEBGCB Ointment treated groups initially showed some signs in the wound sites, but they were not as noticeable as those in the disease control group, as visualized in Figure 4.

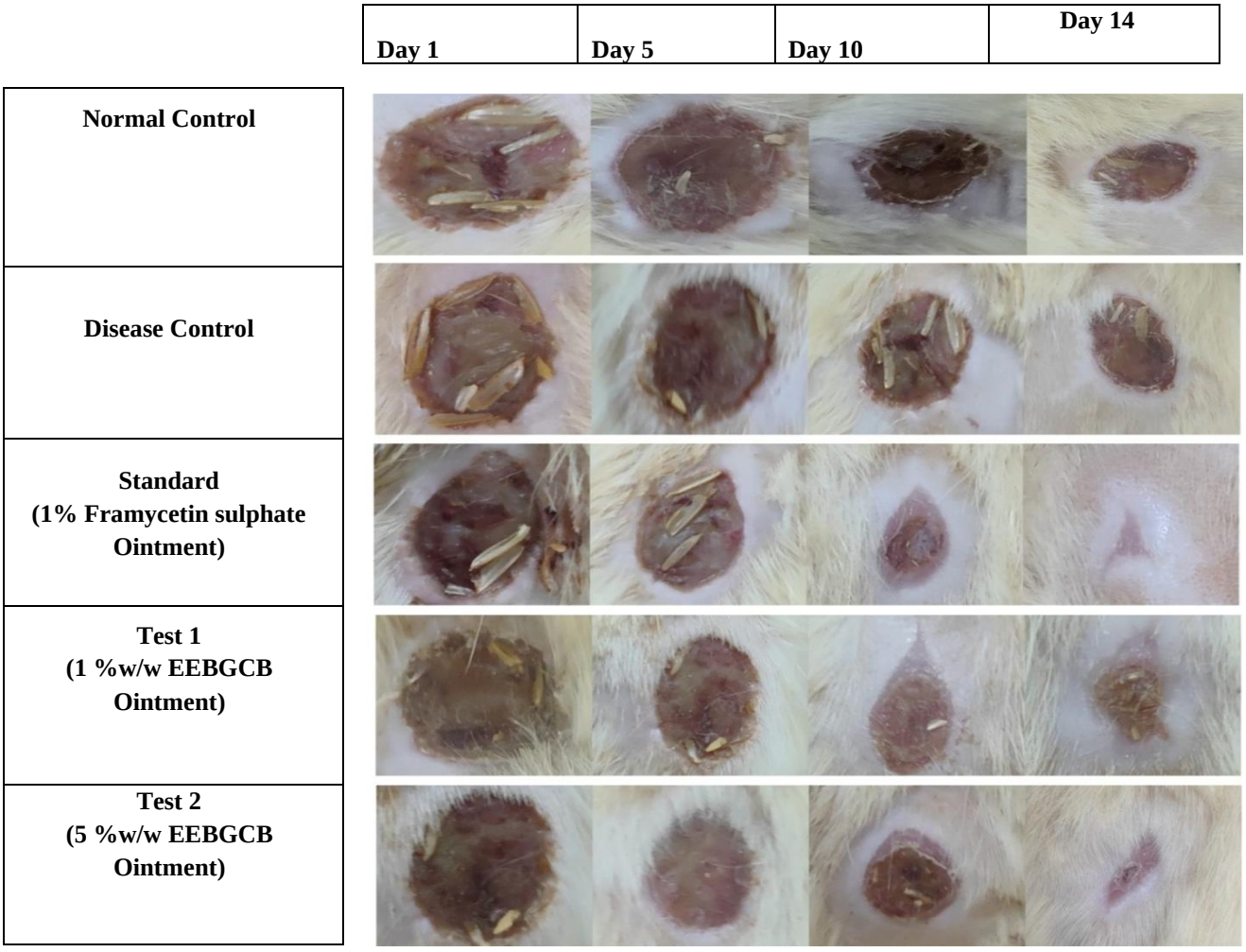

Fig.4 Comparison of wound sites on Day 1, 5, 10 and 14 in various groups (Normal control, Disease control, Standard, Test 1 and Test 2)

2. Wound Contraction Percentage

The percentage wound contraction was calculated and the results were presented in Table-2 and the data can be visualized in Figure 5.

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Table-2 Wound Contraction Percentage

GROUPS	% WOUND CONTRACTION				
	DAY 0	DAY 4	DAY 8	DAY 12	DAY 14
Normal Control	0	31.2±0.40	49±0.37	57.5±0.43	67.3±0.71
Disease Control	0	16.8±0.48 ####	33.5±0.43 ####	46.5±0.43 ####	53.5±0.76 ####
Standard (1% Framycetin sulphate Ointment)	0	42±0.58 ****	76.5±0.43 ****	91.5±0.43 ****	97.7±0.56 ****
Test 1 (1 %w/w EEBGCB Ointment)	0	39.2±0.60 ****	70.5±0.43 ****	92.0±0.97 ****	89.3±0.49 ****
Test 2 (5 %w/w EEBGCB Ointment)	0	40.2±0.60 ****	72.2±0.60 ****	80.5±0.43 ****	95.7±0.56 ****

All the values are expressed as Mean±SEM (n=6)

####P<0.0001 compared to Normal control, ****P<0.0001 compared to Disease control

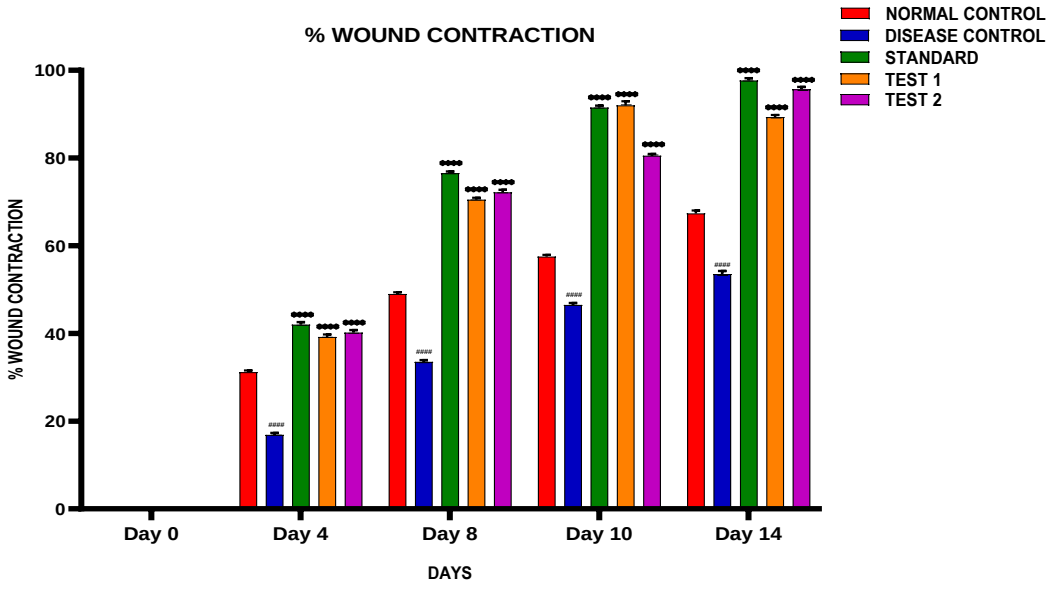

Fig.5 Comparison of % Wound Contraction on Day 0, 4, 8, 10 and 12

Wound contraction is a key indicator of wound healing. The percentage wound contraction increased significantly in the standard (1% Framycetin sulphate) and test groups (1% w/w and 5% w/w EEBGCB ointment) compared to the disease control group. By day 14, the test 2 group achieved 95.7% wound contraction, comparable to the standard group (97.7%), and higher than the test 1 group (89.3%). The observed results highlight the enhanced wound-healing efficacy of the 5% w/w EEBGCB ointment, likely due to its higher concentration of bioactive compounds. The significant difference in contraction rates compared to the disease control group underscores its potential in promoting granulation tissue formation and re-epithelialization.

3. Epithelialization Period

The epithelialization period of all groups was observed and the results were presented in Table -3 and the data can be visualized in Figure 6**.**

Table-3 Epithelialization period of wounds

S NO.	GROUPS	EPITHELIALIZATION PERIOD (DAYS)
1.	Normal Control	20.7±0.333
2.	Disease Control	22.7±0.76#
3.	Standard (1% Framycetin sulphate Ointment)	14.2±0.307****
4.	Test 1 (1 %w/w EEBGCB Ointment)	17.5±0.428****
5.	Test 2 (5 %w/w EEBGCB Ointment)	17±0.365****

All the values are expressed as Mean ± SEM (n=6)

#P<0.01 compared with Normal Control, ***P<0.001, compared to Disease control

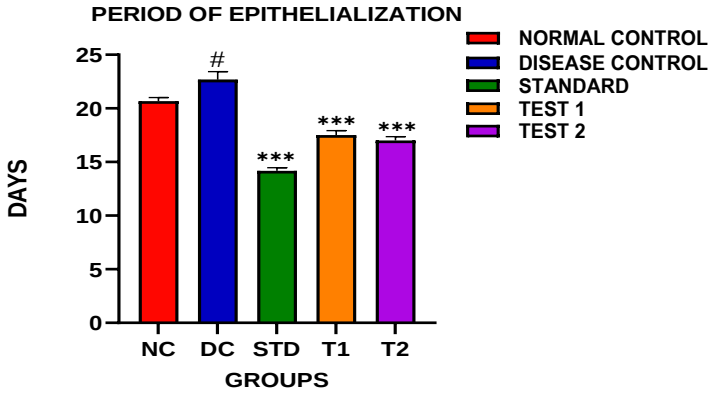

Fig.6 Comparison of Epithelialization Period of wounds

The epithelialization period was shortest in the standard group (14.2 days) and slightly longer in the test 2 group (17 days), compared to the test 1 group (17.5 days) and the disease control group (22.7 days). The shorter epithelialization period observed in the test 2 group suggests that the formulation effectively promotes keratinocyte proliferation and migration. The reduction in healing time is attributed to improved collagen synthesis and anti-inflammatory activity of the herbal components.

4. Estimation of Hydroxyproline

The healed section of wound area was estimated for hydroxyproline and the results were presented in the Table-4 and data can be visualized in Figure 7.

Table-4 Hydroxyproline levels on wounds

S NO.	GROUPS	HYDROXYPROLINE LEVEL (µg/g)
1.	Normal Control	21.8±0.307
2.	Disease Control	19.2±1.01#
3.	Standard (1% Framycetin sulphate Ointment)	31.2±0.833***
4.	Test 1 (1 %w/w EEBGCB Ointment)	26.2±0.601***
5.	Test 2 (5 %w/w EEBGCB Ointment)	29.5±0.428***

All the values are expressed as Mean ± SEM (n=6)

#P<0.01, compared to Normal control, ***P<0.001, compared to Disease control

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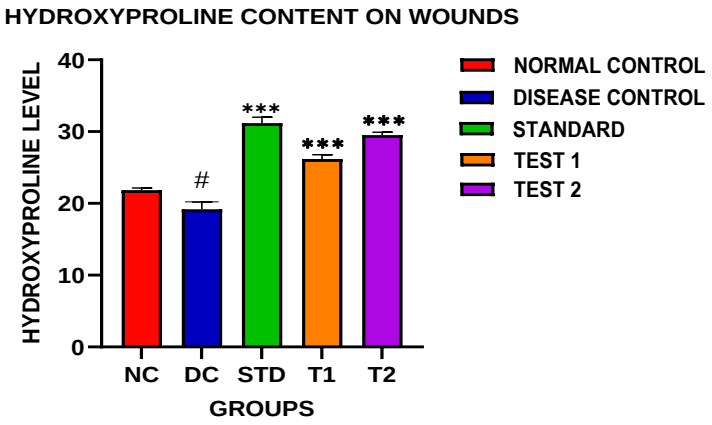

Fig 7 Comparison of Hydroxyproline level on wounds

Collagen deposition contributes to tissue strength and integrity during the remodeling phase of wound healing. Hydroxyproline content, an indicator of collagen turnover, was significantly higher in the test 2 group (29.5 µg/g) compared to the disease control (19.2 µg/g) and normal control (21.8 µg/g) groups (Table 4). The results were comparable to the standard group (31.2 µg/g). The increased hydroxyproline levels in the test 2 (5% w/w EEBGCB Ointment) groups suggest enhanced collagen synthesis, which is critical for wound repair.

5. Histopathological Examination

The healed wound sections from each group were examined for histological changes using hematoxylin and eosin stain and the results were illustrated in the **Figure 8-12.**

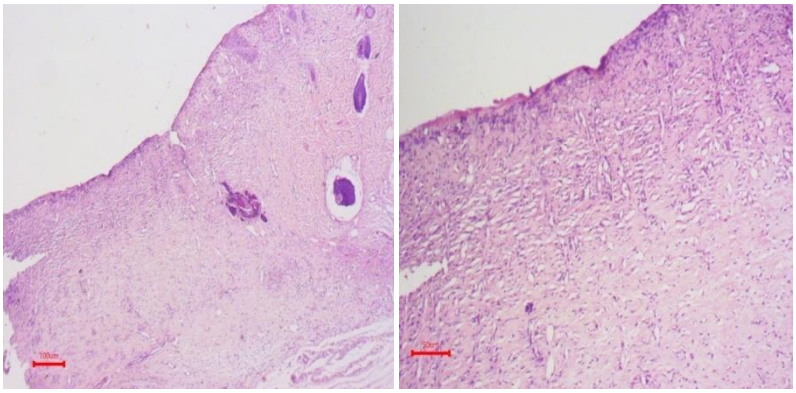

Fig.8 Wound tissue – Normal Control

Normal Control: The sections from Group I rats showed partial epithelialization with a longer new epithelial layer; discrete vascular formation; presence of extracellular matrix with more fibroblasts and thin collagen fibres; presence of few inflammatory cells and less scab formation.

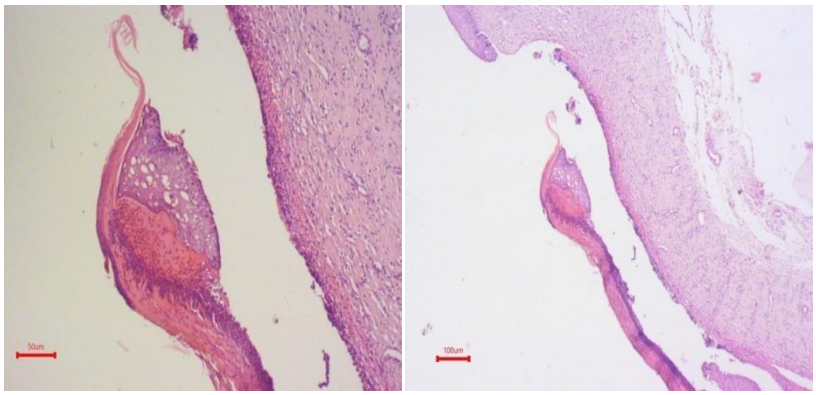

Fig.9 Wound tissue – Disease Control

Disease Control: The sections of the skin displayed a partial epithelialization with a small new epithelial layer; discrete vascular formation; incomplete presence of extra cellular matrix with more fibroblasts and thin collagen fibres; many inflammatory cells and less scab formation.

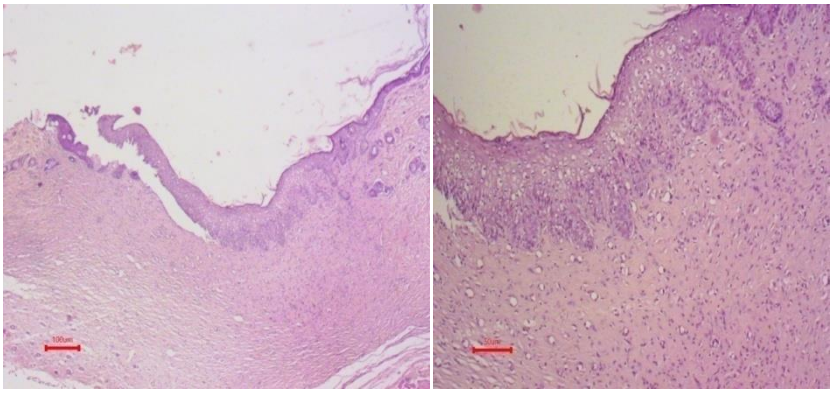

Fig 10 Wound tissue – Standard

Standard: The sections of the skin displayed a complete epithelialization; high vascular formation; presence of extracellular matrix in the whole wound area with few fibroblasts and thick collagen fibres; presence of some inflammatory cells and moderate scab formation.

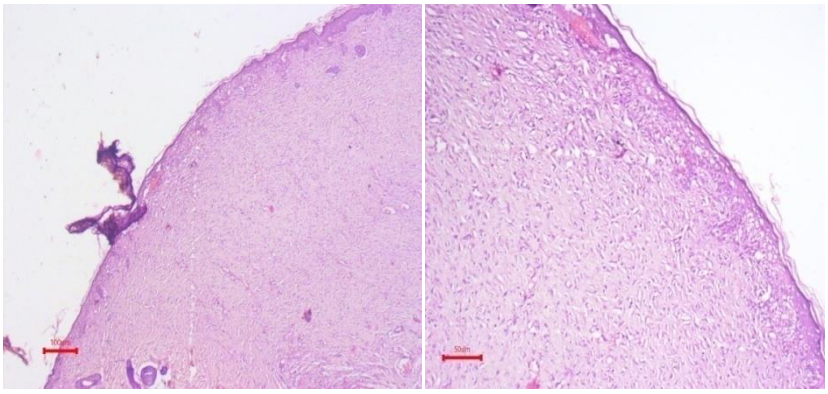

Fig 11 Wound tissue – Test 1 (Low dose)

Test 1 (Low Dose): The sections of the skin showed a complete epithelialization; moderate vascular formation; presence of extracellular matrix with few fibroblasts and thick collagen fibres; presence of few inflammatory cells and moderate scab formation.

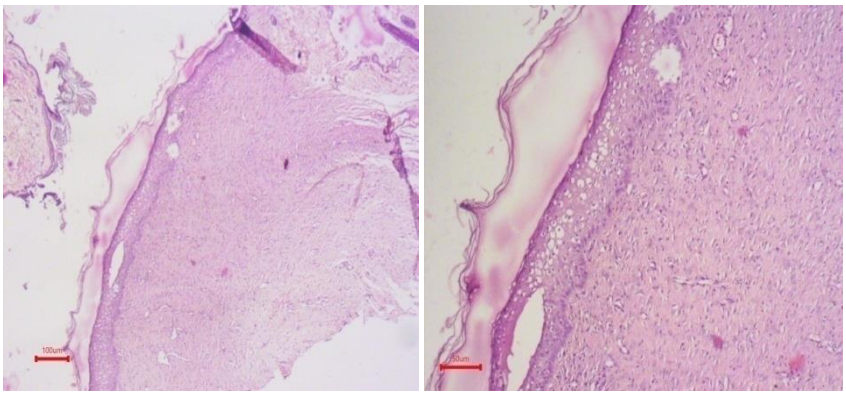

Fig 12 Wound tissue – Test 2 (High dose)

Test 2 (High Dose): The sections from the skin displayed a complete epithelization; high vascular formation; presence of extracellular matrix with few fibroblasts and thick collagen fibres; presence of less inflammatory cells and less scab formation.

The histopathological findings further validate the wound-healing efficacy of the 5% w/w EEBGCB ointment. The increased vascularization and collagen deposition in treated groups indicate accelerated tissue regeneration and remodeling. Reduced inflammatory cell infiltration demonstrates the anti-inflammatory properties of the formulation.

SUMMARY AND CONCLUSION

This study evaluated the wound-healing potential of *Bougainvillea glabra* Choisy Bracts through the formulation and assessment of 1% w/w and 5% w/w EEBGCB ointments. The physicochemical characterization of the ointments, including p^H, consistency, spreadability, and accelerated spoilage, demonstrated satisfactory results, confirming their suitability for topical application.

Acute dermal toxicity studies, conducted as per OECD Guidelines 402, indicated no adverse effects, behavioral changes, or mortality, establishing the safety of EEBGCB ointment up to a dose of 2000 mg/kg.

The *in vivo* wound-healing activity was assessed using an excision wound model in streptozotocin-induced diabetic rats. Parameters such as Wound contraction, Epithelialization period, Hydroxyproline estimation, and Histopathology were evaluated. Both the Test 1 (1% w/w EEBGCB ointment) and Test 2 (5% w/w EEBGCB ointment) groups demonstrated significant wound-healing effects compared to the disease control group. The 5% w/w EEBGCB formulation showed comparable efficacy to the standard treatment (1% Framycetin sulfate). Key findings include enhanced wound contraction; reduced epithelialization period; increased hydroxyproline levels, indicating higher collagen synthesis; Improved histopathological features such as collagen deposition, epithelialization, and vascular formation.

In Conclusion, the comprehensive evaluation of EEBGCB ointments in an excision wound model, along with their physicochemical characterization, has provided valuable insights into their potential as an herbal formulation for wound healing. The *in vivo* findings highlight the efficacy of *Bougainvillea glabra* Choisy bracts as a potential herbal wound healing agent, likely attributed to its polyphenolic compounds and flavonoids. Nonetheless, further research is needed to isolate and characterize the active constituents, elucidate the precise mechanism of action, and identify the specific compounds responsible for the observed effects. Despite these research gaps, *Bougainvillea glabra* Choisy bracts emerges as a natural and promising alternative for enhancing diabetic wound healing and facilitating tissue regeneration.

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Conflict of interest statement: The authors declared no conflict of interest.

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