





## Research Article

# Evaluation of Wound Healing Activity (Excision Wound Model) of Ointment Prepared from Infusion Extract of Polyherbal Tea Bag Formulation in Diabetes-Induced Rats

Aamir Quazi,<sup>1</sup> Mohsina Patwekar <sup>2,3</sup> Faheem Patwekar <sup>2</sup> Amine Mezni,<sup>4</sup>  
Irfan Ahmad <sup>5</sup> and Fahadul Islam <sup>6</sup>

<sup>1</sup>KT Patil College of Pharmacy, Osmanabad, Maharashtra, India

<sup>2</sup>Luqman College of Pharmacy, Gulbarga, Karnataka, India

<sup>3</sup>Department of Pharmaceutical Science, BAMU, Aurangabad, India

<sup>4</sup>Department of Chemistry, College of Science, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia

<sup>5</sup>Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Khalid University, Abha, Saudi Arabia

<sup>6</sup>Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka 1207, Bangladesh

Correspondence should be addressed to Mohsina Patwekar; [mohsina.patwekar@gmail.com](mailto:mohsina.patwekar@gmail.com) and Fahadul Islam; [fahadul29-774@diu.edu.bd](mailto:fahadul29-774@diu.edu.bd)

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In the present investigation, *Ichnocarpus frutescens*, *Ficus dalhousiae*, *Crateva magna*, *Alpinia galanga*, and *Swertia chirata* plants were selected to formulate polyherbal tea bag. The infusion obtained from these polyherbal tea bags was used to formulate 5% and 10% ointment formulation to perform its wound healing activity. The excision wound model was used to assess the wound healing activity in diabetic as well nondiabetic rats. The mean percentage closure of wound area was calculated on the 3<sup>rd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 12<sup>th</sup>, 15<sup>th</sup>, 18<sup>th</sup>, and finally 21<sup>st</sup> day. The wound healing activity of formulation was found to be significantly compared with that of the reference standard and untreated groups. The percentages of closure of excision wound area on the 21<sup>st</sup> day in diabetic animals treated with ointment formulations (F1 and F2) were found to be  $93.91 \pm 1.65\%$  and  $99.12 \pm 5.21\%$  respectively, whereas the chloramphenicol sodium drug solution was found to be  $99.81 \pm 3.16\%$ . The percentages of closure of excision wound area in nondiabetic animals treated with ointment formulations (F1 and F2) were found to be  $96.81 \pm 2.04\%$  and  $98.13 \pm 1.14\%$ , respectively, whereas the chloramphenicol sodium drug solution was found to be  $99.15 \pm 1.41\%$  at 21<sup>st</sup> day. Therefore, from the above results, we have concluded that this polyherbal ointment can be used clinically for the treatment of diabetic and nondiabetic wounds.

## 1. Introduction

Diabetic foot ulcers (DFUs) are one of the most significant consequences associated with diabetic care. DFU treatment involves a multidisciplinary approach that includes the use of proper diagnostic tools, expertise, and experience. To avoid amputations, this starts with patient education and the application of new categories to guide care [1, 2]. New diagnostic methods, such as the 16S ribosomal DNA sequence in bacteria, should become available to acquire a better understanding of the microbiota in DFUs. DFU is said to be

polymicrobial in nature and to have some distinct characteristics depending on its geographical location, such as wound characteristics, antibiograms based on local epidemiology, individualized antimicrobial-driven treatment, routine debridement, regular wound examination, and dressing changes [3]. New biological and molecular therapies that have been shown to enhance infection prevention, the management of the local inflammatory profile, and the efficiency of the cicatrizing mechanism often help with the above characteristics [4–7]. There are several new therapies for ulcers that are designed to speed up the healing process.

As an example, they include adjuvant growth factors, inflammatory modulators, herb extracts, and blood products as well as biological therapies and hazardous pressure injuries. These therapies, however, are not a replacement for regular diabetic foot care and should not be used in place of it [8–10].

Wound healing is the process of repairing the skin and other soft tissues after an injury. An inflammatory reaction happens after an injury, and cells below the dermis (deepest skin layer) begin to produce more collagen (connective tissue). The epithelial tissue (outer skin) regenerates later. Wound healing is divided into three stages: inflammation, proliferation, and remodeling [11].

Angiogenesis, collagen deposition, granulation tissue development, epithelialization, and wound contraction are all characteristics of the proliferative phase. Angiogenesis is the formation of new blood vessels by endothelial cells. Fibroblasts expel collagen and fibronectin to generate a new, provisional extracellular matrix during fibroplasia and granulation tissue development. Following that, epithelial cells crawl across the wound bed to cover it, and myofibroblasts, which grab the wound borders and contract using a mechanism similar to that of smooth muscle cells, compress the wound [12]. For wound therapy and management, plants or chemical entities derived from plants must be discovered and formulated. A variety of herbal products are currently being researched in this direction. Throughout the history, several herbal preparations have been employed in the management and treatment of wounds [13, 14]. *Ichnocarpus frutescens*, *Ficus dalhousiae*, *Crateva magna*, *Alpinia galanga*, and *Swertia chirata* are well-known plants available throughout India, and they are commonly used for the treatment of various diseases including diabetes mellitus [15–18]. Therefore, in the present study, we have selected these plants to formulate polyherbal tea bag formulation which have been subjected for in vitro and in vivo antidiabetic activities. The infusion extract of prepared tea bag formulation was subjected for wound healing activity in diabetes-induced rats. The ointment of different strength was prepared, and the activity was performed. For the present study, we decided to formulate ointment as it is easy to prepare and can effectively be applied topically for any kind of animal model studies. To prepare spray formulation, it requires more expenses and it is somehow costly than ointment preparations.

## 2. Materials and Methods

**2.1. Collection of Plants and Authentication.** The plants *Ichnocarpus frutescens*, *Ficus dalhousiae*, *Crateva magna*, *Alpinia galanga*, and *Swertia chirata* were collected and authenticated from Dr. Madhava Chetty, Department of Botany, Sri Venkateswara University, Tirupati, India, with voucher numbers 0448, 0879, 0550, 0911, and 0612, respectively.

**2.2. Preparation of Extract Ointment for Wound Healing Activity.** The polyherbal tea bags were formulated by taking

TABLE 1: The composition of ointment for wound healing activity.

S. no.	Ingredients	Quantity	
		F1	F2
01	Extract	5% w/w	10% w/w
02	Carbopol 940	0.5% w/w	0.5% w/w
03	Propyl paraben	0.01% w/w	0.01% w/w
04	Ethanol	10 mL	10 mL
05	Triethanolamine	q.s.	q.s.
06	Water	q.s.	q.s.

each selected plant powder in different quantities. The formulated tea bags were immersed in 240 mL distilled water and brewed at 80°C for 5 min. The maximum infusion time for the tea bag was <30 s to 10 min [19]. This infusion extract was used to formulate the ointment of different strengths for wound healing activity. The ointment containing 5% w/w and 10% w/w extract was prepared to perform wound healing activities. The 100 g gel was prepared by the direct dispersion method. First, propylparaben was dissolved in water at 80°C, and then, an accurately weighed quantity of Carbopol 940 was dispersed in water at 40°C with constant stirring for 30 min. Accurately weighed quantity of extract for formulation (5% w/w and 10% w/w) was dissolved in a minimum quantity of ethanol and then incorporated in the above-prepared solution of Carbopol with continuous stirring [20]. The quantities of ingredients used for the formulation are given in Table 1.

**2.3. Experimental Animals and Ethical Considerations.** Swiss Albino rats of either sex weighing between 20 and 30 g were used. The mice were acclimatized to the animal house condition for 1 week before carrying out any experimental work. The mice were fed with a normal animal pellet diet and water ad libitum. They were housed at standard housing conditions of temperature (23°C ± 12°C), humidity (45 ± 5%), and 12 h light and dark cycle.


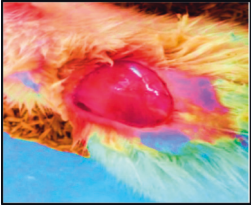


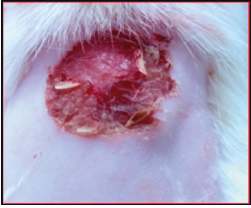
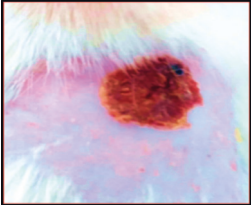
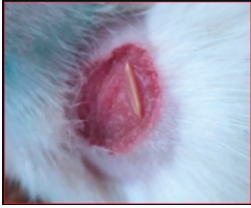
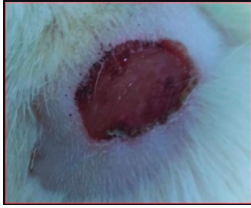








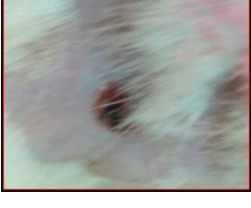
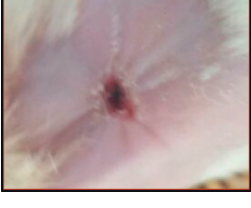


In line with the Committee for the Purposes of Control and Supervision of Experiments on Animals' (CPCSEA) requirements, all of the animals were observed and cared for in accordance with their needs. The animals were kept in polypropylene cages, and all procedures on them were carried out in an aseptic environment. With the approval of the Institutional Animal Ethics Committee (IAEC), the study's procedures were implemented (approval number: CPCSEA/IAEC/JLS/16/07/21/37).

**2.4. Acute Toxicity Studies.** Safety studies for dose titration were carried out according to the Organization for Economic Co-Operation and Development (OECD 425) Guideline on normal mice with three different doses of the tea bag solution. The fasted mice were fed with a single dose of 500, 1000, and 2000 mg/kg bodyweight by oral route to three different groups, respectively. All the mice were keenly examined for 2 h to check for any abnormalities in the behavior of the animals and further continued to monitor and examine the mice for 24 and 72 h [21, 22].

TABLE 2: The comparative wound healing efficiency (wound area and % wound closure) of ointment formulation (F1 and F2) and pure drug in diabetic and nondiabetic wound of albino rats.

Days	Wound parameters	Control group		F1 (5%)		Chloramphenicol sodium		F2 (10%)	
		DW	Non-DW	DW	Non-DW	DW	Non-DW	DW	Non-DW
0	Wound area	317.21 ± 0.00	317.21 ± 0.00	317.21 ± 0.00	317.21 ± 0.00	317.21 ± 0.00	317.21 ± 0.00	317.21 ± 0.00	317.21 ± 0.00
	% wound closure	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
3 <sup>rd</sup>	Wound area	276.91 ± 17.71	267.11 ± 12.71	267.22 ± 12.70	267.23 ± 13.69	276.91 ± 12.17	267.27 ± 19.74	267.12 ± 12.18	267.23 ± 11.27
	% wound closure	15.81 ± 6.31	18.71 ± 7.32	18.89 ± 6.13	18.82 ± 4.31	15.53 ± 3.33	18.29 ± 7.23	16.71 ± 3.73	18.90 ± 7.23
6 <sup>th</sup>	Wound area	248.30 ± 18.82	239.21 ± 14.82	221.41 ± 12.98	221.34 ± 12.79	212.27 ± 18.19	212.67 ± 11.59	221.41 ± 12.19	187.89 ± 17.09
	% wound closure	24.49 ± 7.06	27.81 ± 4.08	33.45 ± 5.72	33.52 ± 1.72	36.21 ± 6.71	36.21 ± 3.66	33.55 ± 6.37	44.19 ± 3.41
9 <sup>th</sup>	Wound area	212.67 ± 18.29	164.52 ± 14.11	172.21 ± 11.19	172.21 ± 11.10	164.23 ± 17.11	122.61 ± 10.53	172.31 ± 09.14	122.66 ± 14.44
	% wound closure	36.21 ± 8.71	51.52 ± 7.23	49.12 ± 6.21	49.13 ± 5.18	51.52 ± 7.12	64.89 ± 2.52	49.11 ± 7.31	64.82 ± 7.62
12 <sup>th</sup>	Wound area	164.52 ± 13.15	122.62 ± 13.31	122.62 ± 10.53	122.56 ± 12.31	122.60 ± 10.43	87.09 ± 8.55	98.51 ± 12.32	57.72 ± 8.81
	% wound closure	51.58 ± 5.19	64.91 ± 5.63	64.91 ± 4.61	64.89 ± 4.61	64.89 ± 7.76	76.22 ± 5.13	72.51 ± 8.51	85.55 ± 3.54
15 <sup>th</sup>	Wound area	119.09 ± 11.34	68.62 ± 8.62	84.07 ± 9.53	84.07 ± 9.53	54.73 ± 7.71	59.19 ± 7.71	54.73 ± 7.71	31.69 ± 5.89
	% wound closure	64.19 ± 5.06	81.71 ± 3.47	76.52 ± 2.30	76.52 ± 6.31	85.51 ± 4.14	84.2 ± 4.53	85.51 ± 4.64	92.97 ± 3.78
18 <sup>th</sup>	Wound area	87.72 ± 8.51	45.41 ± 4.81	58.21 ± 12.59	45.42 ± 8.81	34.79 ± 7.89	28.41 ± 6.89	5.67 ± 8.86	3.87 ± 3.64
	% wound closure	76.21 ± 4.33	89.51 ± 5.76	85.42 ± 6.62	89.51 ± 4.17	92.91 ± 3.82	94.97 ± 3.51	96.21 ± 0.43	96.51 ± 1.14
21 <sup>th</sup>	Wound area	62.18 ± 8.61	34.39 ± 3.18	28.42 ± 5.91	16.10 ± 4.31	5.91 ± 6.12	3.51 ± 1.33	1.92 ± 2.11	2.15 ± 1.23
	% wound closure	83.11 ± 3.41	88.91 ± 1.82	93.91 ± 1.65	96.81 ± 2.04	99.81 ± 3.16	99.15 ± 1.41	99.12 ± 5.21	98.13 ± 1.14
	Endpoint of complete epithelization	29.31 ± 0.37	33.32 ± 1.43	28.61 ± 2.41	25.12 ± 1.81	26.61 ± 2.54	23 ± 2.81	20.13 ± 3.41	18.61 ± 4.44

TABLE 3: The images showing wound healing potential of ointment formulation (F1 and F2) and pure drug in diabetic and nondiabetic wound of albino rats.

Diabetic wound (control group)	F1	Chloramphenicol sodium	F2
			
0 <sup>th</sup> day			
			
6 <sup>th</sup> day			
			
15 <sup>th</sup> day			
			
18 <sup>th</sup> day			
			
21 <sup>th</sup> day			

2.5. Induction of Chronic Diabetes and Experimental Design (Excision Model). Hyperglycemia was induced by a single intraperitoneal injection of freshly prepared streptozotocin (STZ)-nicotinamide (55 mg/kg bodyweight, in 0.1 M citrate buffer (pH 4.5) to a group of overnight fasted rats). To control drug-induced hypoglycemia, a solution of 5%

glucose overnight was given to rats. Hyperglycemia was confirmed on the third day after STZ injection by estimating the glucose level by the glucometer. The rats having a glucose level of 300 mg/dl were used for the study [23]. After induction, the animals were anesthetized by using a suitable anesthetic agent like ether. An impression was made on the



dorsal thoracic region 1 cm away from the vertebral column and a 5 cm away from the ear on the anesthetized rat. The particular skin area was shaved one day before the experiment. The skin of the impressed area was excised to the full thickness to obtain a wound area of about 300 mm<sup>2</sup>.

The animals were divided into eight groups of three each. The group I diabetic wound and group II nondiabetic wound animals were kept untreated as a control. The group III diabetic wound and group IV nondiabetic wound animals were applied topically with a 5% of ointment formulation. The group V diabetic wound and group VI nondiabetic wound animals were applied topically with a 10% of ointment formulation. The group VII diabetic wound and group VIII nondiabetic wound animals were applied topically with a standard drug solution of chloramphenicol sodium succinate. The infusion ointment formulations (F1, 5% and F2, 10%) were topically applied once a day, starting from the day of the operation, till the completion of epithelialization. The measurement of the wound areas of the excision wound model was taken on 0, 3<sup>rd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 12<sup>th</sup>, 15<sup>th</sup>, 18<sup>th</sup>, and 21<sup>st</sup> days. Thereafter, on alternate days, until healing was complete, the percentage of wound closure was calculated [24, 25].

### 3. Results and Discussion

The comparative wound healing efficiency (wound area and % wound closure) of ointment formulation (F1 and F2) and chloramphenicol sodium pure drug in the diabetic and nondiabetic wounds of albino rats is given in Table 2. The images showing the wound healing potential of ointment formulation (F1 and F2) and chloramphenicol sodium pure drug in the diabetic wound of albino rats are given in Table 3.

The mean percentage closure of wound area was calculated on the 3<sup>rd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 12<sup>th</sup>, 15<sup>th</sup>, 18<sup>th</sup>, and finally 21<sup>st</sup> day. The wound healing activity of formulation was found to be significant compared with that of the reference standard and untreated groups. The percentages of closure of excision wound area on the 21<sup>st</sup> day in diabetic animals treated with ointment formulations (F1 and F2) were found to be  $93.91 \pm 1.65\%$  and  $99.12 \pm 5.21\%$ , respectively, whereas the chloramphenicol sodium drug solution was found to be  $99.81 \pm 3.16\%$ . The percentages of closure of excision wound area in nondiabetic animals treated with ointment formulations (F1 and F2) were found to be  $96.81 \pm 2.04\%$  and  $98.13 \pm 1.14\%$ , respectively, whereas the chloramphenicol sodium drug solution was found to be  $99.15 \pm 1.41\%$  at 21<sup>st</sup> day. The polyherbal ointment formulation has shown significant wound healing activity and faster epithelization as compared to reference for both diabetic and nondiabetic wounds. Chloramphenicol sodium succinate is a broad-spectrum antibiotic that is effective against various Gram-positive and Gram-negative bacteria including rickettsia. In diabetic wound, high blood glucose level impairs the function of WBC, which affects the immune system of the body and the body becomes less able to fight bacteria. It is presumed that delayed healing is due to the persistence of prolonged inflammation and inadequate antigenic response [26]. The prolonged inflammation, delayed recruitment of

macrophages, and elevated neutrophils are reported for impaired wound healing in diabetes [27, 28]. Most diabetic wounds are generally infected with complex microorganisms that are composed of both Gram-positive and Gram-negative bacteria [29, 30]. In recent years, plants have been investigated as possible agents for the prevention and treatment of a variety of diseases. It is widely accepted that herbal products are superior to synthetic pharmaceuticals owing to the broad availability of herbal products as well as the great amount of empirical and readily available evidence about their traditional usage [31–35]. Modern scientific techniques, on the other hand, should be used to verify the claims made regarding the medicinal properties of plants, which would result in validation of the traditional system of medicine [36–38].

In the present investigation, it was revealed that in the inflammatory phase, polyherbal ointment formulation showed unique haemostatic properties that are independent of the normal clotting cascade [39]. It promotes the tensile strength of tissue by speeding up the formation of fibroblasts and the synthesis of collagen in the first few days of wound healing. These fibroblast formations induce angiogenesis and collagen formation in the wounded area. The reepithelialization occurred faster than the control. Chloramphenicol sodium succinate is a broad-spectrum antibiotic which assists wound healing activity from keeping wound free from complex infectious microorganisms. The polyherbal extract possesses diverse chemical constituents which impart the synergistic effect and exhibit potent pharmacological activity.

### 4. Conclusion

In recent years, plants have been studied as possible agents for disease prevention and therapy. Because of their broad availability and the wealth of available empirical and accessible evidence on their traditional usage, herbal products are often favored over synthetic ones. Traditional medicine may be supported by current scientific methodologies, which can be used to verify claims of the medicinal properties of herbs. In the present investigation, *Ichnocarpus frutescens*, *Ficus dalhousiae*, *Crateva magna*, *Alpinia galanga*, and *Swertia chirata* plants were selected to formulate polyherbal tea bags. The infusion obtained from these polyherbal tea bags were used to formulate 5% and 10% ointment formulation to perform its antidiabetic activity. The excision wound model was used to assess the wound healing activity in diabetic as well nondiabetic rats. The mean percentage closure of wound area was calculated on the 3<sup>rd</sup>, 6<sup>th</sup>, 9<sup>th</sup>, 12<sup>th</sup>, 15<sup>th</sup>, 18<sup>th</sup>, and finally 21<sup>st</sup> day. The wound healing activity of formulation was found to be significant compared with that of the reference standard and untreated groups. The percentages of closure of excision wound area on the 21<sup>st</sup> day in diabetic animals treated with ointment formulations (F1 and F2) were found to be  $93.91 \pm 1.65\%$  and  $99.12 \pm 5.21\%$ , respectively, whereas the chloramphenicol sodium drug solution was found to be  $99.81 \pm 3.16\%$ . The percentages of closure of excision wound area in nondiabetic animals treated with ointment

formulations (F1 and F2) were found to be  $96.81 \pm 2.04\%$  and  $98.13 \pm 1.14\%$ , respectively, whereas the chloramphenicol sodium drug solution was found to be  $99.15 \pm 1.41\%$  at 21<sup>st</sup> day. Therefore, from the above results, we have concluded that this polyherbal ointment can be used clinically for the treatment of diabetic and nondiabetic wounds. Moreover, numerous data need to be generated from more in vitro and in vivo models before claiming its clinical significance.

### Data Availability

The data used to support the findings of this study are included within the article.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

### Acknowledgments

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